Optimising the Quality and Effectiveness of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Trials



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Submitted in partial fulfilment of the requirements

for the degree of Doctor of Philosophy

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Hilary Term 2015

Volume I

To those that made this research possible;

and those that will benefit in the future.

"Nisi impunitatis cupido retinuisset, magnis semper conatibus adversa"

[“The desire for safety stands against every great and noble enterprise.”]

Tacitus, Annals Book L, VX, IV

Preface

This final document represents a profound personal and professional journey that has progressed through *conclusion, transition* and *launch.* An exciting journey, for which I am forever indebted and grateful to those 'travel companions' who have supported and challenged me; and in some cases, graciously accepted my support and challenge returned.

Prior to commencing this body of work I had absolute certainty that in my commitment to a career at the interface of science and business – spanning the translation gap. In Oxford this divide is physically embodied by Headington Hill, which in *many* ways is more challenging than The Charles separating Cambridge and Longwood – although with less severe weather. However, I was uncertain how to make a sustained and impactful contribution to life science translation, whether that be cycling up Headington Hill, walking across the Anderson Memorial Bridge or, more recently, crawling along in traffic on Sand Hills Road. In Churchillian terms, the "the end of the beginning [the conclusion]" began on a sticky summer afternoon in 2010.

Framed between the two Beagle huts in the UCL quad, armed with a grazed tan briefcase containing a tatty copy of his eponymous report (Cooksey, 2006), Sir David Cooksey – then a stranger, and now a dear friend and mentor – embodied the realisation of a career at the interface of science and business. By the end of the meeting, David made it patent that while such a trajectory was possible and valuable, I would need to pursue (and submit) a Doctorate to minimise the risk of failure and maximise the likelihood of succeeding in this endeavour, which has aptly transpired to be in healthcare risk management. While I have at times poorly defended from and sought distractions from my DPhil, unlike David I am yet to receive a call to assist the Air Ministry to abandon the thesis and design aircraft components. Shortly thereafter I was to have the immense fortune to meet two figures that conferred inspiration, mentorship, friendship - and most importantly academic rigour.

Bursting into a draped room with a bright orange tie with typical haste and intensity, Sir John Bell made half of the DPhil dream a reality. He had the vision, experience and shared frustration with the status quo, to support an interdisciplinary DPhil delving deep into life science translation, at a time where such opportunities were rare, if not non-existent.

Over these two extraordinary years, John has consistently and generously lent his ear and insight in a range of situations: academic, political and personal. It's always a pleasure to spend 90% of a meeting with John discussing the latest political and commercial failures and successes – in which he is usually involved in their execution and/or clean up - and the final 10% of the meeting running down a bullet point list of questions. Direct answers are elicited

in a satisfyingly rapid and perhaps slightly comical exchange, during which the ever helpful, efficient and motherly Dorian begins to 'hover.'

There are few men as illustrious and connected as John, and even less, who have made – and continues to make – such an impact on those people, individuals and systems with whom they interact. While not afraid to 'ruffle a few feathers' to get the job done – coupled with his borderline intolerance of bureaucracy – all of his peers have a consistent fond glint in their eye when John is mentioned. As do I.

The single greatest lesson I take from John is a very personal take on politics, and I have found to be universally applicable: "If one door is closed, just walk out of the other one."

Returning to my first meeting with John, after the characteristic "90:10 meeting" format had been successfully executed, in true 'JB fashion' a swift note typed in trademark blue text was dispatched to the man that completed the DPhil whole, Prof. Andy Carr.

At the time I didn't know why John suggested I meet with Andy first, from a range of possibilities, yet the pairing was complementary intellectually and personally. Subsequently, "systematic" and "rigorous" became my bywords, concluding the era of 'Brindley fluff.' Andy has been a wonderful mentor, personally and professionally.

Professionally, Andy inspired and demanded – in equal measure – academic rigour, which while initially frustrating and difficult to calibrate (as Carr rigour is set to a higher bar), the final data, publications and conclusions of this thesis are deep and methodologically valid thanks to him. These skills and life-long criticality have taken my research – citations generated, journal impact factors and personal pride in my work – to a higher level. For that I am thankful; but I am most grateful for the personal mentorship Andy has actively and passively given so generously and selflessly.

"The Humble Surgeon" whose natural intellect and ambition are impossible to hide – although he tries with unique and genuine warmth – is the best example I am yet to meet of a successful leader (by any measure) in the workplace, who consistently prioritises his family and "sacred" badminton. However, he still refuses a friendly duel on the tennis court. It is this discipline and inspiration more than his extraordinary academic accomplishments, that I cherish and respect most, and seek to implement in my personal and professional life as a hallmark of Andy's mentorship.

Thus the personal and professional *transition* during my DPhil can best be described by this chapter in my life where I identified the need and benefits of rigour and discipline, in both my

professional and personal life, without compromising or suppressing my deep social, academic and commercial entrepreneurial spirit, and integrity.

Additional special mentions for their longstanding support during this *conclusion, transition* and *launch* must be made to an extraordinary friend, mentor and collaborator Kim Bure (readers can judge her proficiency as a proof reader); the team at the SENS Research Foundation whose intellectual and financial support has been invaluable to making this dream a reality.

Lastly, I extend my heartfelt and unbounded thanks to my parents without whom no chapter of my life would be possible. Truly unconditionally they have supported me and bestowed multiple gifts perhaps embodied in this thesis: words to change hearts and minds from my Mother, and a raw entrepreneurial and pragmatic approach from my Father. Ironically, despite facilitating this chapter of my life, I doubt this thesis will provide for riveting entertainment; but I know it will have pride of place on the bookshelf in the corner of the living room, clad in spiders' webs that are an annoyance when trying to turn on the lamp, and alongside travel books. Perhaps appropriate given the journey this represents…

As I now embark on the *launch* phase of my journey, I am mindful of the quotation "To whom much is given, much is expected".

Thank you all for your support, inspiration and patience. I look forward to a lifetime of collaboration and friendship.

Acknowledgements

This body of research would not have been possible without the contributions of my professional and personal networks. For those omitted from the list below – most likely in error – I apologise and thank you for your contribution.

The SENS Research Foundation was the primary funder of this research, and a vanguard funder of CASMI, without their vision and support this DPhil simply could not have happened. Special thanks go to Aubrey De Grey for publishing my first publication (Brindley and Davie, 2009) during my first year as an undergraduate – arguably the first major step in my academic career. While Aubrey and I may not always align intellectually, it is done with good grace and against the backdrop of a lifelong friendship and inevitably a decent ale in hand – which after all is how we first met!

Mike Kope, friend, mentor, 'Californian Father,' life science disrupter and lover of fast cars has been a logistical and intellectual cornerstone over the past two years, with whom I thoroughly look forward to working into the future, and rattling office windows in obnoxiously coloured V8 rental cars. Lisa Fabiny has the patience of a Saint and astonishing attention to detail – without her I, nor the CTSCC, would have remained financially solvent during this period. To Lisa I offer my thanks, apologies for my poor (but improving) admin skills and best wishes to her young family. There are few more genuine people I have ever met than Greg Chin, a gentlemen of formidable intellect, astonishing warmth and who everyday seeks to make the world a better place through education. To Greg, I offer thanks and a genuine excitement for the execution of future plans – we just need to find more JS'! Finally, thanks to Jerri Barrett, Thaddeus Campbell, Heidi Ward and the rest of the team for their support – I look forward to many years of giving back.

Heading East, I have to offer my heartfelt thanks to my 'Boston parents', Brock Reeve and Maureen Herrmann, who continue to make my time at HSCI – in person or remotely – a pleasure. Whether its sorting visa paper work or offering an ear and shoulder during a period of emotional stress, Maureen and Brock are always there for me, as I am for them. Thank you and I look forward to seeing more of you – professionally and personally – now that the DPhil is done.

Crossing the Atlantic, few people have made such a profound personal and professional impact in the last two years than an ex-professional footballer and a well-dressed gentleman from a Welsh mining village. But they were always so much more than that – and today are changing patient behaviour and outcomes in a profound way. Andrew Martello, emotionally astute, more intelligent that he'll ever realise and a fellow earthquake survivor has been a

constant source of support and inspiration. As I hope I can be for him, personally, commercially and on a bike, in the future. Rob Horne has a piercing, unique and extraordinary understanding of the human psyche, along with colleague Dr Rioja, has become a dear friend. Any man whose bibliography can break a hotel printer will always have a place in my heart and rolodex! Gentlemen, I look forward to tomorrow.

This investigation, particularly in early stages, was made possible in significant part by the CASMI team. To them, and particularly Richard Barker and Megan Morys, I offer my thanks. We may not have always seen 'eye to eye,' nor shared the same vision in execution; but we have always been frank and shared the same goal: to improve life science translation. Moving forwards, I hope that I can assist in a meaningful way – and not solely be the 'CTSCC satellite' – you know where I am. Either way, I am inviting myself to the Barker Luberon base!

Elsewhere in Oxford I wish to thank Paul Riley and Georg Hollander, whom I hope to support Oxford's global leadership in regenerative medicine and stem cell biology – and by the time someone other than my examiners read this thesis – I hope have secured full funding for their much needed centre. Other figures with whom I have enjoyed interacting with and now look forward making substantial strides in uniting 'up the hill and down the hill' are Peter Tufano, Felix Reed-Tsochas and Sue Dopson. Finally, thank you to Dorian Kershaw, Houmann Ashrafian – while there is probably a rule prohibiting thanking your examiner – Chas Bountra for their counsel, encouragement and having the strength of mind to continue to make a unique impact.

Industrial collaboration has been critical to the success of this research, and to the development and growth of my future research strategy, to this end I wish to extend my heartfelt thanks to all supporters past and present of the CTSCC. While I value Mike May's counsel that "all things come in threes", they just don't; but his encouragement to 'dig in' and complete this work has been valuable and appreciated. Particular thanks are given to the team at Thompson Reuters: James Evans, Frank Wattler and Brian Larner; Kinapse: Nick Meadows and Nick Edwards; IP Asset: Ian Bingham and Dom Icely; Aegate: Mark De Simone, Leanne Huff and Graham Smith.

Unexpectedly, one of the greatest intellectual challenges of the past two years was actually in substantial part physical. Who ever thought it was a good idea – or even possible – to cycle from Oxford to Venice? Much of this thesis was mentally written to the soundtrack of Will Hutton linking together a string of expletives ending with a request for wine – followed by a reference to Assos cream; Steve Frost offering humour and candour; Oliver Noble-Wood offering inspiration through satire; and of course the wonderful Anna Baskerville singing

something about building a snowman in July. Incidentally, the only permanent scar from this thesis seems to have been inflicted on my right side by Basil.

A significant and repeated realisation throughout this journey has been my aptitude, in descending order, for leadership, management and details – admin, co-ordinating meetings and at times my hellish travel schedule. To past and current members of my nascent team, Anneke Kramm, Anna French, MacKenna Roberts and James Smith I offer my sincere thanks and apologies. As always never hesitate to let me know if and/or how I can help you.

At NDORMS I wish to extend my thanks to *everyone* for giving me a home, and in particular for Nick Gee for repeatedly giving me a key to it! All members of the Carr group – in particular 'the Weekend Warriors' Ben Davies, Richard Smith and Michael Ng; and Ulrike Bilgram and Ann Wilson who have kept the 'wheels oiled' and done so with good humour. The critical intellectual support of Andy Judge, Sir Marc Feldmann, Phillipa Hulley and Dominic Furniss is also noted and appreciated.

Special thanks must be given to Karolina Wartolowska and Rafael Pinedo – Villanueva who perhaps only second to my supervisors, were the intellectual 'Fathers' of this investigation. The 'Queen of Systematic Reviews' and 'King of Expert Elicitation' – thank you and I look forward to many years of collaboration.

Two ladies who have punctuated my DPhil with humour, distraction, support and conversations that make Fay Anderson blush are Isuara Thomas and Afsie Sabokbar. Thank you both – and I am certain that no other member of NDORMS staff is acknowledged in every thesis; but for good reason 'the Mother of NDORMS' is. The 'Lush' incident on the first day is forever burnished in my mind…

Thanks also to a quartet of collaborators who have become friends, responded to e-mails in the early hours, flown around the globe to support conferences I've organised and hosted interns and with whom I hope to collaborate for decades to come. The "Tom Brady of Biotech," Evan Snyder; rodeo star and one of the most gifted engineers of his generation, Jeff Karp; straight talking and supportive in good times and bad, David Williams; and Ivan Wall – without whom I wouldn't read Nature weekly and continually surprise people when they don't expect me to know about the role of Jag1 - or essentially any contemporary basic science concept. Many nights in The Wrestlers to come.

A collection of personal friends whom have supported, sometimes distracted, in various ways throughout this process: David Spencer, Pete Whitehouse, Nick Paddock, Nodd Godding, Stephen Petitt, Stuart Ingram, Majid and Peyman Ezzatti.

Research Disclosures

The research presented herein arises from work conducted in the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, under the supervision of Prof. Andrew Carr and Prof. Sir John Bell during October 2012 and January 2015.

No part of this thesis has been submitted previously for a degree at this, or any other, institution. Where work arising from collaborations with co-authors is included, every effort has been made to clearly acknowledge this and to objectively present the contribution of D.A.B. A full bibliography – including publications arising – is appended.

The primary funder of this research is the SENS Research Foundation, Mountain View, CA, USA.

Secondary funding is also provided via the CASMI Translational Stem Cell Consortium (CTSCC), whose past and present funders include: Centre for the Commercialization of Regenerative Medicine; Celgene Cellular Therapeutics; UK Cell Therapy Catapult; CIRM; Eisai; GE Healthcare; Lonza; OxfordBiomedica, SENS Research Foundation; TAP Biosystems (now Sartorius Stedim); MEDIPOST Co., Ltd.; MEDIPOST America Inc.; the New York Stem Cell Foundation; Roche; Thermo Fisher and the US National Institutes of Health Center for Regenerative Medicine (NIH-CRM). At the time of writing D.A.B. is the Academic Director and Principal Investigator of the CTSCC.



David A. Brindley

28th January 2015

Oxford, UK

Professional Disclosures

D.A.B. is subject to the CAIA Association and CFA Institute's codes, standards and guidelines and as such, must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation.

D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that provides advisory services to life science clients.

No additional conflicts of interest, beyond those stated in appended publications are disclosed. A full register of personal interests is available upon request.



David A. Brindley

28th January 2015

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Abstract

This investigation systematically assesses the quality and effectiveness of risk:benefit appraisal methodologies implemented in the analysis of published randomised controlled trials for pre-licensure biomedical innovations - therapeutics, devices and surgical procedures. The key finding is that, to date, reported applications of risk:benefit methodologies are highly heterogeneous and poorly reflective of the stakeholder needs assessed in the investigation.

A systematic review of published risk:benefit appraisal methodologies was conducted adhering to the PRISMA statement, yielding n=272 records that were assessed for eligibility. Subsequently, n=79 full text articles were assessed for eligibility leading to n=36 records eligible for meta-analysis.

A selection of internally generated quality factors (n=16) were gathered from published literature and practitioners in the life-sciences and non life-science focused industries. These internally generated quality factors were prioritised through an external expert elicitation assessment (n=14). Utility weightings derived for externally verified factors were then used to produce a scorecard to assess the quality and effectiveness of risk:benefit appraisal techniques surveyed. A minimum quality threshold (MAQT) was integrated into the scorecard and applied to n=36 records eligible meta-analysis. Consequently, n=6 records of the original n=272 exceeded the MAQT, and met the minimum stakeholder needs as determined by multi-stakeholder expert elicitation. An effort to apply mixed methods analysis to compare stakeholder viewpoints obtained by expert elicitation and paralinguistic uncertainty was unsuccessful; however, did not substantially or negatively impact the statistical significance of the results obtained.

Expert elicitation respondent evaluation(s) determined a limitation of the investigation was the failure to assess pharmacists attitudes to risk:benefit appraisal, given the changing role of pharmacists in healthcare delivery and incumbent regulatory changes, including the EU Falsified Medicines Directive. An international survey was distributed to European pharmacists (pilot study: n=988; full study: n=3952) which indicated a very strong desire by pharmacists (92.6%) to participate in risk:benefit appraisal.

In order to evaluate the impact of system risks in risk:benefit appraisal, a concurrent detailed investigation into barriers to the translation of regenerative medicines was conducted. The key finding was that regenerative medicines have a number of unique systems risks versus ‘conventional’ biomedical innovations, in particular, pertaining to intellectual property, biomanufacturing, clinical adoption and strategic partnerships.

Appended Publications

Published

Nature Biotechnology (2014) 32: 742–748

The Global Intellectual Property Landscape of Induced Pluripotent Stem Cell Technology; Roberts, R.M., Wall, I.B., Bingham, I., Icely, D., Reeve, B., Bure, K., French, A. & Brindley, D.A.

Cell Stem Cell (2015) 16 (1): 13-17

Generating iPSCs: Translating Cell Reprogramming Science into Scalable and Robust Biomanufacturing Strategies

Silva, M. Daheron, L., Hurley, H., Bure, K., Barker, R., Carr, A.J., Williams, D., Kim, H-W., French, A., Coffey, P.J., Cooper-White, J.J., Reeve, B., Rao, M., Snyder, E.Y., Ng, K.S., Mead, B.E., Smith, J.A., Karp, J.M., Brindley, D.A. & Wall, I.

Journal of Tissue Engineering (2014) 5:1-8

A Quantitative Assessment of Barriers to the Clinical Adoption of Cellular Therapies; Davies, B., Rikabi, S., French, A., Pinedo-Villanueva, R., Morrey, M.E.,Wartolowska, K., Judge, A., MacLaren, R.E., Mathur, A., Williams, D.J., Wall, I.B., Birchall, M., Reeve, B., Atala, A., Barker, R.W., Cui, Z., Furniss, D., Bure, K., Snyder, E.Y., Karp, J.M., Price, A., Carr, A.J.* & Brindley, D.A.* *Joint senior author

British Medical Journal (2014) 348:3253

Use of placebo control in the evaluation of surgery: a systematic review; Wartolowska, K., Judge, A., Hopewell, S., Collins, G.S., Dean, B.J.F., Rombach, Brindley, D.A., Savulescu,J., Beard, D.J. and Carr, A.J.

The Pharmacogenomics Journal (2014) 34:1-7

An Evaluation of Regulatory and Commercial Barriers to Stratified Medicine Development and Adoption; Meadows, N., Morrison, A., Brindley, D.A., Schuh, A. & Barker, R.W.

Trends in Biotechnology (2014), 32:9:436-440

Global Strategic Partnerships in Regenerative Medicine; French, A., Suh, J.Y., Suh, C.Y., Rubin, L., Barker, R.W., Bure, K., Reeve, B. & Brindley, D.A.

Healthcare Insights (2014), 8:9:9-11

'Bench to Bicycle:' A Clinical Perspective on Personalized Medicine: Genomics, Wearable Medical Devices and Regenerative Medicine; Brindley, D.A.

Bioprocess International (2014) 12:3: 14–21

Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence: A Concise Review; Brindley, D.A., French, A.L., Baptista, R., Timmins, N., Adams, T., Wall, I. and Bure, K

Rejuvenation Research (2014) 17:1:84-8

An Assessment of the Key Barriers to the Commercialization and Clinical Adoption of Pluripotent Stem Cell Therapies; French, A., Bure, K. & Brindley, D.A.

Nature (2013) 502:38

Better drug access for terminal patients; Brindley, D.A., Barker, R.W. and Lachmann, P.J. (2013)

Nature Medicine (2013) 19:5:530

Good Genomic Practice (GGP): Essential for the Effective Use of Genomic Technologies to Support Improved Clinical Decision-Making; Barker, R.W., Brindley, D.A.* & Schuh, A.
*Joint first author

Stem Cells and Development (2013) 22: 63-72

The Implementation of Novel Collaborative Structures for the Identification and Resolution of Barriers to Pluripotent Stem Cell Translation; Brindley, D.A., French, A., Suh, J., Roberts, M., Davies, B., Pinedo-Villanueva, R., Wartolowska, K., Rooke, K., Kramm, A., Judge, A., Morrey, M., Chandra, A., Hurley, H., Grover, L., Bingham, I., Siegel, B., Rattley, M.S., Buckler, R, McKeon, D., Krumholz, K., Hook, L., May, M., Rikabi, S., Pigott, R., Morys, M., Sabokbar, A., Titus, E., Laabi, Y., Lemaitre, G., Zahkia, R., Sipp, D., Horne, R., Bravery, C., Williams, D., Wall, I., Snyder, E.Y., Karp, J.M., Barker, R.W., Bure, K., Carr, A.J. and Reeve, B.

Bioprocess International (2013) 11:3: 18–25

Automation of Cell Therapy Biomanufacturing: Minimizing Regulatory Risks and Maximising Return on Investment; Brindley, D.A, Wall, I.B. & Bure, K.

Rejuvenation Research (2013) 16:2:164-70

Commercialization of Regenerative Medicine: Learning from Spin-Outs; French, A., Buckler, R.L. & Brindley, D.A.

Book Chapters

Cell Therapy Manufacturing: Identifying and Meeting Demand Springer Brindley, D.A., Smith, D., Davie, N.L. and Carmen, J. (2013) "Cell Therapy Manufacturing: Identifying and Meeting Demand" featured in "The Commercial Translation of Cell Based Therapies" Springer, edited by Vertes, A.

Cell Therapy Biomanufacturing Risk Management StemBook (August 2014 Edition) Rehki, R., Wall, I., French, A., Bure, K., Carr, A.J. and Brindley, D.A (2014) "Cell Therapy Translation" edited by Williams, D. and Scadden, D.

Accepted and Draft Publications

Stem Cells Translational Medicine (In Press)

Enabling Consistency in Pluripotent Stem Cell-Derived Products for R&D and Clinical Applications Through Material Standards; French, A., Bravery, C., Wall, I., Chandra, A., Archibald, P., Gold, J.D., Artzi, N., Kim, H-W., Barker, R.W., Meissner, A., Wu, J.C., Knowles, J.C., Williams, D., García-Cardeña, G., Sipp, D., Oh, S., Loring, J.F., Smith, J.A., Rao, M.S., Reeve, B., Carr, A.J., Bure, K., Stacey, G., Karp, J.M., Snyder, E.Y. & Brindley, D.A.

RAPS Global Regulatory Affairs (Submitted)

Borderline Regulation of Stem Cell Technologies: Therapies, Devices and Combinational Products; Smith, J., Carr, A.J. & Brindley, D.A.

Draft Patent

Note: At time of press, final patent application figures were being drafted by the appointed patent attorney. However, all figures are to be adapted from those presented herein.

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BRINDLEY, D.A., BELL, J.I. & CARR, A.J.

"A scorecard to assesses quality factors observed in risk:benefit appraisal methodologies as applied in the evaluation of healthcare innovations"

INVENTION SUBMISSION FORM

CONFIDENTIAL

The purpose of the Invention Submission Form is to provide guidance as to the information that is required in order to allow us to assess the patentability of your invention, and to provide a starting point for preparing a patent application relating to the invention. Please note that any kind of disclosure of the invention before a patent application has been filed may hinder the possibility to obtain a patent.

For guidance, patentable inventions include new and useful methods and/or devices, new uses of old materials, and new and useful improvements of any of these, provided that these are not a clearly obvious development of existing technology, or the advantages of which were not readily predictable. In particular, when solving a problem achieves a commercially useful result, the chances are good that an invention has been made. Software solutions may be patentable where they provide an advantageous effect.

If there is more than one solution to a technical problem then each should be written on a separate submission form or they should be clearly separated on one form.

1. TITLE OF THE INVENTION Please provide a title for invention. This should be informal but descriptive e.g. "High Speed Banking".
A scorecard to assess the quality of risk:benefit appraisal methodologies implemented in the evaluation of clinical data

2. YOUR REFERENCE FOR THE INVENTION If available, please provide a reference that should be used in relation to this invention.
NA

2. INVENTOR INFORMATION Please provide the names, addresses, nationalities, and identify the employer of all individuals who contributed to the invention. Please also provide an indication of the extent of the contribution that each individual made to the invention. NB: Can be provided later.
David A. Brindley (British) Andrew J. Carr (British) John I. Bell (Canadian – British Permanent Resident) Note: All named inventors are employees of the University of Oxford Address for Correspondence: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Botnar Research Centre The University of Oxford Nuffield Orthopaedic Centre Windmill Road, Oxford, OX3 7HE UK

3. APPLICANT INFORMATION Please confirm the circumstances under which this invention was made, i.e. as an employee tasked with solving a problem, as a consultant paid under contract, as a Director with a responsibility to the company or otherwise.
The invention was made during the course of employment by the University of Oxford (AJC and JIB). DAB was a student at the University of Oxford; however, was fully funded by the SENS Research Foundation (Mountain View, CA, USA).

4. ORIGIN OF THE INVENTION Please confirm that the invention relates directly to the work of each of the individuals identified in Section 2 and provide details of any products to which this invention is related and/or relevant.
The aforementioned work relates to the work of the individuals named in Section 2. To the inventors' best knowledge no directly competing products exist. However, the invention is relevant in the evaluation of the quality and effectiveness of risk:benefit appraisal methodologies applied in the evaluation of data generated by clinical studies – including but not exclusively – randomized controlled trials.

3. EXISTING TECHNOLOGY Please describe the pre-existing technology that is relevant to the background of this invention. NB reference to prior patents is acceptable and helpful.
1. Evaluation of medical therapy design assumptions based on trial outcomes WO 2013130234 A1 2. System and method for evaluating and comparing medical treatments US 8719051 B2 3. Evaluation of medical therapy design assumptions based on trial outcomes WO 2013130234 A1

4. PROBLEM(S) WITH THE EXISTING TECHNOLOGY Please describe any problem(s) associated with the pre-existing technology. There could be multiple problems.
Existing technologies to the best knowledge of the inventors do not systematically assess the risk:benefit profile of candidate therapeutic interventions in a manner which: • Reflects multi-stakeholder attitudes to quality factors of risk:benefit appraisal methodologies that are critical to data end users • Is reflective of and adheres to current guidance from international regulators – including EMA and FDA • Unable to establish a minimum acceptable quality threshold for examples of risk:benefit appraisal reported in randomised control clinical trials (RCTs)

5. PROBLEM SOLVED BY THE INVENTION Please describe the problem(s) associated with the pre-existing technology that are solved by the invention.
• Assessment and implementation of stakeholder specific quality factor weightings to increase the sensitivity and representativeness of risk:benefit appraisal assessment. • Applies a minimum acceptable quality threshold for examples of risk:benefit appraisal reported in randomised control clinical trials (RCTs)

6. DESCRIPTION OF SOLUTION TO PROBLEM Please describe how the invention solves the problems outlined in Section 5 in as much detail as possible. Please also attach any drawings, schematics, diagrams etc. that could be useful for understanding the invention. If there is more than one solution please separate them appropriately. Preferably, drawings should be in simple black and white line drawing format without shading. **Please do not discuss prior art in this section.**
An academically validated scorecard that assesses quality factors observed in risk:benefit appraisal methodologies as applied to the evaluation of healthcare innovations. All quality factors are weighted to accommodate the beliefs (risk, benefit and uncertainty) of key stakeholders. See attached overview.

7. ADVANTAGES OF INVENTION Please describe any particular advantages the invention has over existing solutions. In particular please provide some comments on the significance of the improvement such as: "it reduces power consumption by 10%" as this will help in supporting the invention when a patent application is filed.
Provides a robust and externally validated method to assess the quality and effectiveness of risk:benefit appraisal methodologies utilised in the evaluation of healthcare innovations. Presently, such a technology is not known to exist.

8. HAVE YOU DISCLOSED ANY DETAILS THE INVENTION TO 3RD PARTIES? Please provide the date, place and circumstances of any such disclosure, and details of the information disclosed.
SENS Research Foundation (Mountain View, CA, USA) Note: Two way CDA signed between DAB and SRF Mrs Kim Bure (Sartorius Stedim Biotech North America, Bohemia, NY, USA) Note: Two way CDA signed between DAB and KEB/SSB

9. DO YOU INTEND TO DISCLOSE ANY DETAILS THE INVENTION TO 3RD PARTIES? Please provide the date, place and circumstances in which you anticipate that you may wish to publicly disclose the invention.
Aim to publish details pertaining to scorecard in academic journals.

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Conferences

The work presented herein has been presented wholly and/or in part at the following meetings:

RAPS 2013 (Boston, MA, USA): Oral presentation.

RAPS 2014 (Austin, TX, USA): Oral presentation and session chair.

IBC Cell Therapy Bioprocessing 2014 (Arlington, VA, USA): Oral presentation.

IBC Cell, Gene and Immunotherapy Commercialisation (San Diego, CA, USA): Oral presentation and co-chair.

CASMI Translational Stem Cell Consortium 2013 (Paris, France): Oral presentation and co-chair.

CASMI Translational Stem Cell Consortium 2014 (Paris, France): Oral presentation and co-chair.

FIRM (Barcelona, Spain): Oral presentation (keynote)

Rejuvenation Biotechnology 2014 (San Jose, CA, USA): Oral presentation and session chair.

TERMIS 2014 (Daegu, South Korea): Oral presentation and session chair.

Singapore Stem Cell Society (Singapore, Singapore): Oral presentation (keynote)

Risk Management Congress (Arezzo, Italy): Oral presentation

Phacilitate 2015 (Washington D.C., USA): Oral presentation and session chair.

Peer-Reviewed Grant Funding

Note: Awards with D.A.B. as lead investigator unless otherwise stated.

Awarded

SENS Research Foundation Fellowship: ~ $100,000

CTSCC Series A: ~ $100,000

CTSCC Series B: ~ $250,000

CTSCC Summer Scholar Programme (2014): ~ $60,000

CTSCC Summer Scholar Programme (2015): ~ $100,000

Aegate UK Pilot: ~ £250,000

Application Pending

RCUK Digital Economy Bid (Co-PI): ~ £3,200,000

Abbreviations

ATMP: Advanced therapy medicinal product
ADR: Adverse drug reactions
ALS: Amyotrophic lateral sclerosis
BLA: Biologic licensing application
CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiological Health
CAR-T: Chimeric antigen receptor T-cell
CQA: Critical quality attributes
EMA: European Medicines Agency
EUTCD: EU Tissue and Cells Directive
ETOPS: Extended range twin engine operations
FMEA: Failure mode and effect analysis
FDA: Federal Drug Administration
GBM: Glioblastoma multiforme
GLP: Good laboratory practice
GCP: Good clinical practice
GGP: Good genomic practice
GMP: Good manufacturing practice
iPSC: Induced pluripotent stem cell
HCT/P: Human Cells, Tissues and Cellular and Tissue-Based Products
HC-SC: Health Canada
MAA: Marketing authorization application
MRC: Medical Research Council
MHRA: Medicines and Healthcare Products Regulatory Agency
MAQT: Minimum acceptable quality threshold
MBS: Mortgage backed securities
MND :Motor neurone disease
MCDA: Multi-criteria decision analysis
NCA: National competent authorities
IND: Investigational new drug applications
PIL: Patient information leaflets
PROMS: Patient reported outcome measures
PBSC: Peripheral blood stem cells
PHS: Public health service
QbD: Quality by design
RCT: Randomised control trials
RFD: Request for designation
rNPV: Risk adjusted net present value
RMS: Risk management strategy
SOC: Standards of care
TTP: Time to progression

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PART I

CURRENT RISK:BENEFIT APPRAISAL LANDSCAPE

Chapter 1

Introduction

1.1. Rationale for Work

The concept of personalised medicine – in all guises – is evocative and intellectually attractive. However, the process by which personalisation is achieved has two major dimensions, technology and systems, that have been unequally, and in some cases inadequately, addressed by existing appraisal efforts (Mt-Isa et al., 2014, Guo et al., 2010, Holden, 2003).

Technology personalisation can be as rudimentary as bespoke replacement joints for age related musculoskeletal disease (Carr et al., 2012) or as comprehensive as monoclonal antibody therapies with companion diagnostics (Gonzalez de Castro et al., 2013, Slamon et al., 2001). Systems personalisation, the efforts to tailor characteristics of the healthcare ecosystem, however is arguably more challenging given its multi-factorial nature, not least the need to effectively co-ordinate multiple stakeholders in healthcare innovation and delivery (Compton-Phillips, 2014).

Risk:benefit appraisal, including the assessment of associated uncertainties, presents the opportunity to better accommodate this inherent duality in personalised medicine as well as facilitate more effective engagement between patients and regulators and confer much needed transparency in biomedicine (Mussen, 2012).

To date, risk:benefit appraisal has been the focus of isolated academic endeavours; public consultations by regulators and patient advocates; and cursory prose in the conclusions of clinical trial reports (Krishna, 2009, Evans, 2011). These endeavours have garnered momentum gradually but have yet to achieve a transformative critical mass.

Therefore, the rationale for this research is best described as an original, substantive and personal effort to evaluate the quality and effectiveness of existing risk:benefit appraisal methodologies in randomised control trials (RCTs) and to establish a robust 'baseline' for future research, contributing to improvements in the system and technological components of biomedical innovation.

1.1.1. Personal Motivation

Fundamentally, the majority of funders – direct and indirect - and end patients in biomedicine are not scientists (Evans, 2011). It is to this 'silent majority' that the scientific community owes the most (Roses, 2008).

For example, a large proportion of the population have made long term contributions to biomedicine: directly, through diligent monthly charitable donations; and indirectly, through pension and retirement investments in global pharmaceutical companies (Ransom, 2006). Yet after a lifetime of giving, few could clearly articulate how their money has been spent and/or, in the case of on-going restricted access to experimental medicines for unmet medical needs, gain access to the innovative therapies for which their investments provided critical support throughout the lengthy development pathway (Brindley et al., 2013a, Fernandez et al., 2012).

Thus despite the inordinate debt the scientific community infinitely accrues to these stakeholders, it arguably fails to make sufficient strides to engage them effectively in the biomedical innovation and delivery process.

To offer a crude, but corporeal analogy, this body of research has been funded by a charitable organisation that is reliant upon public donations to support its researchers. Consequently, I am acutely cognisant of my responsibility as a researcher to clearly convey to a 'grass roots' donor the core principles and relevance of my research – and concurrently make a tractable contribution to the scientific community.

Congruously, the risk:benefit appraisal of healthcare innovations represents an opportunity to facilitate improved patient understanding of the biomedical translation process – including clinical trials - and thus provide a robust and systematic mechanism by which to catalyse and derive benefit from multi-stakeholder engagement (Brass et al., 2011).

In other words, risk:benefit methodology offers an opportunity to translate the *en vogue* nomenclature - patient engagement, personalised medicine, translational medicine - from prose into action.

1.1.2 Professional Motivation

Biomedical translation is a consistent source of excitement, challenge – and at times frustration – as it combines the potential for a substantial contribution to investor and patient outcomes, with an intellectual environment that encourages multi-disciplinary approaches. Moreover, the opportunity to significantly impact this endeavour has never been greater, as isolated technological advancements can now be paired with system-wide societal innovations.

Examples of these cooperative unions: the convergence of social media and pharmacovigilance (Edwards and Lindquist, 2011); the application of open innovation approaches in biomedicine (Edwards et al., 2009); the empowerment of patients at individual and population levels – including wearable medical devices (Schwartz and Collins, 2007, Brindley, 2015); and the changing role of patient advocacy groups (Beall, 2012). Biomedicine is becoming democratised – and it requires a common language to realise its potential.

Healthcare risk management, in particular the triumvirate of risk, benefit and uncertainty, is one potential agent by which to achieve this paradigm shift. The nascent field is also replete with intellectually challenging and societally impactful opportunities to sustain a academic research programme.

In many aspects of life, this triumvirate of risk, benefit and uncertainty initially appears tractable – easily defined with potential implications resolvable to a finite number of outcomes (Hayes et al., 2014). However, increasing personalisation of biomedicine is passively driving escalation in both technological and systems level heterogeneity (Hamburg and Collins, 2010, Meadows et al., 2014). Consequently, it is essential that the regulatory landscape(s) of tomorrow can effectively assimilate the aspirations for homogeneity in regulation with the necessity for heterogeneity in implementation (Fink, 2009).

For example, regenerative medicines – cell therapy, gene therapy, immunotherapy and tissue engineering – offer the portentous transition from chronic disease management to enduring cures yet in turn create a fundamental risk management challenge: how to decrease, as opposed to increase or redistribute, the total system risk in healthcare innovation and delivery (Bravery, 2010, Brindley et al., 2013b).

In the case of autologous cell based immunotherapies for metastatic castration-resistant prostate cancer (Provenge, Sipuleucel-T; Dendreon, Seattle, WA, USA), technological advancement and personalised therapy versus existing standards of care (SOC) were achieved – albeit marginally (Kantoff et al., 2010). However, the significant limiting factors in widespread clinical adoption, and therein achievement of lucrative investor and curative patient outcomes, sadly were system based impediments (Goldman and DeFrancesco, 2009).

Factor(s) Impacting Clinical Adoption and Commercial Success	Type of Risk	Reference(s)
Quality of Defined Mechanism of Action (MOA)	Technology	(Anassi and Ndefo, 2011)
Ease of Administration Route	Technology	(Graff and Chamberlain, 2015)
Prolongation of Time To Progression (TTP)	Technology	(Kantoff et al., 2010)
Improvement over Existing Standards of Care (SOC)	Technology	(Geynisman et al., 2014)
Proportionate Reimbursement	Systems	(Potts, 2013)
Cost-Effective Biomanufacturing	Systems	(Brindley, 2013)
Regulatory Uncertainty	Systems	(Mills, 2008)
Financial Market Liquidity [Proxy for availability of funding to support operations and market stability]	Systems	(Brindley, 2013, Booth, 2009)
Infrastructure Capacity [ie availability of apheresis and biomanufacturing raw materials]	Systems	(Chambers and Neumann, 2011)

Table 1.0: Exemplar System and Technology Risks Impacting Clinical Adoption and Commercial Success of Provenge (Sipuleucel-T)

Additionally, the recent utilisation of adaptive regulatory pathways to approval for regenerative medicines, such as CTL019, a chimeric antigen receptor T-Cell (CART) therapy for relapsed/refractory acute lymphoblastic leukaemia, from University of Pennsylvania (Philadelphia, PA, USA) and Novartis (Basel, Switzerland) (FDA; Breakthrough Status) (Maude et al., 2014, Frauenschuh, 2014), and DCVax-L, an activated dendritic cell vaccine for the treatment of glioblastoma multiforme (GBM), from Northwest Biotherapeutics (Bethesda, MD, USA) (EMA; Adaptive Licensing) (Ancans, 2012), redistribute risks, benefits and uncertainties throughout the translation pathway. Discriminate elucidation of the extent and direction – positive, negative or equivocal – of the risk:benefit

for regenerative medicines, at a systems and technology level, is vital in order to optimally support the field's prosperous development and realisation of patient outcomes.

Therefore, academic depth has been achieved in this research through a detailed investigation into prevailing risk:benefit appraisal methodologies in randomised control trials (RCTs), complemented by academic breadth – and thus maximisation of multi-stakeholder research impact – achieved through the evaluation of systems and technology risks, benefits and uncertainties in regenerative medicines.

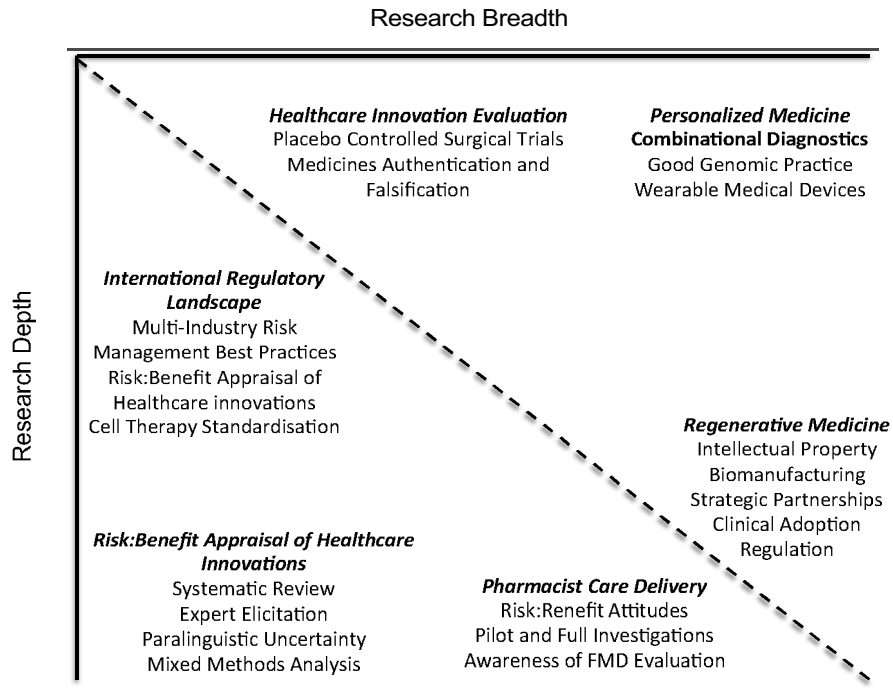


Figure 1.0: Overview of Investigation Research Depth and Breadth

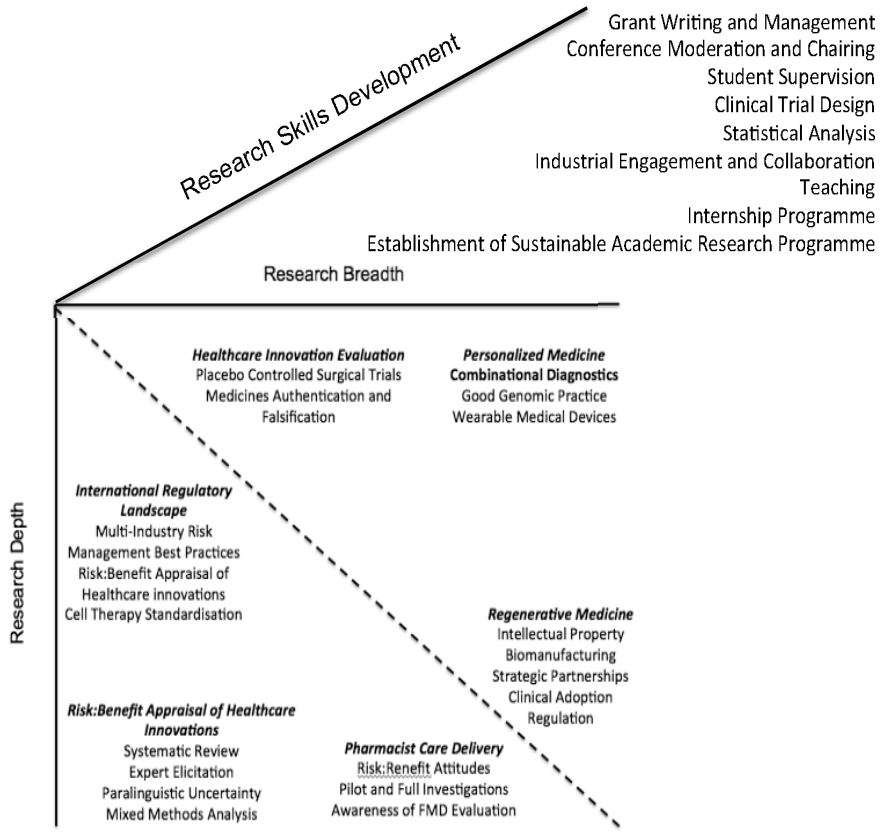


Figure 1.1: Research Skills Acquired and Implemented

1.2. Thesis Overview

Thesis Title: Optimising the Quality and Effectiveness of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Trials

Overall Question: Can we make risk:benefit assessment objective, transparent and broadly reflective of stakeholder requirements?

Chapter 1: Introduction

Chapter 2: Application of Risk:Benefit Appraisal

Chapter 3: Systematic Review of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Clinical Trials

Chapter 4: Expert Elicitation: Pilot Study

Research Question: Is there an inter-stakeholder disparity in the relative importance of quality factors in risk:benefit appraisal?

Hypothesis: Yes, to a significant extent.

Evidence: Multi-stakeholder expert elicitation study.

Chapter 5: Expert Elicitation: Full Study

Research Question: Is there an inter and intra-stakeholder disparity in the relative importance of quality factors in risk:benefit appraisal?

Hypothesis: Yes, to a significant extent.

Evidence: Multi-stakeholder expert elicitation study.

Chapter 6: Integration of Risk:Benefit Scorecard into Systematic Review

Research Question: Can the risk:benefit appraisal scorecard be used to effectively stratify reported risk:benefit appraisals?

Hypothesis: Yes, the scorecard can be effectively applied by multiple stakeholders.

Evidence: Re-ranking and meta-analysis of eligible systematic review records.

Chapter 7: Assessment of Pharmacists' Attitudes to Risk:Benefit Appraisal

Research Question: Do pharmacists believe they have an important role in the risk:benefit appraisal of healthcare innovations?

Hypothesis: Yes, in both the production of risk:benefit appraisal for specific healthcare innovations and conveying this to patients.

Evidence: Direct to pharmacist survey.

Chapter 8: Regenerative Medicine System Level Implications of Risk:Benefit Appraisal

Chapter 9: Healthcare Risk Management: Future Academic Research Strategy and Industrial Impact

Figure 1.2: Investigation Overview

Chapter 2

Application of Risk:Benefit Appraisal

2.1 Risk Management Principles and Applicability in Biomedicine

Risk management, on a spectrum of passive to active, is an unavoidable feature of daily life (Crouch A.C., 1982). Habitual activities such as selecting a mode of transport invoke passive risk analysis (Gardner, 2008), as familiarity with the resulting process(es) and significant evidence of past performance almost reduce any perceived uncertainty (Kahneman, 2012) in the expected risk:benefit ratio of the decision.

Conversely, novel and complex activities are perceived to have greater uncertainty in the expected outcomes and in the risk:benefit ratio of the decision (Adams, 2001). Therefore, rigorous, transparent and systematic risk management decision support tools are utilised and their provision is essential to the efficiency and sustainability of most industries [Table 2.0].

Exemplar Existing Risk:Benefit Methodology and/or System	Dominant Industry Application	Description	Analogy Risk:Benefit Analysis of RCTs
Risk Adjusted Net Present Value (rNPV)	Finance	Adjusts for the time value of money and idiosyncratic investment risk	Application to adjust for clinical trial attrition rates e.g. clinical trial arbitrage around value inflection points (Keegan, 2008, Fernandez et al., 2012)
Extended Range Twin Engine Operations (ETOPS)	Aviation	Based on historic failure rates for aircraft engines, twin engine	Utilising existing (Phase I) safety data to expedite the regulatory

		aircraft are able to fly a prescribed distance from the nearest emergency landing location. Therefore, able to more direct routes as per three/ four engine aircraft.	pathway for existing approved interventions being repurposed for a new indication (Berkowitz et al., 2012, Allison, 2012)
Energy and/or Commodity (Managed) Futures	Energy	Allow energy manufacturers and producers to hedge and/or short supplies based upon whether market is contangoed or backwarded.	RCT actuarial models 'clinical trial insurance' (Allison, 2012)
Failure Mode and Effect Analysis (FMEA)	Engineering	Part of Quality by Design (QbD) which evaluates the consequences of the failure of a component and thus prescribes the required rating (prescribed operational durability) of components – maximising safety and minimising cost.	Progressively and selectively reduce the need for frequent time-consuming release tests on low risk products e.g. established small molecules, reducing costs and barriers to entry. However, this may also lead to additional testing on high risk components e.g. platelets stored at ambient temperatures (Rotter et al., 2012, Sprenger et al., 2012)

Table 2.0: Risk:Benefit Methodologies Applied in Other Fields and Potential Applicability in Biomedicine

Highly quantitative operations, like those in finance, are strongly amenable to the application of risk management tools based on statistical techniques, due to the availability of data and well-characterised systems (Ancans, 2012). However, latterly, for complex decisions involving a range of stakeholders and types of risk, developments in risk management approaches have been informed from advances in social sciences; for example, around risk perception (Kahneman, 2012, Hammond JS, 1999).

Today, bespoke risk management platforms, including those based on multi-criteria decision analysis (MCDA) are utilised to inform product development strategies and decisions by international regulators (Mussen et al., 2009). Despite the breadth of available tools, and

growing lexicon of risk, biomedicine has been slow to adopt such technologies in the era of evidence based medicine – arguably to the detriment of all stakeholders, including patients (Russo and Balekdjian, 2008). This is perhaps best reflected in the 'mission statements' of international regulators, which with few exceptions, focus on protecting public health [from risk(s)] as opposed to supporting biomedical innovation [patient benefit(s)] [Figure 2.3].

2.2 Origins of Risk:Benefit Appraisal of Healthcare Innovations

If one is to accept the premise that the evaluation of risks, benefits and uncertainties is an inherent aim of a clinical trial, it follows that the origins of risk:benefit appraisal methodologies are closely intertwined with the history of clinical trials (Bhatt, 2010, Collier, 2009). A critical distinction, however, is that this investigation focuses solely on the formal application of risk:benefit appraisal methodologies in contemporary RCTs. As such it seeks to evaluate the extent to which regulatory and statistical innovations have supported a transition from implicit to explicit risk:benefit appraisal.

The first record of a pseudo-clinical trial is recorded in the Book of Daniel, whereby King Nebuchadnezzar, military leader of Babylon, prescribed a diet of meat and wine to his subjects (Collier, 2009). However, a few objectors negotiated to observe an alternative vegetable-based diet for a period of ten days and it was apparent that this group were in better health than those adhering to the King's diet. This demonstration of a detrimental effect to public health by an extremely rudimentary study, led the King to acknowledge the problem and lift the dietary restrictions.

Other early efforts to support objective clinical studies include Avicenna's eleventh century description of testing a "[therapeutic] in its natural state without any complications… [and] two cases of contrary types be studied and that the study be made of the time of action and the reproducibility of the effects (Cox, 1994)." Later, in the fifteenth century, surgeon Ambroise Pare trialled an experimental ointment applied to the wounds of soldiers concluding that the prospective therapeutic, ["a digestive made of yolks of eggs, oil of roses

and turpentine"], was inferior to the standard of care [basic alcohols] (Collier, 2009). However, it is widely accepted that the first major controlled clinical trial was undertaken by James Lind, a ship's surgeon, in the eighteenth century (Chalmers et al., 2008).

Lind observed the high mortality rate arising from scurvy amongst sailors in his care, and aware of recommendations pertaining to the antiscorbutic effects of citrus fruits postulated by John Woodhall (Waife, 1953), conducted a systematic clinical investigation. With all participants given a controlled diet, the experiment yielded clear improvements in the active arm [citrus fruit] versus the control arms [vitrol, vinegar and sea water]. However, despite this elegant and conclusive evaluation of technology level risks and benefits, Lind was unable to persuade the British Navy immediately to adopt his dietary regime, principally due to the resultant system risk from the elevated cost of citrus fruit in the 18th century. Later in the early 19th century, Lind's recommendations were implemented utilising the cheaper alternative of lime juice (Chalmers et al., 2008).

Thereafter, clinical trial structures and principles that are familiar to investigators and clinicians today emerged iteratively – including formal risk:benefit analysis. Major steps in this development are the evaluation of placebo [Austin Flint, 1886] (Shapiro, 1959, Crofton, 2006); the first double blind controlled trial [Medical Research Council (MRC) *P.patulinum* for common cold] (Crofton, 2006, Chalmers, 2011); the first randomised trial [MRC streptomycin in pulmonary tuberculosis] (Crofton, 2006); and most recently, the first approval of a therapeutic and combinational diagnostic [Herceptin (trastuzumab; Roche, Basel, Switzerland) (Slamon et al., 2001), a monoclonal antibody against the (breast) cancer molecular marker, HER2, and OncotypeDX (Genomic Health, Redwood City, CA, USA) 1998].

Table 1. Case studies of stratified medicines and clinical diagnostics

Drug, diagnostic	*US approval*		*EU approval*	
	Drug	*Diagnostic*	*Drug*	*Diagnostic*
Herceptin (Roche, Basel, Switzerland), *Hercep Test* (Dako, Glostrup, Denmark)	Sep 1998	Sep 1998	Aug 2000	1999
Ziagen (ViiV Healthcare, Brentford, UK), *Genotyping for the leukocyte antigen (HLA) b allele (HLA-B*5701)*	Dec 1998	LDTs available at the time of label changes	July 1999	LDTs available at the time of label changes
Vectibix (Amgen, CA, USA), *therascreen: KRAS RGQ PCR Kit* (Qiagen, Venlo, The Netherlands)	Sep 2006	July 2012	Dec 2007	November 2007 (CE mark)
Selzentry (ViiV Healthcare), *Trofile assay*	Aug 2007	Developed as LDT during drug development, remains a LDT	Sep 2007	CE marked before EMA approval
Zelboraf (Roche), *BRAF V600E* (Roche)	Aug 2011	Aug 2011	Feb 2012	CE marked before EMA approval
Xalkori (Pfizer, NY, USA), *Vysis ALK Break-Apart FISH Probe Kit* (Abbott, IL, USA)	Aug 2011	Aug 2011	Jul 2012	Aug 2011
Kalydeco (Vertex Pharmaceuticals, MA, USA) *FDA-cleared cystic fibrosis diagnostic for presence of G551D mutation*	Jan 2012	Available unbranded test used during clinical development	May 2012	Available unbranded tests to be used
Breast cancer drugs, *Oncotype Dx* (Genomic Health, Redwood City, CA, USA)	Approved drugs	Classified as LDT in the USA	Approved drugs	2007

Abbreviations: CE, product compliance with EU legislation; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; LDT, laboratory-developed test; PMA, premarketing approval.

Table 2.1: Case Studies of Stratified Medicines and Clinical Diagnostics (Meadows et al., 2014)

Box 1 Case study 1

Zelboraf (vemurafenib)

The efficacy of Zelboraf in metastatic melanoma was demonstrated in clinical trials in which patients whose tumours carried V600 mutations were selected using the cobas 4800 BRAF V600 mutation test.

Zelboraf showed antitumour effects in cellular and animal models of melanomas with BRAF V600E mutations and was thus selected for development using a stratified approach from the outset. This meant that for both therapeutic and diagnostic the development programmes and regulatory filings were done simultaneously and in parallel.

Lessons learned:

1. Early and integrated collaboration between the pharmaceutical and diagnostic developers helped maintain alignment across rapidly evolving and accelerated timelines for clinical trial and regulatory filings. In this case, Roche developed both the medicine and the diagnostic, highlighting the advantages of integrating therapeutic and diagnostic development capabilities.
2. Despite the integrated collaboration, the timelines proved challenging, and Roche Molecular Systems was a reluctant participant until the original Plexxikon (previously Berkeley, CA, USA; acquired by Daiichi Sankyo, Tokyo, Japan) investigator compound was acquired by Roche Pharma.[42]
3. Constructive and collaborative dialogue with the FDA on both the pharmaceutical and diagnostic sides (Center for Drug Evaluation and Research and Office of In Vitro Diagnostic Device Evaluation and Safety) laid the foundation for future companion diagnostic approvals.
4. Simultaneous approval of Zelboraf and the cobas BRAF test enabled collaboration at all levels across the commercial organisations during the launch phase.
5. Setting up testing infrastructure before launch reduced barriers to test adoption by hospital and pathology laboratories.

Box 2 Case study 2

Vectibix (panitumumab)

Vectibix is an example of a drug developed against a known biomarker (epidermal growth factor receptor (EGFR)), and later had its use restricted with the knowledge of another biomarker (KRAS) that identified nonresponders. In the case of EGFR detection, the Dako EGFR pharmDx kit was developed before marketing authorisation, and the use of the diagnostic was specified on the original US label. The KRAS biomarker was revealed after marketing, prompting the development of the therascreen: K-RAS RGQ PCR Kit (K-RAS Kit) *in vitro* diagnostic test intended for the qualitative detection of seven somatic mutations in codons 12 and 13 of the K-RAS oncogene. Amgen partnered with DxS (and then Qiagen) to ensure that a KRAS test kit was available in the EU at the end of 2007 and to file a premarketing approval in the United States.

Vectibix was given an accelerated approval by the FDA based on assessment of all-comers (intention-to-treat population), and a conditional approval by the European Commission based on the assessment of a KRAS wild-type subset, as its benefits outweighed associated risks and it satisfied the criteria of 'meeting unmet medical need'. Vectibix's development represents a rapid response to retrospective analysis to ensure prompt availability of a companion diagnostic.

Lessons learned:

1. Rigorous KRAS hypothesis testing was needed to demonstrate the feasibility of stratification.
2. Commitment to continue with postmarketing clinical trials to further validate the improved risk/benefit profile following testing for KRAS and the availability of KRAS data enabled a negative opinion to become a positive opinion for Vectibix in the EU.
3. The partnership with DxS (and then Qiagen) ensured availability of a CE-marked KRAS test in Europe.
4. The case represents an example where stratification leads to a restricted target population with increased benefit/risk profile without an increase in price.
5. KRAS confirming LDTs, which do not require regulatory approval, are readily available and compete for market share with Qiagen's therascreen kit.[38]

Figure 2.0: Case Studies of Zelboraf (vemurafenib) and Vectibix (panitumumab)

Box 3 Case study 3

Oncotype Dx

Oncotype Dx was developed by conducting prospective and retrospective studies on tissue archives and took 5 years to develop. As the test calculates the Recurrence Score based on an algorithm combining the expression of 21 genes, the test is conducted in the company's own facilities via the Clinical Laboratory Improvement Amendment (CLIA) regimen in the United States. Although this means that the test has so far avoided having to submit to an FDA premarketing approval review and does not require European approval, it does cost ~3000 USD per test. This means that the test has significant reimbursement hurdles despite the anticipated cost savings. These hurdles have been most difficult in Europe where payers and health technology assessment bodies either lack, or are only now building, the capacity to assess molecular diagnostics for cost effectiveness. In September 2013, the UK cost-effectiveness body the National Institute for Health and Care Excellence (NICE) recommended Oncotype Dx as an option to help doctors decide whether to offer chemotherapy to a subset of patients with early breast cancer.

Lessons learned:

1. Genomic Health identified an area of potential cost savings incurred on unnecessary chemotherapy and converted it into a business model that saved more resources than those spent on Oncotype Dx development.
2. Genomic Health has become one of the first stand-alone diagnostic companies to achieve value-based pricing supported by strong pharmacoeconomic data.
3. A strong network of research consortia enabled well-timed availability of tissue sample archives.
4. Claims-backed analytical and clinical validation supported a suite of publications.

Figure 2.1: Case Study of Oncotype Dx

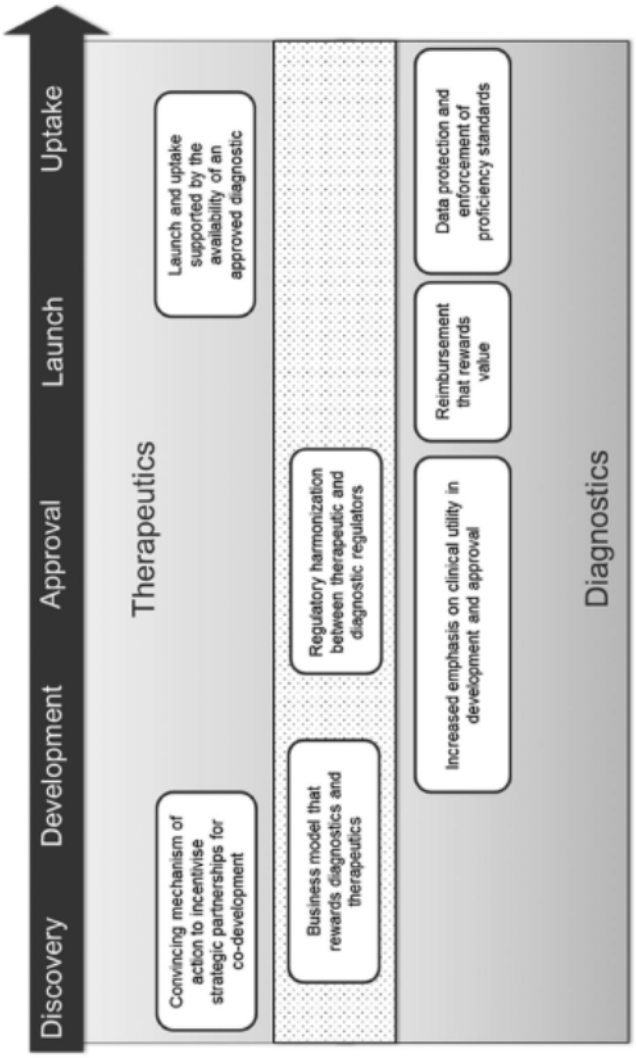


Figure 2.2: Overview of Development
Figure 2.2: Overview of Development Pathway for Combinational Diagnostics

2.3 Risk:Benefit Regulatory Landscape

A corollary of the assertion that a well-structured clinical trial intrinsically assesses the risks, benefits and uncertainties of the healthcare innovations under investigation [Section 2.2] is that the bodies governing and evaluating clinical trials, National Competent Authorities (NCAs – including FDA and MHRA), are responsible for the objective and explicit evaluation of risk:benefit. However, a potential inherent assessment bias is suggested by international NCA mission statements [Figure 2.3], which focus foremost on public safety (risks), and

secondarily – and in large part omit – the evaluation and support of healthcare innovation (benefits).

NCA	Country	Mission Statement
Food and Drug Administration (FDA)	USA	The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors. Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.
Medicines and Healthcare Products Regulatory Agency (MHRA)	UK	The MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe.
Health Canada (HC-SC)	Canada	Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada 's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

Figure 2.3: National Competent Authority (NCA) Mission Statements

The international regulatory landscape for the risk:benefit appraisal of healthcare innovations is fundamentally heterogeneous. From a technology perspective, there are significant differences in regulatory pathways for alternative therapeutic platforms (Sharfstein, 2015). Consider for example the divergence between conventional small molecules as compared to 'first generation' biologics and 'second generation' biologics (cell, gene and immunotherapies) and between medical devices implemented as diagnostics versus

therapeutics. Analogously, from a systems perspective, the scope of regulation is typically defined relative to the translation cycle for biomedical innovations: pre-clinical, clinical and post-market surveillance and/or pharmacovigilance [Figure 2.3] To complicate matters further, there is often a conflation of regulation, statutes and standards, as seen in the ICH guidelines (Glass, 2001).

Consequently, the regulatory landscape for risk:benefit appraisal is implicitly siloed and diverse, and is thus challenging to easily present in a crisp overview fashion across all therapeutic options. Therefore, overviews of the risk:benefit regulatory landscape are herein presented for two specific types of technology: combinational diagnostics [Section 2.3.1.] and combinational regenerative medicines [Section 2.3.2.].

Year	Month	Regulator	Description of Action Related to Risk: Benefit Analysis	Reference
2007	January	EMA	Publication of reflection paper by the Committee for Medicinal Products for Human Use (CHMP) concerning benefit: risk methods in the context of marketing authorisation applications - for public comment(s)	
2008	March	EMA	Publication of reflection paper by the Committee for Medicinal Products for Human Use (CHMP) concerning benefit: risk methods in the context of marketing authorisation applications - adopted by EMA.	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf
2009	February	FDA	Pilot programme to develop a conceptual benefit: risk framework for NDAs and BLAs commenced	
2010	March	EMA	Completion of work package describing existing benefit: risk assessment models being used in the EU	http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109478.pdf
	August	EMA	Completion of suitability assessment of tools and processes used in benefit-risk assessments	http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097750.pdf
2011	June	EMA	Completion of field testing of most approprate benefit-risk models	http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112088.pdf
2012	February	EMA	Completion of refinements of most suitable models to create new risk: benefit tool	
	March	EMA	European Assesors commence training to use benefit: risk tools	
		FDA	Release of guidance: "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Pre-Market Approval and De Novo Classifications"	http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf
	July	FDA	PDUFA V passed and includes includes benefit: risk assessment provisions	http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm
	December	FDA	Publication of five year plan describing implementation approach for NDA/ BLA benefit: risk framework	http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf
2013	September	FDA	Execution of five year benefit-risk framework plan commences	
	October	FDA	Commencement of public workshops entitled "benefit-risk from the regulator's perspective"	

Figure 2.4: Key FDA and EMA Publications and Publically Disclosed Risk:Benefit Assessment Activities

2.3.1 EU and US Regulatory Landscape for Combinational Diagnostics

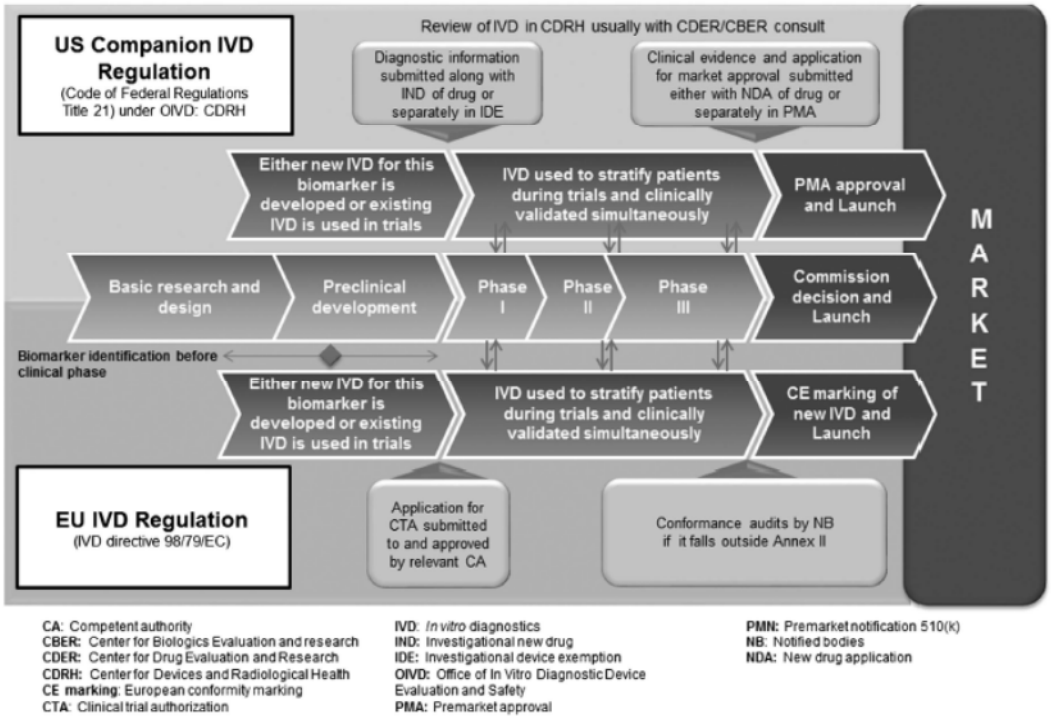


Figure 2.5: Comparison of EU and US Regulatory Pathways for Combinational Diagnostics

The risk management of combinational diagnostics is challenging due to the leveraged nature of risks, benefits and uncertainties in their use. In addition to the inherent risks associated with the deployment of any novel medical technologies in a patient population, additional risks and uncertainties are derived from the sequential and/or concurrent application of patient diagnostics, therapeutics and/or devices. Furthermore, the regulatory pathway for combinational products does not necessarily follow the linear product development process or the singular regulatory path for a therapeutic, device or transplant.

With the exception of regulation pertaining to the use of animal models in research, pre-clinical studies are typically subject to minimal regulation; in particular those which are bounded by hospital and/or ‘art of medicine’ exemptions (Ancans, 2012). However, while this stipulation may be sufficient for the therapeutic component of any combinational therapy, it is not always uniformly true for diagnostic components (Fratkin et al., 2012).

As outlined by the case studies in Section 2.2, the regulation of combinational diagnostics can occur prior to, in parallel with and/or retrospectively to that of any of the therapeutic

components (Meadows et al., 2014). Subsequently, the baseline risks, benefits and uncertainties for all permutations differ, directly driven by the extent and type of existing data pertaining to the treatment components and potentially by reporting and perception biases by regulators and trial sponsors, who may have the 'benefit' or 'hindrance' of existing data [Figure 2.4]. Therein, if a range of serious adverse drug reactions (ADRs) have been previously reported for a therapeutic, regulators may assess a newly proposed therapeutic including a combinational diagnostic in an unduly harsh manner due to this prior information (Madu and Lu, 2010).

Importantly when the ADRs had occurred in patients outside the treatment population identified by a combinational diagnostic, its implementation would now exclude access to the therapeutic agent by virtue of its use. A contemporary example of a significant decrease in the size of a potential patient population with a correlated increase in treatment specificity is Kalydeco (Ivacaftor, Vertex Pharmaceuticals, Cambridge, MA, USA). In addition, its development pathway – a novel partnership between a disease foundation [Cystic Fibrosis Foundation] and industry – mitigated the systems risk associated with its development and adoption (Ledford, 2012, Higgins, 2012).

Therefore, it is challenging to confer homogeneity to the risk:benefit appraisal of secondary regulatory guidance and requirements, while significant heterogeneity persists for novel technological combinations in primary regulation. Thus academic investigators developing novel technological platforms must remain cognisant that risk:benefit is a vector function – possessing both magnitude and direction – which offers both opportunity and obstacle in conferring rigour and rationality to the regulation of their innovations. Inevitably, this trend has and will continue to facilitate increased engagement of academic investigators in regulatory thought leadership, decision-making and implementation – requiring greater research breadth and fundamental changes in academic careers for continued progress.

2.3.2 EU and US Regulatory Landscape for Combinational Regenerative Medicines

Regenerative medicines, defined herein broadly as any combination of cell based cell therapy, gene therapy, immunotherapy and/or tissue engineering approaches, present a number of unique risk:benefit appraisal challenges, in particular at the interface of technological risk(s) [novel therapeutic modalities often with limited clinical data] and systems risk(s) [significant overlap of multiple regulatory pathways – therapeutic(s), device(s) and/or transplant(s)] (Fink, 2009). As such, regenerative medicines are of immense academic interest and potentially lucrative commercial impact in any investigation into risk:benefit appraisal. In particular, as the majority of product candidates available to clinicians remain pre-licensure within clinical trials, there are significant opportunities to employ innovative strategies in adaptive and/or expedited approval processes (Oye et al., 2013, Eichler et al., 2012).

TABLE 1. SUMMARY OF SELECT REVENUE-GENERATING CELL THERAPY AND REGENERATIVE MEDICINE PRODUCTS IN 2012, A MARKET PROJECTED TO BE GENERATING $900 MILLION[a]

Company	*Lead product(s)*	*Indication*	*Market launch*	*Allogeneic/ autologous*	*Estimated revenue (million $/year)*	*Current markets*
Advanced Biohealing, a Shire company (Dublin, Ireland)	Dermagraft	Diabetic foot ulcers	2001	Allo	>100	US, Canada
Dendreon (Seattle, WA)	Provenge	Prostate cancer	2010	Auto	>100	US
Organogenesis (Canton, MA)	Apligraf	Venous leg ulcers/ diabetic foot ulcers	1998/2000	Allo	>100	US, Saudi Arabia
NuVasive (San Diego, CA)	Osteocel Plus	Skeletal defects	2005	Allo	>50	US
Orthofix (Curaçao, Netherlands Antilles)	Trinity Evolution	Musculoskeletal defects	2009	Allo	>50	US
Genzyme, a Sanofi Company (Boston, MA)	Carticel	Articular cartilage repair	2007	Auto	>10	US, EU
Anterogen (Seoul, South Korea)	Cupistem	Crohn disease	2012	Auto	<10	S. Korea
Avita Medical (Perth, Australia)	ReCell	Burns, scars	2007	Auto	<10	EU,UK, Australia, Canada
FCB Pharmicell (Seoul, South Korea)	Heartcelligram	Acute myocardial infarction	2011	Auto	<10	S. Korea
Genzyme, a Sanofi company (Boston, MA)	Epicel	Severe burns	2007	Allo	<10	US, EU
Japan Tissue Engineering (Gamagori, Japan)	J-TEC Epidermis / Cartilage/ Corneal Epithelium	Burns, cartilage repair, ocular repair	2012	Auto	<10	Japan
Medipost (Seoul, South Korea)	Caristem	Articular cartilage repair	2012	Allo	<10	S. Korea
TiGenix (Leuven, Belgium)	ChondroCelect	Articular cartilage repair	2009	Auto	<10	EU

[a]Overall there were 36 commercial cell products in 2012 (including 15 from the US, 14 from Europe, 3 from South Korea, and 3 from Japan). All of the market leaders are for use in skin, bone, or cartilage repair, excluding Provenge which is, approved for the treatment of late-stage prostate cancer.

Figure 2.6.: Regenerative Medicines with Marketing Authorisation Granted by NCAs Worldwide (French et al., 2013)

In general cell-based products are considered to be medicinal/biologics products or devices, and thus are subject to up to three regulatory legislation regimes: public health, pharmaceutical and medical device regulations (Hoppe and Denoon, 2011). However in certain cases only public health legislation will be applicable. Historically, the failure of product developers to adequately represent their technologies for regulatory evaluation and/or the failure of regulators to consistently implement and enforce the body of national regulations, contributed to various early regenerative medicines being given different designations – device versus therapeutic – in multiple jurisdictions. Apligraf (Organogenesis, Canton, MA, USA), for example, was designated as a medical device in the US and a therapeutic in the EU– with far-reaching implications for reimbursement and patient access (Bravery, 2010).

The following examples of US and EU regulatory codes – adapted from (Smith et al, In Press) illustrate the differences in opinions on product classifications and regulatory routes that are perpetuated worldwide. In the EU and US, there is substantial overlap in the criteria for whether or not cellular products will be regulated as medicinal products, though clear differences for regulation as a device. If a product meets the latter criteria, it is regulated only under public health legislation, which is a significant distinction as no pre-market approval is required.

Relevant US Regulation:

- Public Health Service Act 42 USC 264, Section 361
- Public Health Service Act 42 USC 262, Section 351
- 21 CFR 1271 Human Cells, Tissues and Cellular and Tissue-Based Products
- 66 FR 5447 Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing
- 21 CFR 3 Product Jurisdiction
- 21 CFR 312 Investigational New Drug Application

- 21 CFR 812 Investigational Device Exemptions
- Draft Guidance for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells (PBSCs), July 2007
- 21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

Relevant EU Regulation:

- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
- Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
- Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), 2010/C82/01
- Reflection paper on classification of advanced therapy medicinal products, December 2012
- Draft: Reflection paper on classification of advanced therapy medicinal products, June 2014
- Manufacture of biological active substances and medicinal products for human use, Annex 2 to Volume 4 of EU guidelines for good manufacturing practice for medicinal products for human and veterinary use

In the EU, such products are regulated by the EU Tissue and Cells Directive (EUTCD) and Directive 2004/23/EC. In the US, they must conform to Good Tissue Practices and are regulated under Section 361 of the Public Health Service (PHS) Act (42 USC 264), referred to as '361 Products'.

Classification Criteria:

1. It is minimally manipulated (US) or not substantially manipulated (EU). (Table 2)
2. It is intended for homologous use, meaning that the cells are used for essentially the same function in the donor and host.
3. It is not combined with another product/article.
    i. EU: a medical device or an active implantable medical device under Regulation (EC) No 1394/2007 (the ATMP regulation)
    ii. US: as determined in 21 CFR 1271.10: "The manufacture of the [Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/P)] does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and"
4. US only: "Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a. is for autologous use;
        b. is for allogeneic use in a first-degree or second-degree blood relative; or
        c. is for reproductive use."

US	EU
(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) for cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3) Specific manipulations considered to be minimal (66 FR 5447 at 5457): • cutting • grinding • shaping • centrifugation • soaking in antibiotic solution • sterilization by ethylene oxide treatment or irradiation • cell separation • density gradient separation • lyophilization • freezing • cryopreservation • selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets	The cells or tissues have not been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved (Regulation (EC) No 1394/2007). Specific manipulations not considered substantial according to Annex I of the same regulation: • cutting • grinding • shaping • centrifugation • soaking in antibiotic or antimicrobial solutions • sterilization • irradiation • cell separation, concentration or purification • filtering • lyophilization • freezing • cryopreservation • vitrification

Table 2.2: Definitions of manipulations considered minimal (US) or not substantial (EU) (adapted from Smith et al, In Press)

In the US, if one of the above criteria is not met, the product is regulated under Section 351 of the PHS Act (42 USC 262) as either a biologic, drug or device, and therefore requires FDA approval. Products regulated under Section 351 are designated as '351 products.'

In the EU, if one of the above criteria is not met, the product is regulated as an advanced therapy medicinal product (ATMP) under The ATMP regulation and Directive 2001/83/EC. Importantly, Directive 93/42/EEC concerning medical devices, explicitly does not apply to "transplants or tissues or cells of human origin nor to products incorporating or derived from tissues or cells of human origin," with the exception of devices incorporating medicinal products derived from human blood or plasma that do not include blood cells (as noted in

Article 3 of Directive 2001/83/EC). As such, in the EU, an ATMP-device combination cannot be regulated primarily as a device, regardless of whether it can otherwise be argued to satisfy the definition.

For both ATMPs and 351 products, pre-market approval is required, with demonstration of safety and efficacy as essential requirements.

Product Type	**US Regulations**	**EU Regulations**
Public Health Legislation for Cell Containing Products	(1) Good Tissue Practices (2) Section 361 PHS act (42 USC 264)	(1) EU Tissue and Cell Directive (EUTCD) (2) Directive 2004/23/EC
Combinational Cell-Device Products	(1) Section 351 PHS Act (42 USC 262) (2) 21 CFR 1271 (3) The primary mode of action dictates the regulatory route: *Biologics:* regulated primarily by Center for Biologics Evaluation and Research (CBER) and 21 CFR 312 applies OR *Devices:* regulated primarily by the Center for Devices and Radiological Health (CDRH) and 21 CFR 812 applies Note: though one center is designated as the lead center, the other still has some involvement in regulation	(1) Directive 2001/83/EC (2) Regulation (EC) No 1394/2007 (the ATMP regulation) Note: Directive 93/42/EEC, the medical device directive, explicitly does not apply to ATMPs
Point of Care Autologous Therapies and Devices	(1) 21 CFR 1271 does not apply if cell processing occurs within the same surgical procedure (2) Information on what constitutes the same surgical procedure can be found in “Draft Guidance	(1) Same regulations apply as to cellular or device products that are not ‘point of care’

	for Industry: Cell Selection Devices for Point of Care Production of Minimally Manipulated Autologous Peripheral Blood Stem Cells”	
Borderline Classifications	(1) 21 CFR 3 describes submission of a Request for Designation (RFD) (2) “Number of Marketing Applications for a Combination Product’, an FDA paper for comment has information	(1) Regulation (EC) No 1394/2007 (the ATMP regulation) gives recommendations
Additional Comments	N/A	(1) Member states can impose additional requirements and are responsible for clinical trial authorization, rather than the central EMA

Table 2.3: Regulatory routes/documentation applicable to stem cell and/or device products

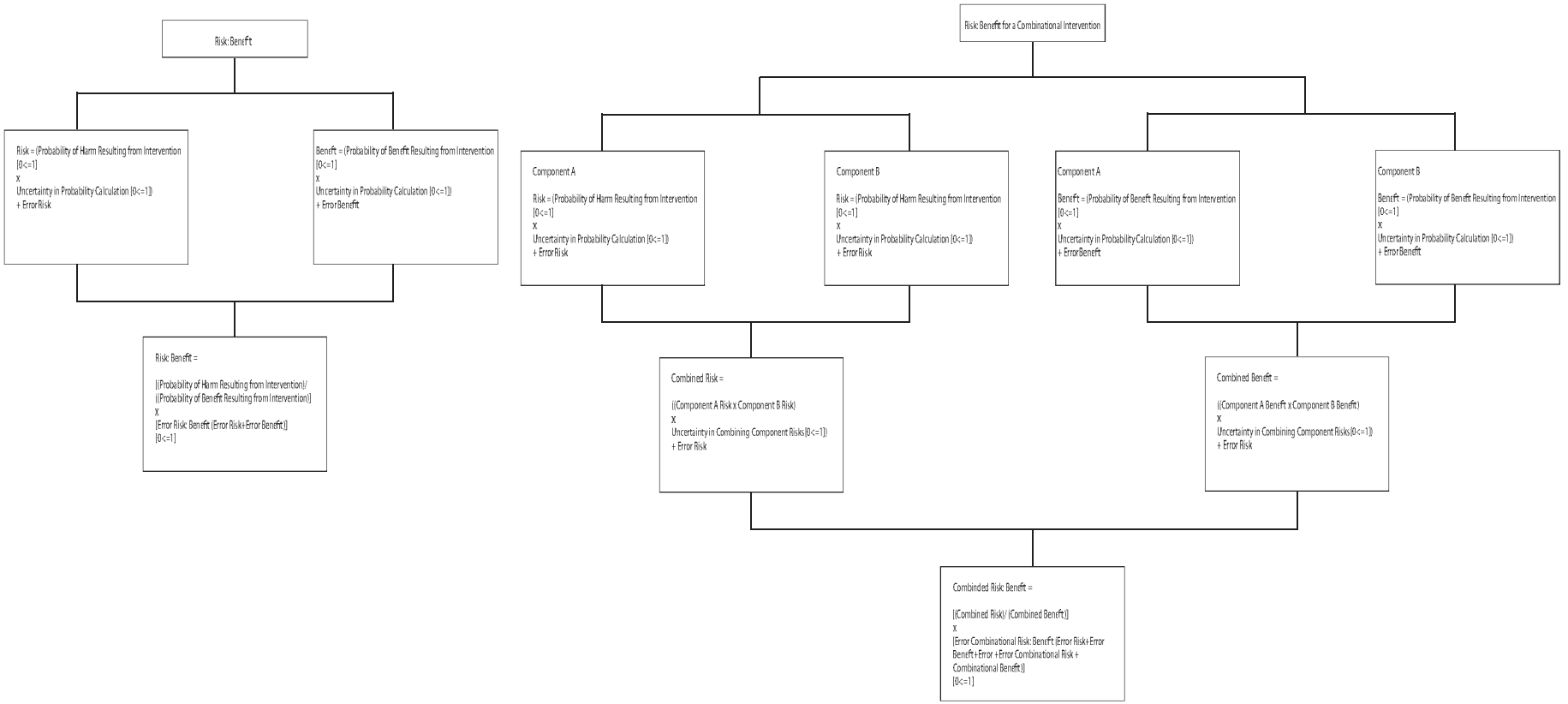


Figure 2.7: Comparison of Relative Complexity of Risk:Benefit Assessments for 'Conventional' (Single Component) Versus 'Combinational' (Multi-Component) Technologies

2.4 Contemporary Risk:Benefit Appraisal Methodologies

Regulatory agencies and clinicians have always conducted informal risk:benefit analysis when evaluating potential treatment outcomes for individuals and populations. However, the provision of formal, systematic and rigorous risk:benefit analysis tools is more recent, driven by the emerging need to effectively regulate higher complexity products in increasingly complex biomedical ecosystems [Figures 2.4 and 2.7] and the growth of risk management advances in other industries (Ashby D, 2000).

Factor Impacting Biomedical Ecosystems	Potential Application of Risk:Benefit Analysis
Adaptive Licensing	The need to rigorously assess the change in risk:benefit profile of interventions throughout the regulatory pathway in order to inform progressive changes in accessibility to patients (Eichler et al., 2012, Oye et al., 2013, Barker, 2010).
Increased Product Complexity [Figure 2.7]	Multi-component products, including therapeutics with companion diagnostics and cells based therapies plus scaffolds, present a need to effectively evaluate all components without contributing to an unduly complex regulatory pathway (Bravery, 2010, Barker et al., 2013, Fink, 2009, Miller, 2012, Place et al., 2009, Sterne et al., 2009).
Increased Stakeholder Involvement	Requirement to objectively evaluate a range of stakeholder viewpoints, provided in a range of formats, in order to inform regulatory decisions. For example, the contribution of patient advocacy groups to 'high-risk' interventions, including Glybera (Alipogene tiparvovec, uniQure, Amsterdam, Netherlands) (Miller, 2012, De Marco, 2013). Additionally, from an investment perspective, industry and venture capital community engagement with academia earlier in the development pathway necessitates anticipatory formal assessments of multiple types of risks and benefits, including clinical and financial (Booth, 2007, Booth, 2009, Booth and Salehizadeh, 2011).
Generic Products	Evaluating the appropriateness of expedited regulatory pathways for generic products, including biosimilars (De Marco, 2013).
Product Repurposing	Evaluating the appropriateness of expedited regulatory pathways for the use of licensed products for new indications (Paul and Lewis-Hall, 2013).

Table 2.4: Key Developments in Systems Medicine and Implications for Regulators

The recent growth in risk:benefit analysis and its research and implementation in the evaluation of biomedical innovations are a function of both non-biomedical and biomedical sector specific factors (Booth and Salehizadeh, 2011). However, the origins of both growth drivers are that all innovation(s) generates greater understanding and in doing so, provides a catalyst for novel developments, each with their own previously unseen risks (Crouch A.C., 1982). Therefore, the total level of system risk – and its associated uncertainty – is not a zero sum game.

In non-biomedical sectors, this relationship between the core innovation and the simultaneous increases in both the understanding of existing challenges and the uncertainty regarding the new environment it fosters, is extensively studied. For example, mortgage backed securities (MBSs) were a financial innovation designed to assist individual institutions in better managing global credit risks. However, the products' behaviour was poorly characterised, and therein a source of uncertainty, in the debt tolerant environment that resulted and was sustained. Subsequently, the roots of the recent financial crisis arise from unexpected correlations between idiosyncratic risks for individual securities and interdependent (and in many cases disastrous) factors for similar products. Consequently, the broad growth and heightened demand for risk management tools has understandably extended into healthcare, both to ensure 'safer' bets on technology and preserve the limited capital available.

2.5 Regulatory Stimuli for Growth of Risk:Benefit Appraisal

There is a wide consensus that the development pathway for biomedical innovations is excessively risky, in part due to perceived risk aversion by international regulators. Historically, 'the named patient exemption' has been used to circumvent burdensome regulation and enable patient access to novel interventions (Sietsema, 2012). This approach, however, is not broadly practicable and has been criticised from an ethical viewpoint, in part for incentivising potentially dangerous medical tourism. In response, combined pressure

from industry and patient advocacy groups has stimulated investigative research into regulatory innovations, including risk:benefit analysis, by international regulators.

The European Medicines Agency (EMA) has supported research into two main risk:benefit analysis frameworks: PrOACT-URL and BRAT [Figure 2.8]. Both have been produced and evaluated in collaboration with industry and academia and focus on licensed products (Levitan et al., 2011, Walker et al., 2009). Conversely, the US Federal Drug Administration (FDA) has focused on implementing risk:benefit analysis for pre-market products (Sietsema, 2012). That said, to date there has been limited interest and/or demand from international regulators concerning the implementation of quantitative risk:benefit assessment models. This is likely to be in part due to an unsatisfactory lack of a requirements-based approach that utilises systematic, multi-stakeholder analysis to identify essential model features (Guo et al., 2010, Boada et al., 2008).

BRAT Framework

1. Define decision context
2. Identify outcomes
3. Identify data sources
4. Customise framework
5. Assess outcome importance
6. Display and interpret key benefit: risk metrics

PrOACT-URL Framework

1. Problem
2. Objective
3. Alternatives
4. Consequences
5. Trade-off
6. Uncertainty
7. Risk-tolerance
8. Linked decision

Figure 2.8: Major Existing Risk:Benefit Frameworks Developed and/or Supported By International Regulatory Agencies

Thus existing efforts focus on framework style assessment tools that are not overtly systematic and base their appraisals mostly on qualitative methodologies. Additionally, the

exemplar frameworks described do not easily include multivariant features to accommodate specific product types for given indications [Figure 2.8].

2.6 The "Risk:Benefit" or "Benefit:Risk" Debate

As with many burgeoning scientific research areas, the nomenclature concerning the risk:benefit analysis of biomedical interventions is tortuous at best, stemming in part from the persistent use of a range of synonyms to describe the same practical frameworks as shown in Figure 2.7. Consequently, it is extremely difficult and confusing either as a researcher or practitioner to navigate academic literature and regulatory guidance effectively.

Synonyms for '*Risk:Benefit*'	**Synonyms for '*Analysis*'**	**Synonyms for '[*Biomedical] Interventions*'**
Risk - Benefit	Appraisal	Medicines
Risk Benefit	Evaluation	Devices
Benefit:Risk	Technique	Products
Benefit – Risk	Framework	Procedures
Benefit Risk	Decision-Support Tool	Technologies
Benefit – Harm and any variant thereof	Multi-Criteria Decision Analysis (MCDA)	Product and/or Service Trade Names
Benefit – Cost and any variant thereof	Examination	Therapeutics
	Investigation	Treatments
	Protocol	Remedy
	Audit	Drug
	Test	Therapy
	Study	Technical Descriptions e.g. monoclonal antibody
	Division	Physical Descriptions e.g. lozenge
	Survey	
	Comparison	
	Indexing	
	Cataloguing	

Table 2.5: Exemplar Synonyms for Biomedical Risk:Benefit Analysis

Given the range of stakeholders and product types impacted by risk:benefit analysis, there is relatively unsurprising breadth in potential descriptors – and thus investigational - search terms. In turn though this contributes to stakeholder uncertainty, as demonstrated by clinical trial investigators and regulators alike being bewildered by the range of methodologies

available and the selection of the most appropriate fit for their purposes (Quartey and Wang, 2012).

At the outset, the broad investigational landscape necessitated outlining a narrow specific definition of inclusion criteria for studies and methodologies [See Section 3.2]. Perhaps most critically, an early decision was made to use the descriptor “risk:benefit,” as opposed to “benefit:risk’, based on the prevalence in other industries of the former descriptor and the recognition that the use of the latter in biomedicine was principally driven by the desire to focus regulator and patient perception on “[product] benefits” rather than concordance with accepted practices from other industries.

In short, the use of “benefit:risk” as opposed to the reverse is as much a symptom of existing deficiencies in biomedical risk management as it is an advancement. It is clear that the most expeditious route to improving stakeholder attitudes and adoption towards “risk:benefit” methodologies is to advance fundamental technical understanding and further contribute to overall improvements in available methodologies, as opposed to ‘rebranding’ them for specialized biomedical usage. Additionally, the efforts to harmonise nomenclature with other industries is hoped to uncover and embrace increased opportunities for multi-disciplinary technological improvements.

2.7 Limitations of Existing Risk:Benefit Appraisal Methodologies

Following an initial assessment of existing risk:benefit analysis methodologies, as described in academic literature and published regulatory guidance [Figure 2.9], a selection of the previously noted and/or subsequently observed limitations of their theoretical basis and/or practical implementation was compiled. These provisional gaps provided the foundation for the ‘internally generated quality factors’ that were later utilised in the investigation.

- Limited transparency in final assessment e.g. “black box methodology”
- Poor interpretability and/or risk communication (Heller et al., 2003)
- Difficulty or challenge in practical implementation

- Overtly qualitative as opposed to quantitative (Steiner, 2009)
- Failure to accommodate multi-stakeholder viewpoints e.g. use of utility weightings (Ouellet et al., 2009)
- Utilisation of probabilistic as opposed to stochastic analysis (Alvarez-Guerra et al., 2010)
- Low transferability to alternative technologies and/or jurisdictions
- High dissimilarity to ad hoc risk:benefit appraisal techniques applied in reported RCTs
- Conflation of cost-effectiveness and risk:benefit
- Incorrect equivalence of risks and harms
- Significant potential for data and/or user biases
- Limited comparability of data obtained using alternate risk:benefit methodologies e.g. need for consistent units
- Generation of patient, not population, level risk:benefit metrics or vice-versa
- Inconsistent follow-up periods
- Poor integration into clinical trial structures – often applied retrospectively
- Small, non-representative sample sizes (Cates, 1999, Bender, 2012)
- Failure to assess uncertainty (Bach et al., 1998, Hart et al., 2013, O'Connor and Hatabu, 2012) [Figure 2.5]
- Insufficient usage of risk management tools from alternate fields
- Lack of clear indication when risk:benefit is conducted in published RCTs
- Inconsistent utilisation of appropriate statistical techniques (Ades and Cliffe, 2002, Ades et al., 2008)
- Failure to assess impact of missing data (Sterne et al., 2009, Trickey et al., 2013)
- Limited integration of patient risk stratification
- Inconsistent evaluation of alternate treatment options (Lancsar and Louviere, 2008)

- Low usability for all stakeholders e.g. use of overly specialised and/or poorly described statistical techniques

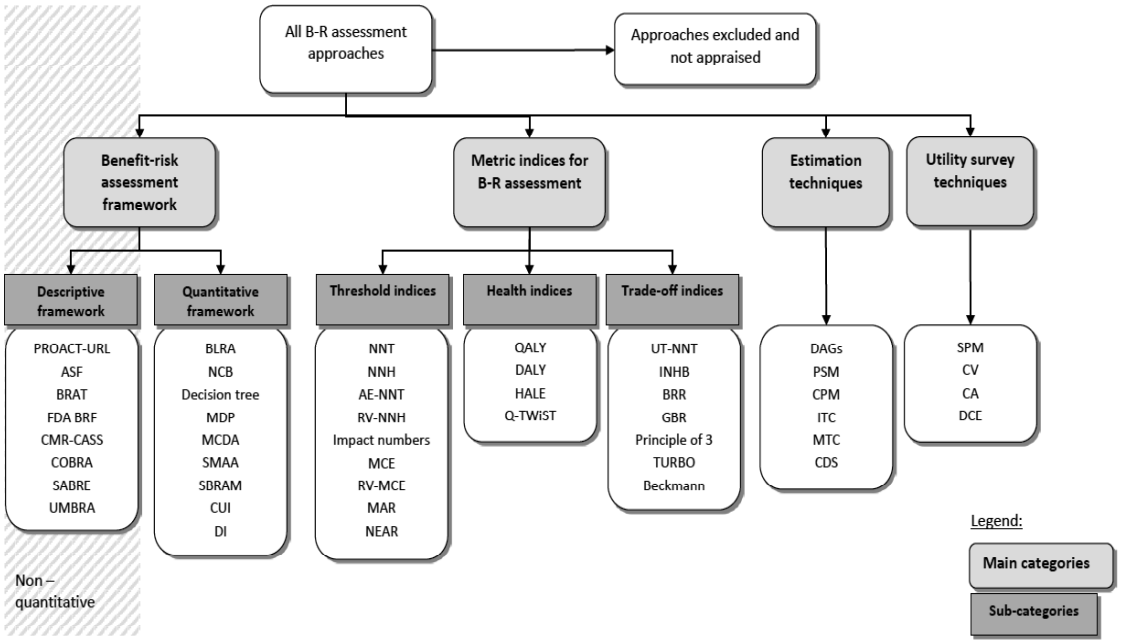


Figure 2.9: Common Existing Risk:Benefit Methodologies (Ashby et al 2012)

Hence the majority of risk:benefit methodologies assessed in previous studies have been examined from an overtly statistical viewpoint, with limited consideration of if, and if so how, such techniques could be or are already being practicably implemented in published randomised control trials (RCTs).

Source of Risk:Benefit Calculation Error	Description
Measurement	Errors attributable to measurement techniques
Data Interpretation	Errors attributable to the interpretation and assessment of calculation input data
Calculation	Errors arising from mathematical operations
Assessor Bias	Errors arising from human factors in data assessment and manipulation
Other	Errors arising from exogenous factors

Table 2.6: Types of Calculation Error in Risk:Benefit Appraisal Calculations

Key Term	Description
Benefit	Clinically positive impact(s) of an intervention and/or non-clinical positive impact(s) of an intervention e.g. convenience of an oral formulation compared to an injectable
Risk	The probability that harm – usually restricted to the viewpoint of a patient – could result from the intervention
Harm	Undesired consequences – usually restricted to the viewpoint of a patient – resulting from the intervention
Hazard	The source of a potential risk – usually restricted to the viewpoint of a patient – including novel interventions
Risk:Benefit Ratio	The ratio of defined 'risks' to defined 'benefits' in characterising a given intervention
Uncertainty	Confidence interval for a given intervention. Also described as the net difference between the probability of "potential risk(s)" [suspected; but not yet proven] less "identified risk(s)" [confirmed; therein proven] for causal relationship.
Pharmacovigilance	"Scientific activities relating to the detection, assessment, understanding and prevention of adverse effects or any other [intervention] related problem"

Table 2.7: Key Terminology in the Risk:Benefit Appraisal of Healthcare Innovations (Note: Definitions adapted from (Sietsema, 2012)

Consequently the lexicon of risk:benefit analysis is complex and heterogeneously applied. In academic lead investigations the terms "risk [the probability of an undesired outcome]" and "harm [the consequences of a realised undesired outcome]" are often used interchangeably yet as noted here incorrectly. While in industry, risk:benefit analysis is commonly considered only as a component of the post-licensure pharmacovigilence process, an unhelpfully restrictive scope that hinders broader evaluation and endorsement.

Term	Definition Applied
Quality	The technical robustness of the risk:benefit methodology selected and the diligence with which it was applied
Effectiveness	The extent to which the outputs of a given risk:benefit assessment can be accessed and assessed by stakeholders to inform their decision making process(es) – individually and/or in collaboration

Table 2.8: Definitions of "Quality" and "Effectiveness" Utilised in the Investigation

Chapter 3

Systematic Review of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Trials

3.1 Introduction

To date, the scant number of published attempts to evaluate one or more risk:benefit appraisal methodologies have exhibited many of the same limitations as the methodologies themselves [Figure 2.9]. In particular, such investigations have failed to integrate multi-stakeholder viewpoints, including those of end users, such as clinicians (Sarac et al., 2012). Therefore, in an effort to contribute objectivity and clarity to the disparate field, an investigation into the *"Quality and Effectiveness of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Trials"* was proposed, followed by an effort to produce and optimise a technique to aid RCT investigators in selecting the most appropriate risk:benefit methodology for their needs.

The investigation initially sought to conduct a systematic review conforming to the PRISMA (Liberati et al., 2009) (Moher et al., 2009) and QUORUM guidelines (Clarke, 2000), yet early literature searches produced heterogeneous examples of risk:benefit appraisal methodologies and their deployment to support innovation development and clinical

adoption. Therefore several modifications to these conventional protocols were required as they had principally been designed to collate, contrast and compare clinical trial data rather than evaluate the specific methodologies utilised to express the data yielded.

Academic rigour and robustness preserved, a prototype scorecard was produced to assess the presence and criticality of features in risk:benefit appraisal methodologies and their contribution to the overall quality and effectiveness of the method. Thereafter, the resultant similarity and difference data of these attributes for the risk:benefit appraisal methodologies was utilized to appropriately 'weight' the critical factors that contribute to the quality and effectiveness of these methodologies when applied in RCTs.

3.1.1 Hypothesis

In assessing the quality and effectiveness of existing risk:benefit appraisal methodologies utilised in published RCTs, the significant heterogeneity in the methods themselves will require a complex strategy to discern the differences. An (adapted) systematic review utilising a prototype scorecard will assist in better determining the criticality of defined quality factors.

3.1.2 Aims and Goals

i. To define robust search terms to identify published RCTs that conduct and report a formal risk:benefit appraisal(s)
ii. To produce a systematic and transparent methodology for ranking critical quality factors for individual risk:benefit appraisal methodologies
iii. To assess any heterogeneity in the quality and effectiveness of existing risk:benefit appraisal methodologies

3.2 Materials and Methods

The fundamental analysis tools of this investigation are systematic review and the various selection criteria chosen to accurately inform that review.

3.2.1 Systematic Review

To affect change in the implementation of risk:benefit appraisal in RCTs, it is essential to establish a baseline dataset that comprehensively identifies where the appraisal has been published in academic literature to date. It is important to ensure the validity and utility of any results yielded because this dataset – or components thereof – represent the 'state of the art' that current and future investigators will review and seek to emulate. Thus any limitations in published methodologies are likely to become repeated in future investigations, limiting the clinical and commercial utility of data yielded.

"The work which deserves, but I am afraid does not always receive, the most credit is that in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out.(Egger et al., 2000)" This relationship between "discovery and explanation", outlined compellingly by Lord Rayleigh in 1884, remains today, and is embodied in this investigation.

Systematic reviews have grown in utilisation and importance as the age of 'big data' has emerged, further increasing the volume of data requiring synthesis to inform innovation development and clinical decision-making (Wang, 2013). Moreover, the principle aim of the technique is to mitigate uncertainty – a parallel aim of this investigation.

3.2.2 Selection Criteria

A systematic review was conducted adhering to Cochrane Collaboration guidance and presented in accordance with the QUORUM (Clarke, 2000) and PRISMA guidelines (Liberati et al., 2009). Studies were eligible for inclusion in initial screening if they reported an RCT for

any type of healthcare innovation – therapeutic, device, transplant and/or surgical intervention.

Other publication types, including Editorials, Letters, Commentaries and Conference Abstracts were excluded from the investigation; as were animal studies and those pertaining to alternative therapies, including herbal remedies. The decision was also taken to exclude dental studies due to appreciable differences in international regulatory pathways for dental clinical trials.

The inclusion criteria did not omit any clinical indication(s), patient population(s) or data reporting methodologies. Full search terms, inclusion and exclusion criteria are outlined in Figures 3.0 - 3.3.

Search String: PubMed and EMBASE		
(benefit$ or effective or effectiveness) adj (risk$1)).tw. risk$		
AND	**IN**	**NOT**
assessment profile appraisal analysis methodology pharmacovigilance post-marketing surveillance evaluation characterization modeling decision support tool	clinical trial exp randomized controlled trial/ randomization/ rct.tw. random allocation.tw randomly allocated.tw. allocated randomly.tw. randomized controlled trials as Topic/ randomized controlled trial/ double blind method/ single blind method/ clinical trial/ controlled clinical trial.pt. randomized controlled trial.pt. clinical trial.pt. exp clinical trials as topic/ standards guidance regulations directives statue guidance amendment consultation position statement evaluation consultation pharmacopeia monograph recommendation proposal	meta-analysis as Topic/ meta analy$.tw. metaanaly$.tw. review/ comment/ letter/ editorial/ animal/ (analgesic adj trial).tw. acupuncture.tw. acupressure.tw. dental.tw. case report.tw. case study.tw. pacing.tw. stimulation.tw. growth factor$.tw. hormon$.tw. herbal$.tw. traditional medicine$.tw. alternative medicine$.tw. complementary medicine$.tw. ethnomedicine$.tw. ethnobotany.tw.

Figure 3.0: PubMed and EMBASE Systematic Review Search Terms

Cochrane
benefit* or effective or effectiveness):ti,ab,kw and (risk*) and (assessment* or profile* or appraisal* or analysis or methodology or pharmacovigilance or post-marketing surveillance or evaluation or characterization or modeling or decision support or tool) and (clinical trial or randomized controlled trial or randomization or random allocation or randomly or allocated or allocated randomly or randomized Controlled Trials as Topic or randomized controlled trial or double blind method or single blind method or clinical trial or controlled clinicals trial or randomized controlled trial or clinical trial or Clinical Trials as topic or standards or guidance or regulations or directives or statue or guidance or amendment or consultation or position statement or evaluation or consultation or pharmacopeia or monograph or recommendation or proposal) not (meta-Analysis or meta analy* or review or comment or letter or editorial or animal or analgesic trial or acupuncture or acupressure or dental or case report or case study or pacing or stimulation or growth factor* or hormone* or herbal* or traditional medicine* or alternative medicine* or complementary medicine* or ethnomedicine or ethnobotany)

Figure 3.1: Cochrane Central Systematic Review Search Terms

In order to ensure the most academically robust investigation, and yield practicable conclusions to inform regulatory and clinical practices, the following strict inclusion criteria were devised.

Systematic Review Record Inclusion Criteria
1. Published randomised control trials (RCTs) 2. Available in recognised peer-reviewed publications 3. Concern data obtained for products that at the time of publication were pre marketing authorisation 4. Implemented a defined risk:benefit analysis technique 5. Sufficient results were disclosed to evaluate the utility of the methodology

Figure 3.2: Systematic Review Record Inclusion Criteria

Systematic Review Record Exclusion Criteria
1. Primarily concerned cost and/or reimbursement:benefit analysis 2. Primarily concerned value based pricing models 3. Have significant sections of text, essential to the understanding of analysis conducted, retracted for reasons relating to commercial confidentiality 4. Not full RCTs - e.g. cohort studies, perspectives and purely theoretical discussions of risk:benefit methodologies 5. If results and/or full publication have been subsequently retracted 6. If meta-analysis and/or Cochrane reviews of a range of RCTs 7. English language versions of publications were not available 8. Animal studies only e.g. veterinary trials 9. Primarily concerned harms and not risks analysis [See Tables 2.7 and 2.8]

Figure 3.3: Systematic Review Record Exclusion Criteria

3.2.2.1 Search Strategy

The search terms outlined in Figures 3.0 and 3.1. were used to interrogate the PubMed, EMBASE and Cochrane databases on 22nd January 2013, with all records since the inception of the respective databases included. One deviation from the PRISMA guidelines was that additional records from "other sources" would not be identified, as a full search of clinicaltrials.gov, and cross-referencing thereafter with all recovered and outstanding publications yielded from the clinical trials identified would be impractical. Additionally, a key aim of this investigation was to assess what guidance and/or examples of risk:benefit analysis were available to researchers, and as such, it was felt that this would be a search strategy likely to be implemented by this critical stakeholder group.

The terms for the search were based on the findings of an initial literature review of academic literature and public guidance from worldwide NCAs [Section 2.0]. Search terms were adapted in order to accommodate the maximum search term length of the selected data sources, and to reflect the broad range of potential syntaxes and nomenclature utilised by investigators in reported studies.

Two reviewers were utilised to independently screen the initial records identified, and thereafter, to assess the full text of suitable publications. The final list of eligible records was determined through consensus. References of all eligible articles were also screened to source additional relevant records where possible.

3.2.2.2 Duplicate Publications

Duplicate records were then removed through manual screening [Figure 3.0]. In the event that multiple versions of the same publication and/or clinical trial data were returned from the same and/or multiple databases, only the publication reporting the main trial outcome(s) was included in the data set for detailed analysis and synthesis. All journal supplements that reprinted a full and/or abridged version of a previously reported clinical trial were also excluded.

3.2.2.3 Data Extraction

Remaining records from the record identification stage were screened for inclusion in a full eligibility screen through an assessment of titles and abstracts against the inclusion and exclusion criteria outlined [Figures 3.2 and 3.3]. Additionally, any publications that were not available from online sources and the Nuffield Orthopaedic Centre NHS Library (Oxford, UK), were requested from the British Library (London, UK), the Bodleian Library (Oxford, UK) and Library of Congress (Washington, DC, USA) respectively.

A standardised publication screening template [Figure 3.4] was utilised to evaluate the final suitability of publications for inclusion in data synthesis, and to record details pertaining to non-technical aspects of the publication. For example, clinical indication, journal impact factor and number of citations allude to the likely impact of the research on clinical practice [Figure 3.7].

To mitigate the risk of errors compromising the integrity of the data obtained, two reviewers extracted all data and the final data-set for synthesis was agreed through consensus.

3.2.2.4 Risk of Bias Assessment

For conventional systematic reviews, with the end-point(s) of synthesising RCT outcomes, the Cochrane guidelines (Rotter et al., 2012) recommend the assessment of intra-study bias. As this is not an end-point of this investigation, which focuses on the methodologies utilised to generate as opposed to analyse risk:benefit data yielded, a formal intra-study bias analysis was not conducted.

A detailed discussion of the potential impact(s) of risk of bias in risk:benefit appraisal in presented in Figure 2.10.

3.2.2.5 Data Synthesis

All eligible records (n=36) were screened for general study features and risk:benefit specific study features [Figure 3.4] .The initial number of risk:benefit specific study features (n=16) [Figure 3.5] was refined and reduced to (n=14) based upon the frequency and homogeneity of their utilisation in reported studies.

Thereafter, results eligible for inclusion in qualitative synthesis were assessed according to the internally generated quality metrics [Figures 3.4 and 3.5] and ranked accordingly. A brief assessment of key record attributes, including clinical indication(s) and the number of citations generated, was also conducted [Figure 3.7.].

Due to the heterogeneity of data obtained – in terms of clinical indications, statistical methodologies and study designs – it was not feasible to combine the result of individual studies, or sub-groups thereof, into a meta-analysis. All statistical analysis was conducted in Microsoft Excel (Microsoft Corporation, Seattle, WA, USA) and PRISM (GraphPad Software, San Diego, CA, USA).

Systematic Review: Initial Qualitative Synthesis Scoring Methodology

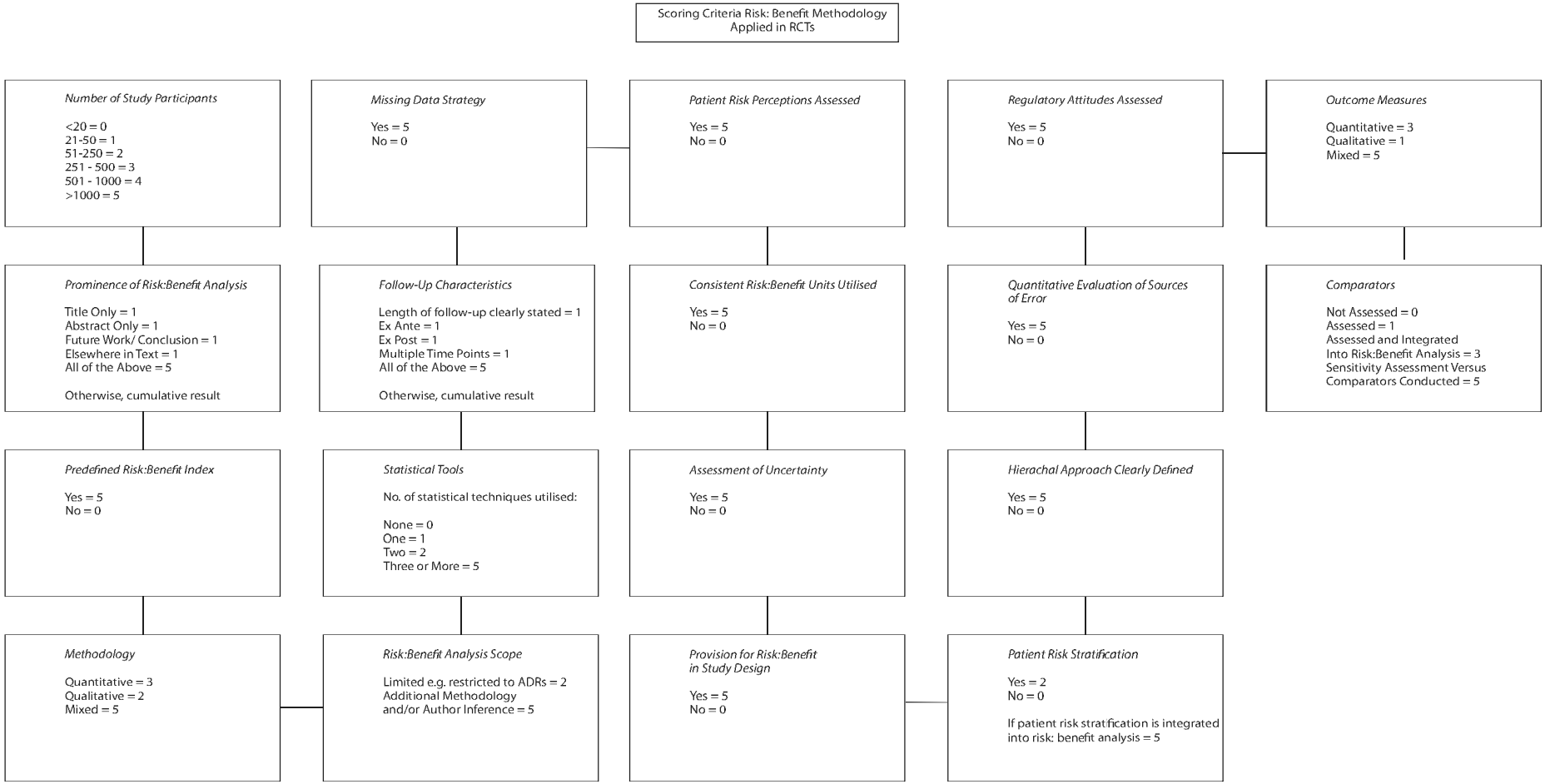


Figure 3.4: Qualitative Synthesis: Initial Scoring Methodology

Systematic Review: Refined Qualitative Synthesis Scoring Methodology

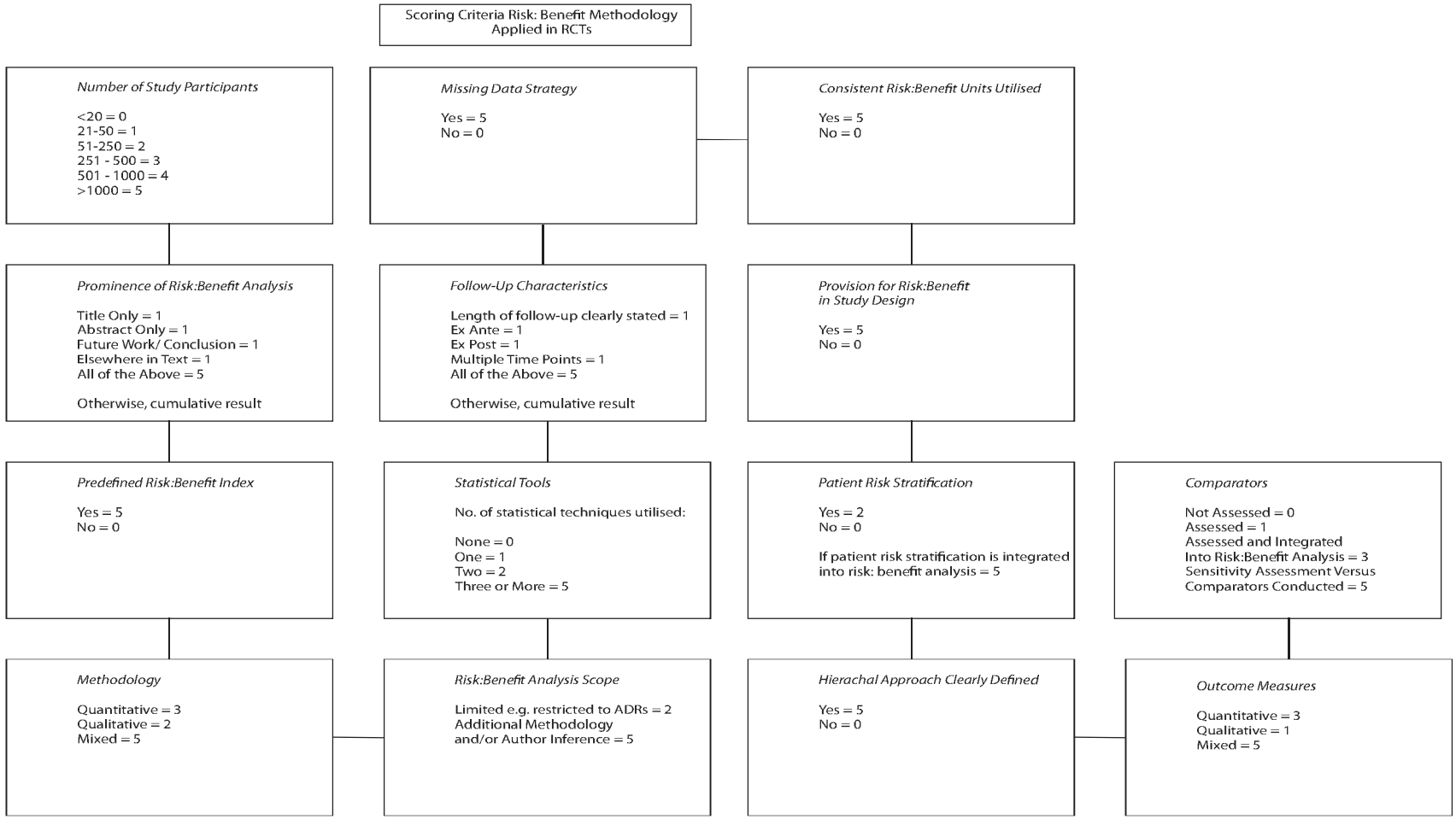


Figure 3.5: Qualitative Synthesis: Refined Scoring Methodology

3.3 Results

3.3.1 Systematic Review

3.3.1.1 Record Identification, Screening and Eligibility Assessment

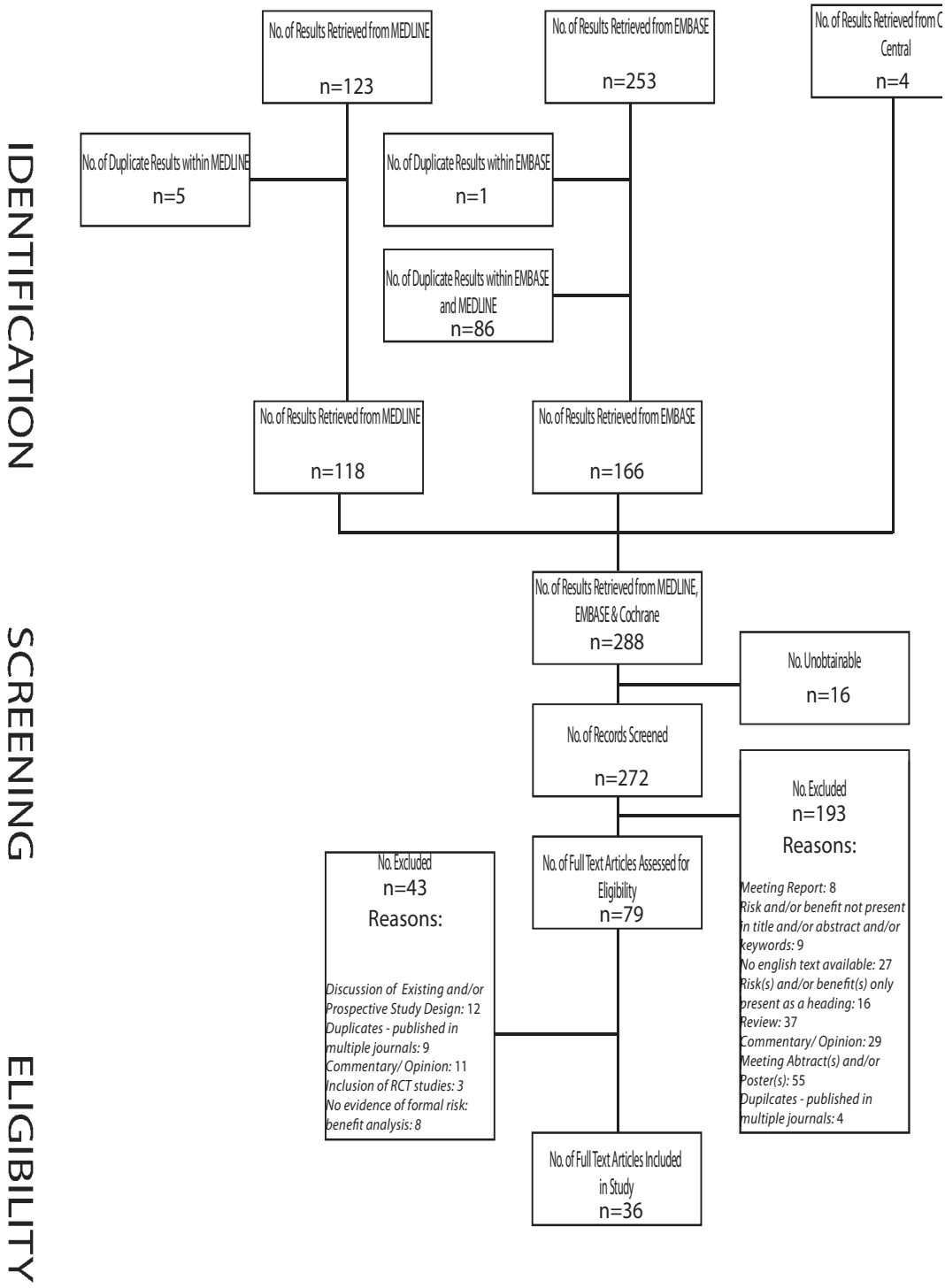


Figure 3.6: PRISMA Information Flow Through Completed Systematic Review Stages

Approximately one tenth of the initial papers captured were eligible for a full text review. After the removal of duplicates, the primary reasons for non-inclusion were the availability of English translations of studies and ineligible document classifications, such as commentaries and meeting abstracts.

Notably a number of records included sub-headings such as “Assessment of Risk and Benefit”, however did not conduct a formal risk benefit appraisal, offering only cursory – and in many cases unsubstantiated – prose. The Canadian Medical Association Journal stipulates that RCT reports include a Risk and Benefit section and thus a significant number were returned in the initial search, and later excluded through screening due to the lack of a formal appraisal.

3.3.1.2 Eligible Full Text Articles

Overview							*Research Profile*	
Reference Number	*Citation*	*Database Source*	*Number of Participants*	*Indication*	*Field*	*Funding*	*Journal impact factor.*	*Number of citations to date.*
1	1991. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. American Journal of Medicine, 90, 450-9.	Medline	817	Severe Hypoglycemia	Endocrinology	Public	5.43	49
2	1992. A multicentre, randomized trial on the benefit/risk profile of amiodarone, flecainide and propafenone in patients with cardiac disease and complex ventricular arrhythmias. Antiarrhythmic Drug Evaluation Group (A.D.E.G.). European Heart Journal, 13, 1251-8.	Medline	141	Complex ventricular arrythmia and cardiovascular disease	Cardiology	Not disclosed	10.478	Unknown
3	ADAMS, H. P., JR., EFFRON, M. B., TORNER, J., DAVALOS, A., FRAYNE, J., TEAL, P., LECLERC, J., OEMAR, B., PADGETT, L., BARNATHAN, E. S., HACKE, W. & AB, E.-I. I. I. 2008. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke, 39, 87-99.	Medline	808	Acute Ichemic Stroke	Cardiology	Private - delivered by an academic institution.	5.756	21
9	BAI, W., HENNEICKE-VON ZEPELIN, H.-H., WANG, S., ZHENG, S., LIU, J., ZHANG, Z., GENG, L., HU, L., JIAO, C. & LISKE, E. 2007. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas, 58, 31-41.	Medline	244	Menopausal symptoms	Gynecology	Not disclosed	2.32	3
10	BEISCHER, W., DEMBSKI, J. C., GRUSS, J. D., HOFGARTNER, F., HORSCH, A., HORSCH, S., KUHLMANN, H. W., LOOSE, D. A., MIETASCHK, A., SCHWILDEN, E. D., SPENGEL, F., SPITZER, W., STABEN, P., STALLKAMP, B., STURZEBECHER, C. S., TOKHI, M. & VON BILDERLING, P. 1998. Low-dose iloprost infusions compared to the standard dose in patients with peripheral arterial occlusive disease Fontaine stage IV. DAWID Study Group. Vasa, 27, 15-9.	Medline	302	Peripheral arterial occlusive disease Fontaine stage IV	Cardiology	Not disclosed	1.308	Unknown
20	BUTTGEREIT, F., DOERING, G., SCHAEFFLER, A., WITTE, S., SIERAKOWSKI, S., GROMNICA-IHLE, E., JEKA, S., KRUEGER, K., SZECHINSKI, J. & ALTEN, R. 2008. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet, 371, 205-14.	Medline	288	Rhuematoid Arthritis	Musculoskeltal	Private - delivered by an academic institution.	38.28	161
30	COLWELL, J. A. 1996. The feasibility of intensive insulin management in non-insulin-dependent diabetes mellitus. Implications of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM. Annals of Internal Medicine, 124, 131-5.	Medline	153	Non-Insulin Dependent Diabetes Mellitus	Endocrine	Public/ Charitable	16.7	2
35	DHAINAUT, J.-F., LATERRE, P.-F., JANES, J. M., BERNARD, G. R., ARTIGAS, A., BAKKER, J., RIESS, H., BASSON, B. R., CHARPENTIER, J., UTTERBACK, B. G., VINCENT, J.-L. & RECOMBINANT HUMAN ACTIVATED PROTEIN, C. W. E. I. S. S. G. 2003. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Medicine, 29, 894-903.	Medline	1271	Multiple Organ Dysfunction	General Medicine	Private	5.399	134
37	DORSCHNER, W., STOLZENBURG, J. U., GRIEBENOW, R., HALASKA, M., SCHUBERT, G., MURTZ, G., FRANK, M. & WIENERS, F. 2000. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. European Urology, 37, 702-8.	Medline	98	Urinary incontinence	Urology	Private - delivered by an academic institution.	8.493	60
42	GAJDOS, V., SOUBEYRAND, B., VIDOR, E., RICHARD, P., BOYER, J., SADORGE, C. & FIQUET, A. 2011. Immunogenicity and safety of combined adsorbed low-dose diphtheria, tetanus and inactivated poliovirus vaccine (REVAXIS ()) versus combined diphtheria, tetanus and inactivated poliovirus vaccine (DT Polio ()) given as a booster dose at 6 years of age. Human Vaccines, 7, 549-56.	Medline	760	Polio Vaccination	Infectious diseases	Private - delivered by an academic institution.	3.58	1
46	HALASKA, M., RALPH, G., WIEDEMANN, A., PRIMUS, G., BALLERING-BRUHL, B., HOFNER, K. & JONAS, U. 2003. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World Journal of Urology, 20, 392-9.	Medline	358	Detrusor Instability	Urology	Not disclosed.	2.411	159
50	HEID, F., SCHMIDT-GLINTZER, A., PIEPHO, T. & JAGE, J. 2007. Epidural ropivacaine -- where are the benefits? A prospective, randomized, double-blind trial in patients with retropubic prostatectomy. Acta Anaesthesiologica Scandinavica, 51, 294-8.	Medline	40	Anesthetic agents	Anesthesia	Undisclosed	2.188	Unknown
51	HELBLING, B., JOCHUM, W., STAMENIC, I., KNOPFLI, M., CERNY, A., BOROVICKA, J., GONVERS, J.-J., WILHELMI, M., DINGES, S., MULLHAUPT, B., ESTEBAN, A., MEYER-WYSS, B., RENNER, E. L. & SWISS ASSOCIATION FOR THE STUDY OF THE, L. 2006. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. Journal of Viral Hepatitis, 13, 762-9.	Medline	124	Fibrosis/ Cirrhosis	Musculoskeletal	Undisclosed	4.088	59

55	HOFFMANN, K., AUER, T., STUCKER, M., HOFFMANN, A. & ALTMEYER, P. 1998. Comparison of skin atrophy and vasoconstriction due to mometasone furoate, methylprednisolone and hydrocortisone. Journal of the European Academy of Dermatology & Venereology, 10, 137-42.	Medline	10	Skin atrophy and vasoconstriction.	Dermatology	Undisclosed	2.98	Unknown
57	INVESTIGATORS, E.-P., BULLER, H. R., PRINS, M. H., LENSIN, A. W. A., DECOUSUS, H., JACOBSON, B. F., MINAR, E., CHLUMSKY, J., VERHAMME, P., WELLS, P., AGNELLI, G., COHEN, A., BERKOWITZ, S. D., BOUNAMEAUX, H., DAVIDSON, B. L., MISSELWITZ, F., GALLUS, A. S., RASKOB, G. E., SCHELLONG, S. & SEGERS, A. 2012. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. New England Journal of Medicine, 366, 1287-97.	Medline	4832	Pulmonary Embolism	Cariology	Private	53.298	79
59	KAUFMANN, R. M., KRAFT, B., FREY, R., WINKLER, D., WEISZENBICHLER, S., BACKER, C., KASPER, S. & KRESS, H. G. 2010. Acute psychotropic effects of oral cannabis extract with a defined content of Delta9-tetrahydrocannabinol (THC) in healthy volunteers. Pharmacopsychiatry, 43, 24-32.	Medline	16	Drug induced psychotropic effects	Psychiatry	Public/ charitable	2.071	1
60	KIRCH, W., BURGER, K. J., WEIDINGER, G. & WELZEL, D. 1990. Efficacy and tolerability of the new calcium antagonist isradipine in essential hypertension. Journal of Cardiovascular Pharmacology, 15 Suppl 1, S55-9.	Medline	86	Hypertension	Cardiology	Undisclosed	2.287	13
61	KIRCHNER, M. & MARSHALL, D. 2006. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthritis & Cartilage, 14, 154-62.	Medline	314	Osteoarthritis	Musculoskeletal	Undisclosed	4.365	52
63	KLEIN, G., KULLICH, W., SCHNITKER, J. & SCHWANN, H. 2006. Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomised study comparing oral enzymes with non-steroidal anti-inflammatory drugs. Clinical & Experimental Rheumatology, 24, 25-30.	Medline	90	Osteoarthritis	Musculoskeletal	Undisclosed	2.148	37
65	KORTING, H. C., SCHOLLMANN, C., WILLERS, C. & WIGGER-ALBERTI, W. 2012. Bioavailability, antipsoriatic efficacy and tolerability of a new light cream with mometasone furoate 0.1%. Skin Pharmacology & Physiology, 25, 133-41.	Medline	31	Inflammatory skin disorders	Dermatology	Public/ Private	2.92	3
66	KRUG, N., HOHLFELD, J. M., GELDMACHER, H., LARBIG, M., HEERMANN, R., LAVALLEE, N., NGUYEN, D. T., PETZOLD, U. & HERMANN, R. 2005. Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. Allergy, 60, 354-9.	Medline	165	Seasonal allergic rhinitis.	ENT	Public/ Private	6.271	17
68	LASSEN, M. R., DAVIDSON, B. L., GALLUS, A., PINEO, G., ANSELL, J. & DEITCHMAN, D. 2007. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. Journal of Thrombosis & Haemostasis, 5, 2368-75.	Medline	1238	Thromboprophylaxis	Haematology	Undisclosed	5.731	218
72	LEYNADIER, F., MEES, K., ARENDT, C. & PINELLI, M. E. 2001. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. Acta Oto-Rhino-Laryngologica Belgica, 55, 305-12.	Medline	470	Seasonal allergic rhinitis.	ENT	Undisclosed	1.861	Unknown
73	LLORCA, P.-M., LANCON, C., DISDIER, B., FARISSE, J., SAPIN, C. & AUQUIER, P. 2002. Effectiveness of clozapine in neuroleptic-resistant schizophrenia: clinical response and plasma concentrations. Journal of Psychiatry & Neuroscience, 27, 30-7.	Medline	37	Schizophrenia	Psychiatry	Undisclosed	5.34	32
75	LUPORINI, G., BARNI, S., MARCHI, E. & DAFFONCHIO, L. 1998. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. European Respiratory Journal, 12, 97-101.	Medline	140	Metastatic lung cancer	Oncology	Undisclosed	5.895	45
77	MACPHEE, G. J., MCPHAIL, E. M., BUTLER, E. & BRODIE, M. J. 1986. Controlled evaluation of a supplementary dose of carbamazepine on psychomotor function in epileptic patients. European Journal of Clinical Pharmacology, 31, 195-9.	Medline	8	Epilepsy	Neurological	Undisclosed	2.845	33
88	OBERMAYR, R. P., MAYERHOFER, L., KNECHTELSDORFER, M., MERSICH, N., HUBER, E. R., GEYER, G. & TRAGL, K.-H. 2005. The age-related down-regulation of the growth hormone/insulin-like growth factor-1 axis in the elderly male is reversed considerably by donepezil, a drug for Alzheimer's disease. Experimental Gerontology, 40, 157-63.	Medline	24	Growth hormone secretion.	Endocrinology	Undisclosed	3.644	33
93	REINALTER, S. C., GRONE, H. J., KONRAD, M., SEYBERTH, H. W. & KLAUS, G. 2001. Evaluation of long-term treatment with indomethacin in hereditary hypokalemic salt-losing tubulopathies. Journal of Pediatrics, 139, 398-406.	Medline	12	Tubulopathies	Hepatology	Undisclosed	4.115	24
104	THRAILKILL, K. M., QUATTRIN, T., BAKER, L., KUNTZE, J. E., COMPTON, P. G. & MARTHA, P. M., JR. 1999. Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. RhIGF-I in IDDM Study Group. Diabetes Care, 22, 585-92.	Medline	223	Diabetes	Endocrinology	Undisclosed	7.141	84

112	WANG, T. Y., WHITE, J. A., TRICOCI, P., GIUGLIANO, R. P., ZEYMER, U., HARRINGTON, R. A., MONTALESCOT, G., JAMES, S. K., VAN DE WERF, F., ARMSTRONG, P. W., BRAUNWALD, E., CALIFF, R. M. & NEWBY, L. K. 2011. Upstream clopidogrel use and the efficacy and safety of early eptifibatide treatment in patients with acute coronary syndrome: an analysis from the Early Glycoprotein IIb/IIIa Inhibition in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial. Circulation, 123, 722-30.	Medline	9166	Acute coronary syndrome	Cardiology	Private/ public.	14.816	15
115	WOHLRAB, J., BECK, G. M., NEUBERT, R. H. H., SISCHKA, U. & KREFT, B. 2010. Hydrocortisone aceponate activity and benefit/risk ratio in relation to reference topical glucocorticoids. Skin Pharmacology & Physiology, 23, 177-82.	Medline	31	Use of topical steroids in general dermatological indications.	Dermatology	Undisclosed	2.92	2
EMBASE								
40	CHAWLA, S. P., GRUNBERG, S. M., GRALLA, R. J., HESKETH, P. J., RITTENBERG, C., ELMER, M. E., SCHMIDT, C., TAYLOR, A., CARIDES, A. D., EVANS, J. K. & HORGAN, K. J. 2003. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer, 97, 2290-2300.	Embase	257	Chemotherapy induced nausea and vomiting.	Oncology	Undisclosed	4.771	152
72	GALLI, E., BASSI, M. S., MORA, E., MARTELLI, M., GIANNI, S., AURICCHIO, G., ARABITO, E. & ROSSI, P. 2006. A double-blind randomized placebo-controlled trial with short-term beta-glucuronidase therapy in children with chronic rhinoconjunctivitis and/or asthma due to dust mite allergy. Journal of Investigational Allergology and Clinical Immunology, 16, 345-350.	Embase	125	Chronic rhinoconjunctivitis	Opthalmology	Undisclosed	2.269	2
95	KAVANAUGH, A., FLEISCHMANN, R. M., EMERY, P., KUPPER, H., REDDEN, L., GUERETTE, B., SANTRA, S. & SMOLEN, J. S. 2013. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-Week results from the randomised, controlled OPTIMA study. Annals of the Rheumatic Diseases, 72, 64-71.	Embase	1032	Rhuematoid Arthritis	Musculoskeletal	Private-public	8.727	18
103	LEHERT, P., POIRIER-LITTRE, M. F., PRINGUEY, D. & GALINOWSKI, A. 1998. New statistical proposals to evaluate the benefit/risk ratio of long-term treatment of depression. Application to a one-year double-blind study comparing medifoxamine with fluoxetine. Clinical Drug Investigation, 15, 285-295.	Embase	313	Clinical depression	Psychiatry	Private-public	1.822	Unknown
144	SINGH, R., ALPERN, L., JAFFE, G. J., LEHMANN, R. P., LIM, J., REISER, H. J., SALL, K., WALTERS, T. & SAGER, D. 2012. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clinical Ophthalmology, 6, 1259-1269.	Embase	263	Diabetic retinopathy	Opthalmology	Undisclosed	2.083	1

Table 3.0: Eligible Records Generated During Systematic Review

All eligible full text articles underwent a provisional meta-analysis to provide an overview of the types of clinical specialities and healthcare innovations employing risk:benefit appraisal. The majority of records were from MEDLINE (n=31 of 36), with the remainder from EMBASE (n=5 of 36). A range of clinical specialities were covered and the majority of records had generated a small – modest number of citations.

3.3.1.3 Eligible Records Meta-Analysis

Record Source		***Clinical Specialty***	
Medline	31	Diabetes	4
EMBASE	5	Cardiology	8
Total Eligible Records	*36*	Gynecology	1
		Musculoskeletal	12
No. of Study Participants "n"		General Surgery	6
Total "n"	24,287	Infectious Disease	1
Average "n"	675	Psychological	2
Median "n"	194	Oncology	2
Min "n"	8	*Total*	*36*
Max "n"	9,166		
Range "n"	9,158	***Journal Impact Factor***	
Standard Deviation "n"	1,675	Average Journal Impact Factor	7.13
		Median Journal Impact Factor	4.10
Funding Source		Min Journal Impact Factor	1.31
Public	1	Max Journal Impact Factor	53.30
Undisclosed	22	Range Journal Impact Factor	51.99
Private Sector	6	Standard Deviation Journal	
Hybrid: Public-Private	7	Impact Factor	10.27
Total	*36*		

Figure 3.7: Systematic Review Meta-Analysis of Eligible Records

A range of clinical specialities were surveyed, with a particular focus on musculo-skeletal indications. The distribution of study participant numbers and journal quality – utilising impact factor as an approximate proxy for quality – were better than expected, given the heterogeneity of results. Conversely, the distribution of funding sources was unexpected, the majority of which were “undisclosed.” Consequently, the assessment of agency relationships, and its potential to impart data bias(es), is challenging for readers.

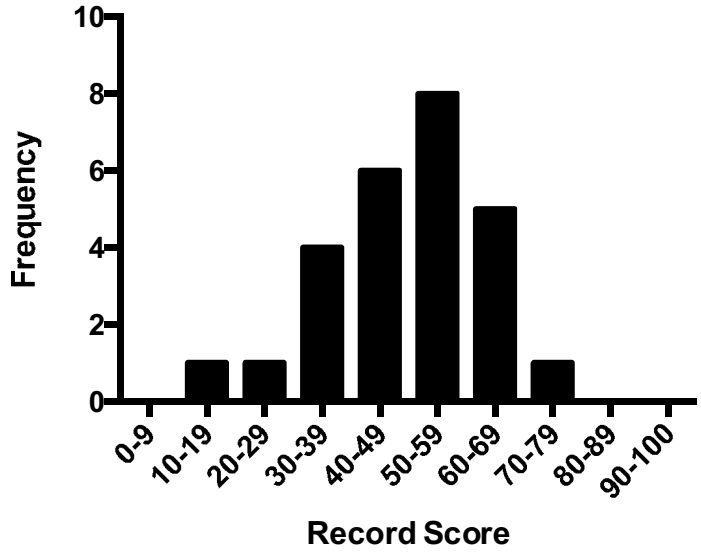
3.3.1.4 Record Initial Ranking: Assessed Using Externally Generated Quality Factors

Reference Number	No. of Participants	Prominence of R/B Analysis	Predefined R/B Index	Methodology	Scope of R/B Analysis	Statistical Tools	Frequency of Follow-Up	Missing Data Strategy	Consistency of R/B Units	Provision made for R/B in Study Design	Patient Risk Stratification	Hierarchical Approach to R/B	Outome Measures	Comparators		
MEDLINE	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	TOTAL (/70)	% TOTAL
103 (Embase)	3	2	5	5	5	0	5	5	5	5	5	0	5	4	54	77
115	1	5	5	5	5	0	5	0	5	5	2	0	5	4	47	67
10	3	1	5	5	2	1	1	0	5	5	5	0	5	1	39	56
1	4	5	0	3	2	5	5	0	0	5	5	0	3	0	37	53
9	2	2	0	5	5	1	2	0	5	5	0	0	5	4	36	51
35	5	1	0	5	5	5	5	0	0	0	5	0	5	0	36	51
95 (Embase)	5	2	0	5	5	0	5	0	0	0	2	0	5	1	30	43
2	2	2	0	3	2	1	2	0	5	5	0	0	3	4	29	41
3	4	2	0	5	5	1	5	0	0	0	2	0	5	0	29	41
57	5	1	0	3	2	5	2	0	0	0	2	5	3	1	29	41
40 (Embase)	2	2	0	5	5	1	5	0	0	0	2	0	5	1	28	40
144 (Embase)	3	2	0	5	5	0	5	0	0	0	2	0	5	1	28	40
61	3	1	0	5	5	0	5	0	0	0	2	0	5	1	27	39
112	5	1	0	5	2	1	5	0	0	0	2	0	5	1	27	39
46	3	1	0	5	5	1	5	0	0	0	0	0	5	1	26	37
50	1	1	0	5	5	0	5	0	0	0	0	0	5	4	26	37
68	5	2	0	5	2	0	5	0	0	0	2	0	5	0	26	37
73	1	2	0	5	5	0	5	0	0	0	2	0	5	1	26	37
72 (Embase)	2	2	0	5	5	0	5	0	0	0	2	0	5	0	26	37
55	0	1	0	5	5	0	5	0	0	0	0	0	5	4	25	36
63	2	2	0	5	5	0	5	0	0	0	0	0	5	1	25	36
72	3	2	0	5	2	0	5	0	0	0	2	0	5	1	25	36
37	2	2	0	5	5	0	5	0	0	0	0	0	5	0	24	34
51	2	1	0	5	5	0	5	0	0	0	0	0	5	1	24	34
77	0	2	0	5	5	0	5	0	0	0	2	0	5	0	24	34
75	2	1	0	5	2	0	5	0	0	0	2	0	5	1	23	33
20	3	2	0	5	5	1	0	0	0	0	0	0	5	1	22	31
42	4	2	0	3	2	0	2	0	0	0	0	0	5	4	22	31
65	1	2	0	5	2	0	5	0	0	0	0	0	5	1	21	30
104	2	1	0	5	2	0	5	0	0	0	0	0	5	1	21	30
66	2	1	0	5	2	0	5	0	0	0	0	0	5	0	20	29
93	0	2	0	3	5	0	5	0	0	0	0	0	3	0	18	26
88	1	2	0	3	2	0	5	0	0	0	0	0	3	1	17	24
30	2	1	0	5	2	0	0	0	0	0	0	0	5	1	16	23
60	2	2	0	3	2	0	5	0	0	0	0	0	2	0	16	23
59	0	2	0	2	2	0	0	0	0	0	0	0	2	0	8	11
Correlation with Overall Quality	0.35	0.36	0.72	0.34	0.33	0.32	0.18	0.55	0.69	0.73	0.71	0.05	0.33	0.44		

Figure 3.8: Initial Ranking of Eligible Studies Based on Internally Generated Quality Factors

In the initial assessment utilising internally generated quality factors, there is significant disparity between the highest (77%) and lowest ranked (11%) studies. Most studies were consistently deficient in certain factors, such as the implementation of a missing data strategy and the provision clear follow-up criteria. However, almost all studies – albeit to differing degrees – received scores for the prominence of risk:benefit analysis in published data. The latter may be in part due to the electronic search strategy utilised.

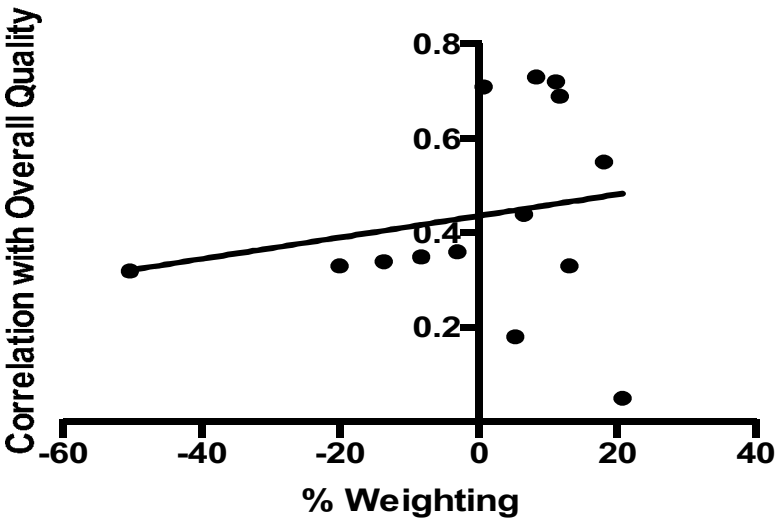
3.3.1.5 Distribution of Record Initial Ranking: Assessed Using Externally Generated Quality Factors



Skewness	0.6740
Kurtosis	-1.049

Figure 3.9: Distribution of Record Scores Based Upon Unweighted Scoring

The distribution of record scores assessing the quality factors identified in Section 3.2.2.5 generated a normalised distribution with dominant left-tail. Overall, the analysis is suggestive of an overall poor quality of risk:benefit appraisal methodologies utilised with few records scoring greater than 50% (n=6).



	% Weighting vs. Correlation with Overall Quality
Pearson r	
r	0.1993
95% confidence interval	-0.3704 to 0.6601
R squared	0.03973
P value	
P (two-tailed)	0.4945
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	14

Figure 3.10: Correlation between Overall Record Score and Specific Quality Factors

There was a positive, yet not statistically significant, correlation between the impact of specific individual quality factors on the overall score generated. The greatest correlation between specific factors and the overall record score generated were for: the presence of a pre-defined risk:benefit index; ex ante provision for risk:benefit appraisal in study designs; and, where possible, the integration of patient risk stratification into risk:benefit appraisal(s).

3.4 Discussion

The perceived growth in importance and utilisation of risk:benefit appraisal methodologies in RCTs is not matched by the extent and quality of implementation demonstrated in the records assessed. Moreover, the exclusion of the majority of records identified in initial literature searches (n=193 initial screening; n=43 full text eligibility assessment) suggests that while risk, benefit and uncertainty are being expressed *en vogue* as terms within publications, they are rarely supported by rigorous and substantive quantitative analysis. Hence, the large number of commentaries, opinion pieces and meeting reports identified by search terms, despite these being explicitly excluded from the investigation in initial search terms [Figure 3.6].

The lack of a 'gold standard' to assess the quality and effectiveness of risk:benefit appraisal methodologies is surprising and a critical multi-stakeholder challenge, likely to be presently hindering the development of novel healthcare innovations (Steiner, 2009). The prototype scorecard developed and implemented worked sufficiently well to warrant further development and investigation. However, future iterations require greater representative integration of multi-stakeholder viewpoints along with validation of the specificity and reliability of the tool (Thompson et al., 2008).

Overall, the poor 'state of play' is a concern in an era of increasing technical complexity and heightened systems risks and uncertainties that trouble the development of biomedical innovations.

3.4.1 Record Identification, Screening and Eligibility Assessment

The literature search terms devised were successfully implemented with minimal challenges, retrieving a total of n=380 records cumulatively from MEDLINE, EMBASE and Cochrane Central. However, there was significant overlap between the datasets in terms of duplicate results, with inter and intra literature databases [Figure 3.6.].

Following the removal of duplicate records, n=288 records were screened for eligibility, of which n=16 were unavailable from any of the literature sources detailed in Section 3.2.2.3. The reason(s) for the inaccessibility of some records are unclear; as there are few commonalities amongst said papers. It is apparent that in some cases articles were published in online only journals which have now ceased to exist and were not deposited physically or electronically; and in other cases publications may have been retracted by the author(s) and/or journal(s) and erroneously removed entirely from catalogues.

Of the n=272 records screened the majority, n=193, were excluded for a range of reasons, as per record inclusion and exclusion criteria outlined [Figures 3.2 – 3.3].

Exclusion Factor	Percentage of Total Screened Articles Excluded (n=193)
Meeting Report	4.15%
Risk and/or benefit not present in title and/or abstract and/or keywords	4.66%
No English text available	13.99%
Risk(s) and/or benefit(s) only present as a heading	8.29%
Review	19.17%
Commentary/Opinion	15.03%
Meeting Abstract(s) and/or Poster(s)	28.50%
Duplicates – published in multiple journals and/or supplements	2.07%
Other	4.15%

Table 3.1: Proportion of Records Excluded Through Screening

Frequently while record abstracts were available in English, the full publication texts were not, without requesting from a source outside of the stated repositories [Section 3.2.2.3] and/or obtaining an *ad hoc* professional translation. Thus an inherent trade-off between the size of the dataset obtained and its representativeness of what a researcher and/or clinician would likely be able to access if seeking information pertaining to the risk:benefit profile of a given healthcare innovation. Translations of foreign language texts was deemed unrepresentative of the manner in which the records would actually be utilised, and in order

to ensure consistency, all records would need to be translated and verified by the same translators and reviewers.

Meeting abstracts and/or posters were challenging to exclude pre-screening as some journals publish posters as original research, often – and somewhat curiously – in the clinical trial section of the publication. The exclusion of such records proved valuable as in many cases data presented in meeting reports and/or posters was also reported in full RCTs reports captured in full eligibility screening.

Of the n=79 full text articles assessed for eligibility, n=43 were excluded.

Exclusion Factor	Percentage of Total Full Text Articles Excluded (n=79)
Discussion of Existing and/or Prospective Study Design	27.91%
Duplicates – published in multiple journals and/or supplements	20.93%
Commentary/Opinion	25.58%
Studies Evaluating Multiple RCT Structures	6.98%
No Evidence of Formal Risk:Benefit Analysis	18.60%

Table 3.2: Proportion of Full Text Records Excluded Screening

In addition to records being excluded due to similar factors as [Table 3.1], the full screen unearthed a number of records that discussed clinical trial reporting and/or structure best practices, although did not demonstrate to investigators the application of risk:benefit appraisal methodologies, only suggestions for their use and development.

Consequently, the final dataset of n=36 full text articles met the inclusion criteria for the study.

3.4.2 Meta-Analysis of Eligible Full Text Records

Given that all RCTs for every clinical trial since the inception of the databases - PubMed, EMBASE and Cochrane Central - were eligible for inclusion in the study, it is both alarming and disappointing that only n=36 studies were identified that performed a formal risk benefit analysis. It is apparent that there has historically been more discussion and public consultation concerning the risk:benefit appraisal of healthcare innovations than tangible and transparent implementation by clinical trial investigators. A meta-analysis of eligible records [Table 3.0] indicated significant inter-study heterogeneity in terms of the risk:benefit appraisal basis for study participant numbers; clinical indications of technologies evaluated; and impact factor of reporting journals. Unfortunately, it was not possible to collate the number of citations generated for all records due to inconsistencies in journal reporting and bibliographic metrics. Clear, and in some respects unexpected, trends were observed with respect to record sources and the disclosure of study funding sources.

The majority (~86%) of all records oddly were sourced from Medline, with the remainder from EMBASE, a larger and broader database [Figure 3.6]. As Medline records formed the baseline dataset – that is to say that any duplicate records found in the EMBASE dataset were removed, and retained in the Medline dataset – it is possible that this priority had an effect on the distribution. Nevertheless n=26 unique records were identified through Medline and no eligible records were identified from Cochrane Central.

	Medline[1]	Embase[2]
Focus	Biomedicine and health	Broad biomedical scope with in-depth **coverage of drugs and pharmacology**
Produced by	US National Library of Medicine	Elsevier
Access	Available free of charge via PubMed OR Through institutional subscription via OvidSP. Available via MUHC libraries portal muhclibraries.ca > Quick Links section	Through institutional subscription. Available via MUHC libraries portal muhclibraries.ca > Quick Links section
Content	Journal articles, mostly from peer-reviewed journals	Journal articles, mostly from peer-reviewed journals **+ conference abstracts since 2009**
# of records	Over 20 million	Over 27 million, **including all Medline records**
# of journals (2012)[3]	Approximately 5600	Approximately 8000, **including Medline unique journals**
Journal origins (2012)	40,5% North America 48,5% Europe	33,8% North America 49,7% Europe

Table 3.3 :Comparison of Medline and EMBASE Database Properties

Over half (~61%) of all eligible records did not disclose a study funding source, making it challenging for a researcher to identify a potentially major sources of bias, such as funding from a sponsoring pharmaceutical company with a vested commercial interest in the outcome of the data presented. Encouragingly approximately 20% of all records reported hybrid public:private funding, thus an example of systems risk sharing in the development of healthcare innovations (French et al., 2014b, Reeve, 2010). It is noteworthy to include that of the n=8 clinical specialities represented by the n=36 eligible records, approximately a third (~34%) reported data pertaining to musculoskeletal interventions [Figure 3.7].

3.4.3 Record Initial Ranking Using Externally Generated Quality Factors

Applying the scoring methodology outlined in Section 3.2.2.5 the n=36 eligible records reporting a formal risk:benefit appraisal were ranked with the results presented in Figure 3.8. that demonstrates a significant distribution in the quality of the appraisals reported. For example, only n=5 of n=36 studies (~14%) of eligible records scored more than 50% of the maximum possible score. [Maximum = 77%; Minimum = 11%; Mean = 38%]. The overall assessment has a notable negative skew, indicating the poor overall quality of risk:benefit appraisal methodologies reported in eligible records.

In particular, very few (n=3 of 36) records defined a risk:benefit index *ex ante*, that is to say prior to the commencement of data collection, which is analogous to starting a clinical trial without fully defining the patient outcomes to be monitored. Even with data blinding, there is considerable potential concern for a selection bias when retrospectively defining factors to be integrated into any risk:benefit assessment.

Only one record Figure 3.8, fittingly the highest ranked study, reported a missing data strategy, which is essential when trying to mitigate and/or measure uncertainty. By comparison, most clinical trial protocols include a broad missing data strategy for clinical outcomes, for example the failure to return a Patient Reported Outcome (PROMS) proforma (de Bock et al., 2013). Based on this data set, it is not common practice to devise and/or publish risk:benefit appraisal specific missing data strategies. This is an important consideration for future studies as the impact of specific types of missing data may differ between that on broad study outcomes and its sub-investigation, including risk:benefit appraisal. Additionally, in the long term such a strategy would be an essential component of a risk management strategy (RMS) and/or pharmacovigilance reporting to regulators (Arlett et al., 2014, Wise et al., 2009).

Generally poor intra-study consistency of risk:benefit units was observed, which is unhelpful to those seeking to evaluate the relative risks and benefits of a given innovation. This may be due to the poor overall quality of RCTs captured through the literature search. The range of nomenclature and statistical techniques available for describing the relative risks and benefits of a given product or intervention is challenging – and were incorrectly applied by some investigators in the sample. Thereby the overall quality of the risk:benefit appraisal conducted was limited.

For the remaining period where risk:benefit appraisal is an optional, as opposed to mandated component of clinical trial submissions, there is likely to be a conflation of regulation, standards, guidance (through public consultations an white papers arising) and

specialism specific best practices. Consequently, this heterogeneity in guidance available to investigators, contributes to heterogeneity in expectation and implementation of risk:benefit appraisal methodologies. For example, while the FDA and EMA have published guidance pertaining to risk:benefit appraisal for new Investigational New Drug applications (INDs), there is limited – or in some cases no – formal regulation published in this area (Mt-Isa et al., 2014).

The majority of formal regulation pertaining to risk management can be found for licensing applications (BLA and/or MAA) of approved products, which are rarely fully published due to commercial sensitivity. Specific stakeholder groupings, have provided risk management guidance for 'GxP best practices,' including Good Manufacturing Practice (GMP; engineering), Good Clinical Practice (GCP; medicine) and GLP (Good Laboratory Practice; basic science). However, there is a lack of both specificity and codification in the implementation of such best practices as they pertain to the risk:benefit appraisal of healthcare innovations in RCTs.

3.4.4 Distribution of Record Initial Ranking: Assessed Using Externally Generated Quality Factors

The dominant left tail in the distribution of scores Figure 3.9 indicates the overall poor quality of risk:benefit appraisal methodologies surveyed. The extent and frequency of the poor quality is also of concern, providing limited data of sufficient quality to effectively inform clinical decision-making and product development (Walker et al., 2009).

Future iterations of the prototype scorecard must be validated to ensure the validity of the selected factors and their relative importance to a range of stakeholders engaged in product development and adoption [Sections 4.0 and 5.0].

Of the quality factors assessed, only three showed significant correlation with the overall quality of reported risk:benefit appraisals: presence of a pre-defined risk:benefit index; provision for risk:benefit analsysis in the study design; and integration of patient stratification into the risk:benefit assessment [Figure 3.10].

A more detailed analysis of the correlation between the internally and externally generated quality factors and the overall quality of risk:benefit appraisal methodologies assessed indicates a positive relationship and therein some agreement between the importance of the factors assessed by the scoring methodology [Figure 3.10] Inherently though a 'formal' statistically significant correlation between individual quality factors and the overall quality of risk:benefit appraisal in specific studies is unlikely in this dataset given the heterogeneity of interventions, clinical indications and outcome measures.

The weak positive correlation observed [Figure 3.10] simply verifies that there is some positive relationship between the presence of defined quality factors, their assessment and contribution to the overall ranking of studies. As such, there is no reason to suggest that any errors in specific calculation steps conducted.

3.5 Study Limitations

While every effort was made to maximise the suitability, rigour and impact of the study, a number of limitations remain – either unavoidably and/or as stimuli for subsequent parts of the study. Arguably, the initial search terms used to identify records for deeper analysis are the most substantial limiting factors in the study.

A deliberately broad definition of "healthcare innovations" was utilised in order to obtain data relating to therapeutics, devices and surgical interventions, and thus maximise the representativeness of the risk:benefit appraisal landscape generated. Given the relatively small final number of eligible studies, this feature of the investigation proved to be important and valid. However, the data generated did highlight some differences in the product development pathway for therapeutics when compared to implants and devices.

In part due to fundamental differences in the regulatory requirements for therapeutics [proof of safety and efficacy] versus devices [safety only and equivalence], the types of studies where risk:benefit appraisal may have been conducted in some cases differed. While RCTs are the most common method to evaluate candidate therapeutics, other structures including case control studies, are utilised to evaluate devices (Tervonen et al., 2011). The assessment of some emerging technologies, including cell based therapies, due to the nascent nature of the field, regularly trial novel technologies in 'n of 1' clinical trials and under hospital exemptions, which were excluded from this RCT focused analysis (Ankrum et al., 2014).

Consequently, there may be a selection bias present in the records identified. Based on consultation with risk:benefit appraisal experts, however, no major publications appear to have been omitted from the assessment and only implemented risk:benefit methodologies were assessed. Therefore, purely theoretical methods, including non-analytical frameworks were omitted as they provide limited assistance to a potential investigator seeking to design and/or evaluate an RCT (Powell, 2011).

As a relatively new branch of an academic field, risk:benefit appraisal may not yet be commonplace to be explicitly integrated into clinical trials co-ordinated by academic investigators. Therefore, combined with the assumption that large volumes of risk:benefit analyses are provided within regulatory submissions that are confidential, non-published components risk:benefit assessments conducted are not captured. Thus the risk:benefit landscape presented is very much a current 'public state of the art' representation, as opposed to fully representative of the use of risk management tools in industry and NCAs. Nevertheless, this is a valid and important analysis presenting the body of guidance available to current and future investigators.

"Harms" were excluded from search terms as the standardised reporting of "harms" in RCTs was only introduced in 2004 (Ioannidis et al., 2004), with varying degrees of adoption.

Consequently, while “harms” may represent a contribution to the risk component of risk:benefit analysis, they were deemed insufficiently standardised to support the implementation of the prototype scorecard. Most RCTs report “harms” in terms of adverse (drug) events (ADRs) (Boers et al., 2010), which mitigates the risk to sample quality of this omission.

Any studies reviewing solely – and or mostly – cost-effectiveness were excluded as this is very much a system risk; and in addition to be relatively rare in published RCTs, would have been difficult to integrate into a standardised assessment methodology. To address this issue pertaining to the potential breadth of risk:benefit appraisal, PART III of this investigation evaluates system risks from the viewpoint of emerging stakeholders and novel therapeutic technologies.

Modest deviation from QUORUM/ andPRISMA guidelines for systematic reviews, including the development and implementation of a prototype scorecard, was necessary to assess and rank the quality of risk:benefit appraisal methodologies reported. There is no reason to suggest that this has impacted the quality of the analysis conducted and findings derived. However, it may be challenging to compare multiple systematic reviews of risk:benefit appraisal methodologies in the future if substantially different adaptions are utilised.

3.6 Conclusion

The provision and utilisation of existing risk:benefit appraisal methodologies in RCTs is inadequate and heterogeneous. Despite growing discussion of risks, benefits and uncertainties in literature and the clinical community, the number of examples of risk:benefit appraisal methodologies implemented in published RCTs is minimal across all types of interventions and clinical indications.

Based upon the results presented, the prototype scorecard created to assess the presence and quality of factors critical to the quality and effectiveness of risk:benefit appraisal

methodologies produced a good distribution in data obtained, and could have an impact on clinical practice and the development of healthcare innovations if developed further.

One major deficiency in the prototype scorecard is the failure to appropriately ‘weight’ the relative importance of specific quality factors to individual stakeholders and the broad biomedical community, which will be addressed in PART II, the next stage of this investigation.

PART II

ASSESSMENT AND VALIDATION OF A RISK:BENEFIT APPRAISAL SCORECARD

Chapter 4

Pilot Study: Assessing the Relative Importance of Risk:Benefit Appraisal Quality Factors

4.1 Introduction

The scoring methodology devised to evaluate risk:benefit appraisals for this investigation was principally internally generated from a systematic review [Section 3.0] of the publically available literature and informal review and communication with subject matter experts. Therefore, in order to reduce – and where possible eliminate – the potential for bias, and maximise the representativeness of the data from a multi-stakeholder viewpoint, a technique to externally validate the methodology and appropriately weight the quality factors assessed was sought.

A number of techniques are available for eliciting the opinions and perceptions of multiple stakeholders pertaining to a specific factor and/or research question. For example, in health economics and epidemiology it is often necessary to elicit the opinions of a convened panel of experts to derive valid estimates in scenario and decision support modelling tools (Philips et al., 2004). Amongst the most common data collection techniques utilised are Delphi studies (Linstone and Turoff, 1975).

Group based techniques such as Delphi studies aim to convene a group of recognised experts on a given subject, and through debate and discussion, seek to determine consensus regarding a specific factor for which there is insufficient publically available data. Aside from the obvious challenges relating to convening a large number of experts, and the incurred expenses, Delphi studies share a number of limitations common to group-based data gathering. For example, the method fails to adequately record individual preferences and group probability distributions assume a potentially inaccurate normal distribution that fails to account sufficiently for uncertainty in responses (Cooke, 1991). Therefore to meet the aims and objectives of this investigation, a technique that robustly assessed individual attitudes of multi-stakeholder experts to a range of factors, which accounted for personal probability distributions and gave an indication of any associated uncertainty, was sought.

Expert elicitation is commonly used in health economics, environmental science and finance to determine individual expert beliefs, perceptions and uncertainties in a statististical form – a probability distribution (O'Hagan, 2006). Additionally, the technique yields mean weightings and uncertainty functions around the data obtained (Leal et al., 2007).

Uncertainty is a critical and oft neglected component of risk:benefit appraisal, particularly concerning novel technologies with limited prior data – as in healthcare where significant uncertainty around positive (benefit) and negative (risk) user outcomes exist. Aleatory uncertainty describes random uncertainty, which varies stochastically between respondents, with little or no correlation to respondents' actual response uncertainty (Bojke et al., 2010). Conversely, epistemic uncertainty describes a non-random uncertainty that is correlated with respondents' actual response uncertainty (Bojke et al., 2010). It is this type of uncertainty that is recorded by expert elicitation and is of interest in assigning externally validated weightings to the scoring methodologies described in Section 4.2.

4.1.1 Hypothesis

There is significant inter-stakeholder heterogeneity in the relative importance of quality attributes in the risk:benefit appraisal methodologies as demonstrated by a thorough expert elicitation pilot study which assessed the criticality of defined quality factors.

4.1.2 Aims and Goals

i. To evaluate inter and intra stakeholder attitudes to critical quality factors impacting the effectiveness of individual risk:benefit appraisal methodologies
ii. To rank published attempts to deploy to risk:benefit appraisal methodologies to evaluate healthcare innovations, based upon key quality factors and the attitudes of multiple stakeholders towards these factors
iii. To determine if there is a significant difference between the unweighted and weighted risk:benefit appraisal methodology rankings

4.2 Materials and Methods

4.2.1 Stakeholder Selection

In order to externally assess the relative importance of each internally generated quality factor, and any uncertainty around the data gathered, an expert elicitation exercise was conducted [Sections 4.2. and 4.3].

Given the high probability of respondent unfamiliarity with both risk:benefit appraisal and the technique of expert elicitation, a small pilot study (n=5) was conducted with key stakeholders [Table 4.0.] to confirm the suitability of the technique. Then based upon delivery and respondent feedback, areas of improvement were identified and corrected prior to embarking on a larger and more statistically significant study.

Stakeholder	Current Role
Basic Scientist	Senior Post-Doctoral scientist in leading academic research institution
Clinician	Surgical Registrar
Statistician	Experienced Statistician currently working in a public health role
Regulator	An ex- biologics regulator (CMC Assessor) with a major EU national competent authority, currently working as an independent regulatory consultant
Investor	VP Global Partnerships with a global biopharmaceutical company

Table 4.0: Pilot Expert Elicitation Study Respondents and Current Roles

4.2.2 Pilot Expert Elicitation Data Collection

All respondents were shown a standard presentation [Appendix 1.0.] including some background slides to ensure uniform baseline knowledge amongst respondents. Additionally, a common exemplar question – on a subject matter unrelated to risk:benefit appraisal - was utilised to enable participants to familiarise themselves with the technique prior to answering 'live' questions. Thereafter, the order in which questions were addressed to respondents was randomised to control for any response bias resulting from increased familiarity with the technique and/or fatigue (Presser, 2004).

Responses to variations on a common question stem were elicited using a histogram technique, whereby experts specify relative subjective probabilities pertaining to a given factor on a frequency chart in the form of a histogram. This technique is also intuitive for respondents without statistical and/or data collection training (Gigerenzer et al., 1991).

Expert elicitation data collection usually undergoes a calibration exercise to control for response errors, such as sampling error arising from environmental inconsistencies (Bojke et al., 2010). However, given that the 'true' values to the research questions posed were unknown this was not possible. Therefore, every effort was made to ensure strict inclusion

and exclusion criteria for participants, thereby achieving a natural calibration by virtue of the characteristics of respondents.

4.2.2.1 Synthesis of Collected Data

All personal responses were recorded based upon the histograms produced. Thereafter, the collected data was aggregated for each respondent to produce a single distribution.

It is noteworthy to highlight that mathematical aggregation, the linear pooling method employed here, is different to behavioural aggregation as in the Delphi technique that yields a consensus response.

4.2.2.1.1 Inter-stakeholder Quality Factor Weightings

$$Discrete\ Probability\ Function\ (x) = \left[\frac{Strength\ of\ Response\ (\theta)}{\sum_{n+i}^{n} Internal\ Frequency\ (\rho)}\right]$$

Equation 4.0

$$Continuous\ Probability\ Function\ (\gamma) = \sum_{n+i}^{n} Discrete\ Probability\ Function\ (x)$$

Equation 4.1

$$Factor\ Weighting\ (\beta) = \sum_{n+i}^{n} Discrete\ Probability\ Function\ (x)$$

Equation 4.2

$$Continuous\ Probability\ Function\ (\gamma) = \sum_{n+i}^{n} Discrete\ Probability\ Function\ (x) = Factor\ Weighting\ (\beta)$$

Equation 4.3

$$Adjusted\ Average\ (z)$$

$$= \left[\frac{\sum_{n+i}^{n} Internal\ Frequency\ (\rho)}{\sum_{n+i}^{n} Cumulative\ Interval\ Frequencies\ (j)}\right] . \sum_{n+i}^{n} Internal\ Frequency\ (\rho)$$

Equation 4.4

4.2.2.1.2 Inter-stakeholder Variance Probability Distribution and Weightings

$$Weighted\ Average\ (\phi) = Adjusted\ Average\ (z)\ .\ Strength\ of\ Response\ (\theta)$$

Equation 4.5

$$\%\ Weighting\ (b) = \left[\frac{Weighted\ Average\ (\phi)}{\sum_{n+i}^{n} Weighted\ Average\ (\phi)}\right] .100$$

Equation 4.6

$$\%\ Net\ Weighting\ (\omega) = \left[\%\ Weighting\ (b) - \left(\frac{100}{\text{No. of Factors Assessed } (\upsilon)}\right)\right]$$

Equation 4.7

$$Net\ Weighting\ \%\ Difference\ (\tau) = \left[\left(\frac{\%\ Net\ Weighting\ (\omega)}{\left(\frac{100}{\text{No. of Factors Assessed } (\upsilon)}\right)}\right) . \frac{100}{1}\right]$$

Equation 4.8

4.2.2.1.3 Inter-stakeholder Variance Impact on Record Ranking

$$Weighted\ Record\ Ranking\ (\mu)$$

$$= Unweighted\ Record\ Ranking\ (\psi) . Net\ Weighting\ \%\ Difference\ (\tau)$$

Equation 4.9

The results of the expert elicitation pilot study were used to externally validate – through the use of utility weightings – the relative importance of the internally generated quality factors used to rank eligible studies [Section 4.3.]. Utility weightings were then used to re-rank the quality of eligible studies based on stakeholder preferences captured [Table 4.1].

4.2.2.2 Expert Elicitation Pilot Evaluation

Improvements to the pilot for the final expert elicitation protocol that would be used in the full study (n~60) were informed by user evaluation questionnaires [Appendix 2.0.], as it was critical for the protocol to be equally accessible to all stakeholders studied. Pilot evaluation questionnaires were intended to assess potential enhancements to the expert elicitation methodology, and to the evaluation questionnaires themselves ahead of the full study.

Respondents were asked to complete the questionnaire immediately following their participation in the expert elicitation exercise. However, no guidance was given from data collection staff, nor was a time limit imposed on questionnaire completion to mitigate the risk of passive and/or active coercion biases. Data obtained was analysed by a combination of quantitative and qualitative synthesis [Section 4.3].

4.3 Results

4.3.1 Pilot Expert Elicitation Study: Cumulative Externally Generated Quality Factor Weightings

Question Number	*Factor*	*% Weighting*	Net % Weighting	% Difference
1	No. of Study Participants	6.55	-0.59	-8.32
2	Indication of R/B Analysis	6.92	-0.22	-3.09
3	Clear Scoring Criteria	7.94	0.80	11.14
4	Highly Quantitative	6.17	-0.98	-13.67
5	Range of Stakeholder Viewpoints	8.08	0.93	13.08
6	No. of Statistical Techniques	3.55	-3.60	-50.37
7	Frequency of R/B Assessment	7.52	0.38	5.32
8	Missing Data Strategy	8.43	1.29	18.08
9	Consistency of Units	7.98	0.83	11.67
10	Provision for R/B Analysis	7.74	0.59	8.32
11	Patient Risk Stratification	7.19	0.05	0.68
12	Hierarchal Description of Technique(s)	8.62	1.48	20.73
13	Highly Quantitative Outcomes	5.71	-1.43	-20.08
14	Assessment of Alterative Treatment(s)	7.61	0.46	6.50

Table 4.1: Externally Generated Quality Factor Weightings Derived from Pilot Expert Elicitation Study

The most important and thus 'overweighed' factors assessed were: the range of stakeholder viewpoints assessed, the provision of a missing data strategy and the inclusion of a hierarchical description of the risk:benefit assessment methodologies utilised. Conversely, the least important and thus 'underweighted' factors assessed were: the number of statistical techniques employed and the reporting of highly quantitative outcomes. This data is also depicted in a forest plot overleaf.

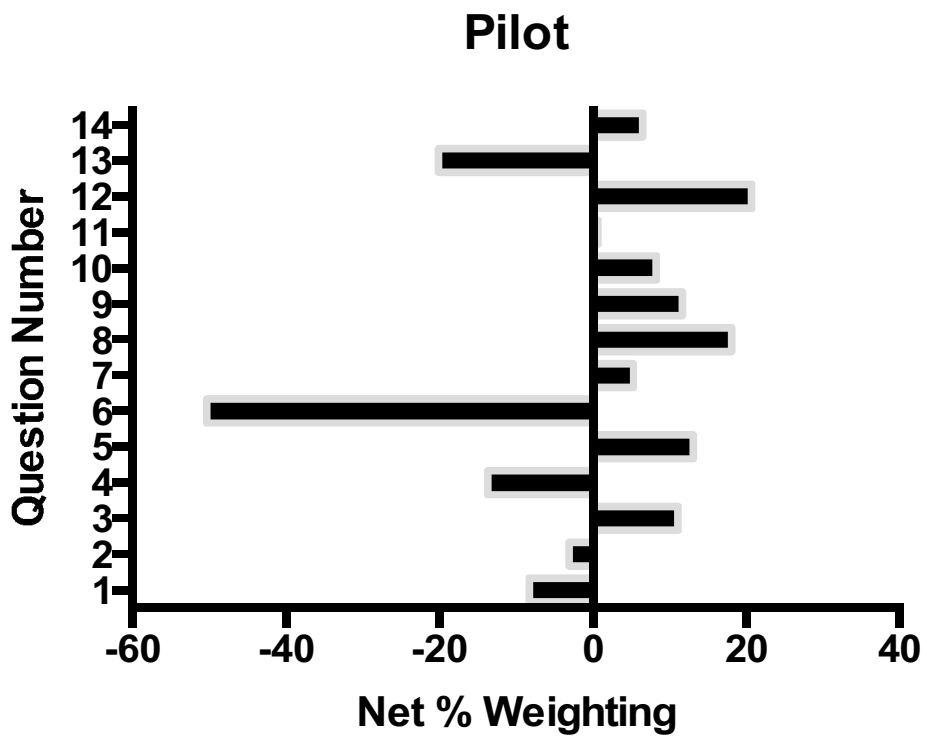


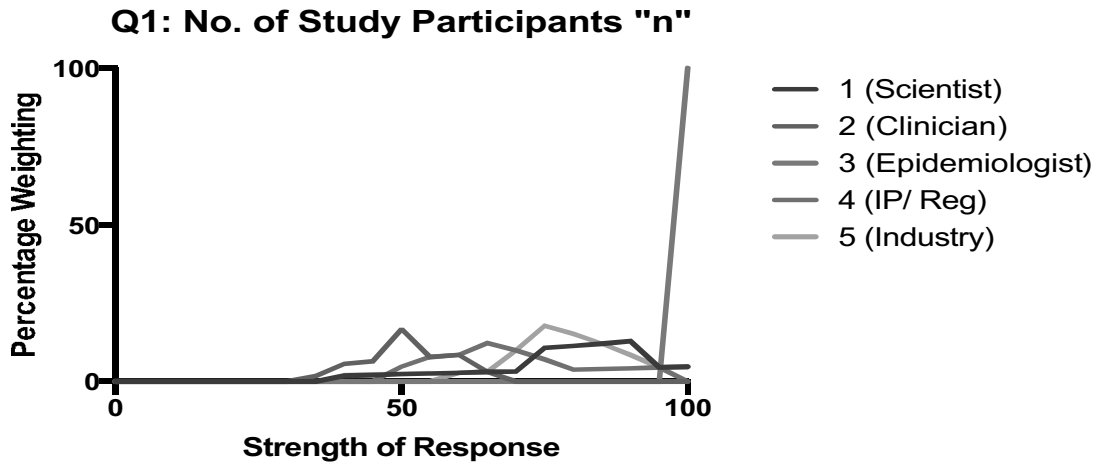
Figure 4.0 Forest Plot of Externally Generated Quality Factor Weightings Derived from Pilot Expert Elicitation Study

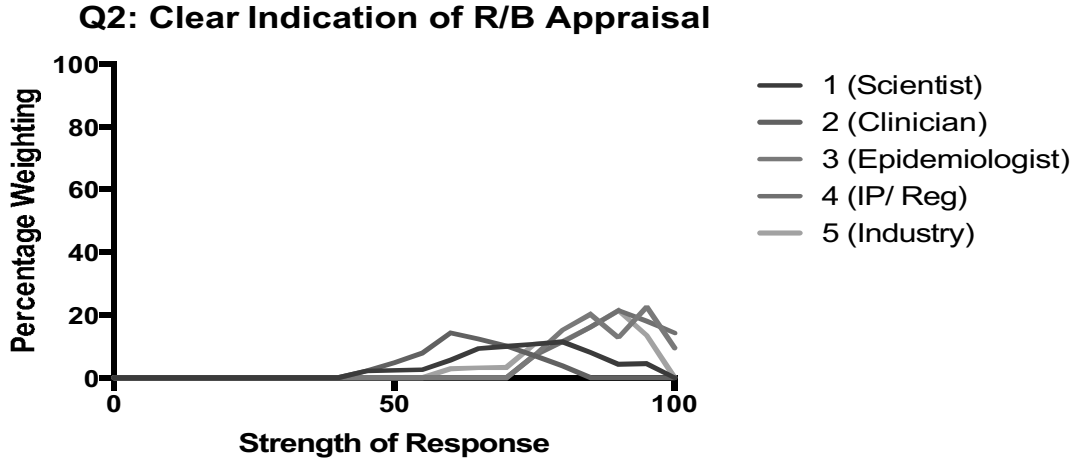
Note: For key to quality factor number, please see Table 4.1 overleaf.

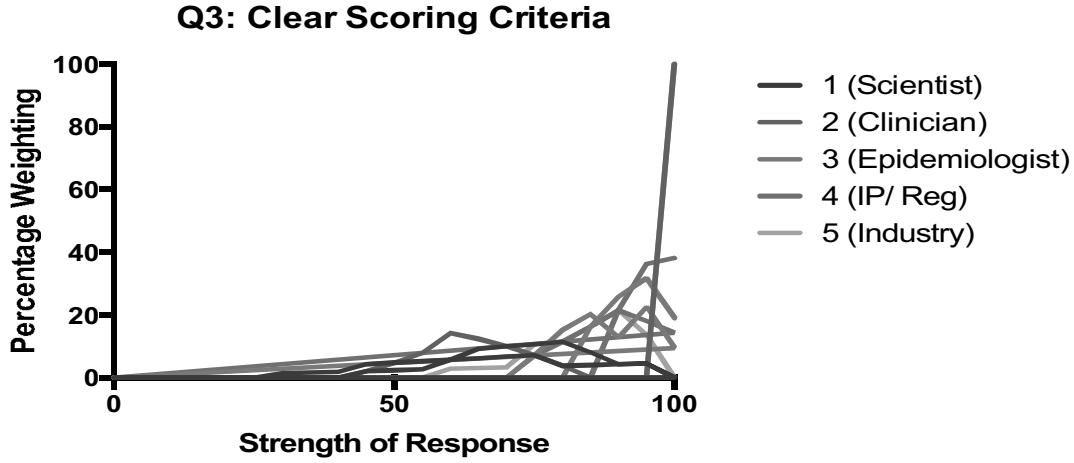
The cumulative results for all stakeholders indicate a range in the relative importance of the quality factors assessed to the quality and effectiveness of risk:benefit appraisal methodologies. Notably, Questions 6 [“Number of Statistical Techniques Utilised;” -50.37%] and 13 [“Utilisation of Highly Quantitative Outcome Measures;” -20.08%] are not regarded as particularly critical to the stakeholder group surveyed. Conversely, the reporting of a clear “Hierarchical Technique” in Question 12 was deemed critical [+20.73%].

4.3.2 Pilot Expert Elicitation Study: Externally Generated Quality Factor Weightings Intra-Stakeholder Variance

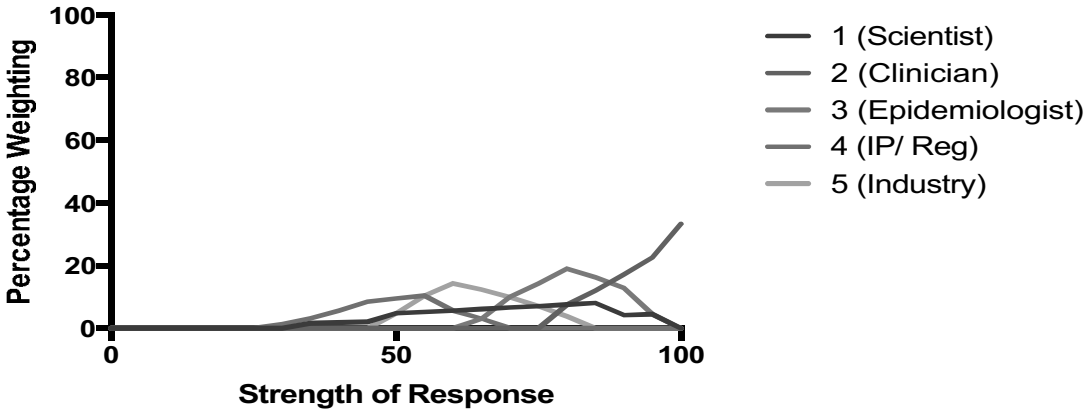
Note: Figures below are cumulatively presented as Figure 4.1



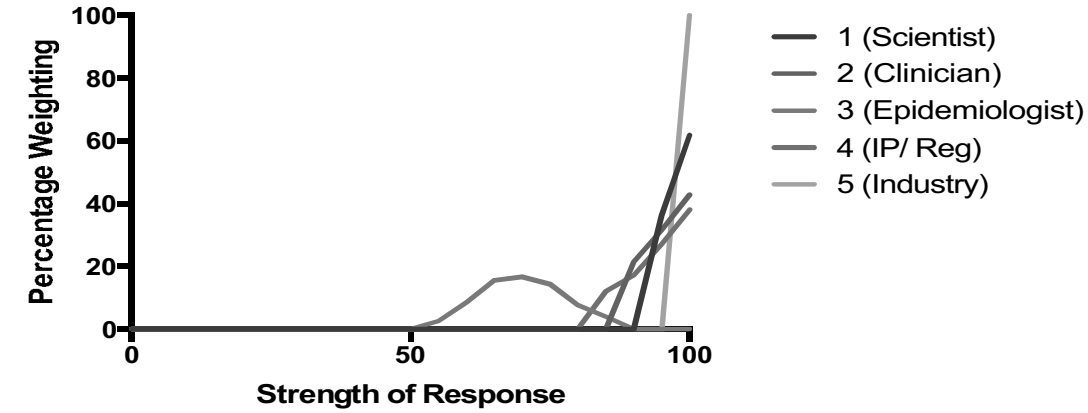




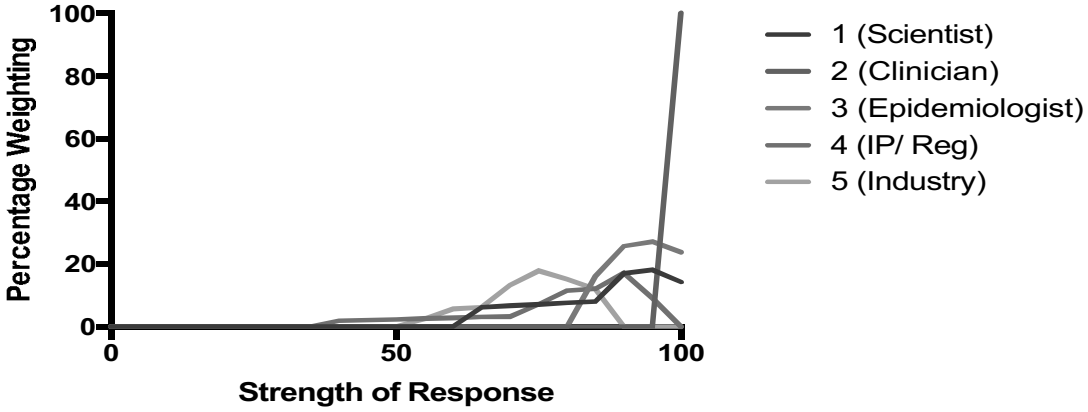
Q4: Highly Quantative R/B



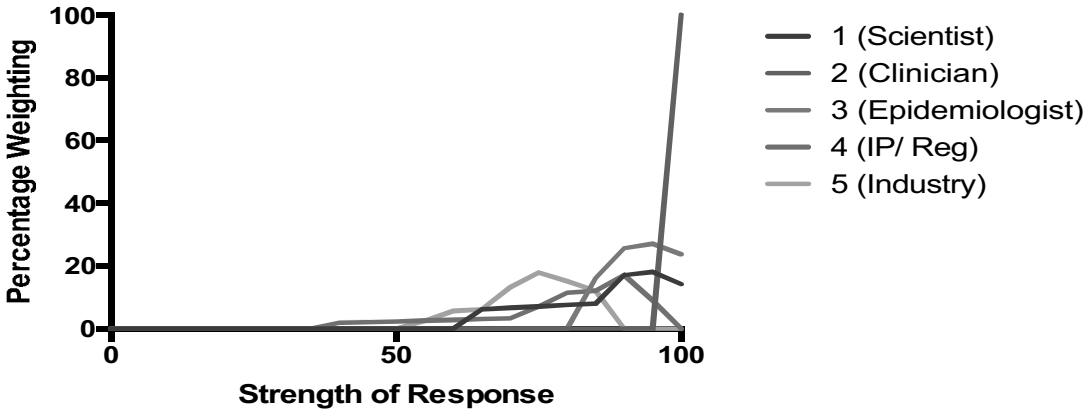
Q5: Range of Stakeholder Viewpoints Assessed



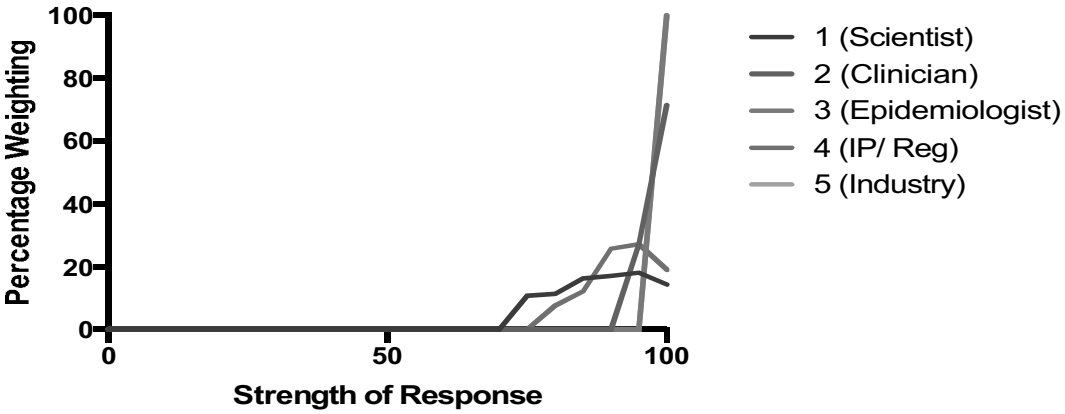
Q6: No. of Statistical Techniques Utilised



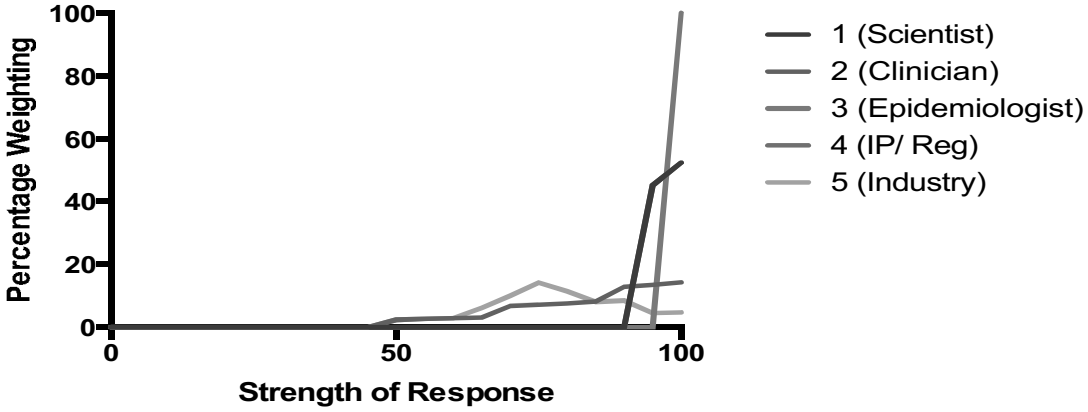
Q7: Frequency of Risk:Benefit Appraisal

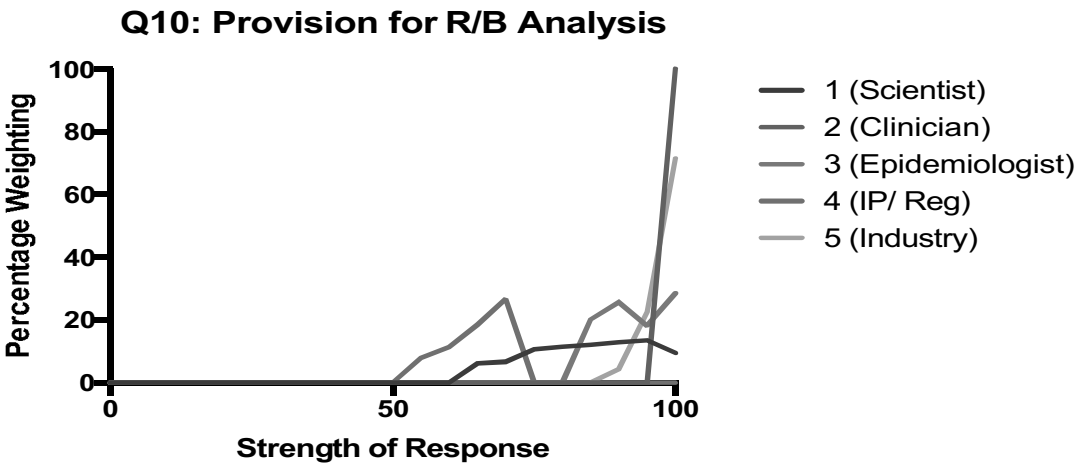


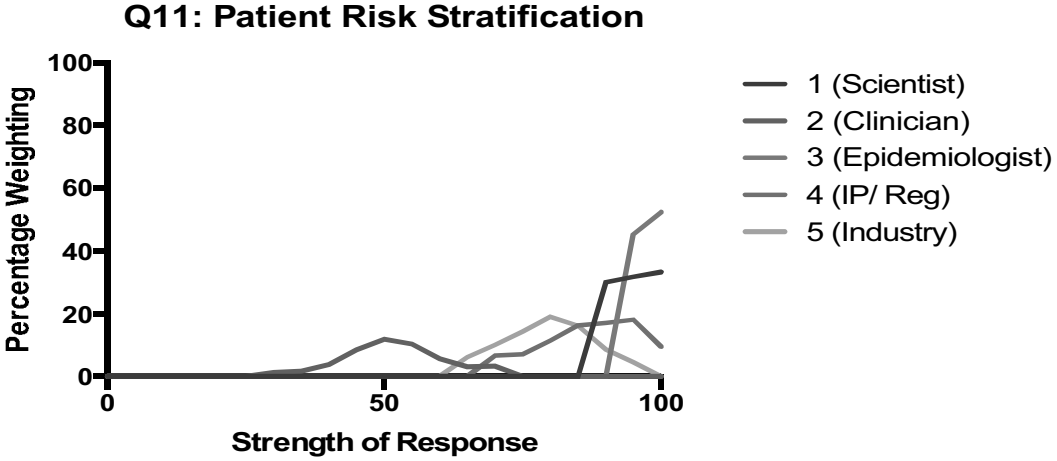
Q8: Missing Data Strategy

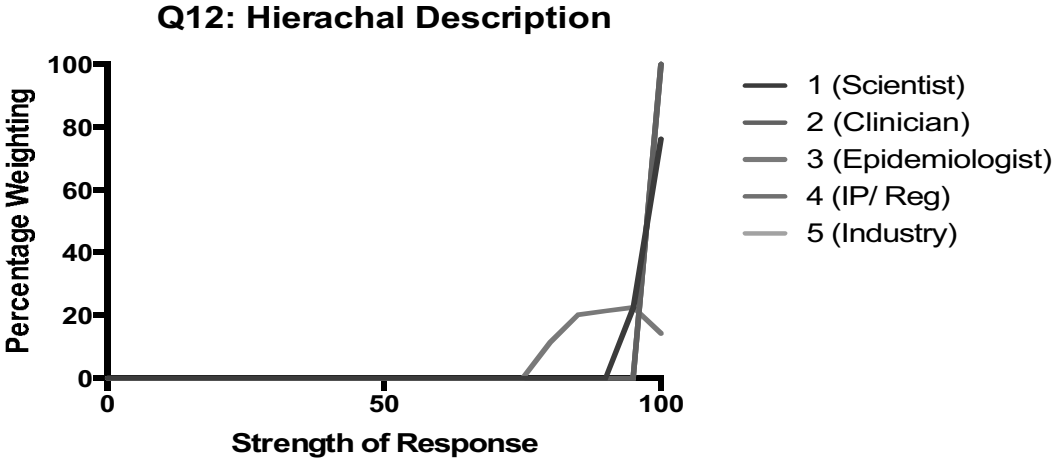


Q9: Consistency of R/B Units




Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response
1 (Scientist)
2 (Clinician)
3 (Epidemiologist)
4 (IP/ Reg)
5 (Industry)


Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response
1 (Scientist)
2 (Clinician)
3 (Epidemiologist)
4 (IP/ Reg)
5 (Industry)


Q12: Hierachal Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response
1 (Scientist)
2 (Clinician)
3 (Epidemiologist)
4 (IP/ Reg)
5 (Industry)

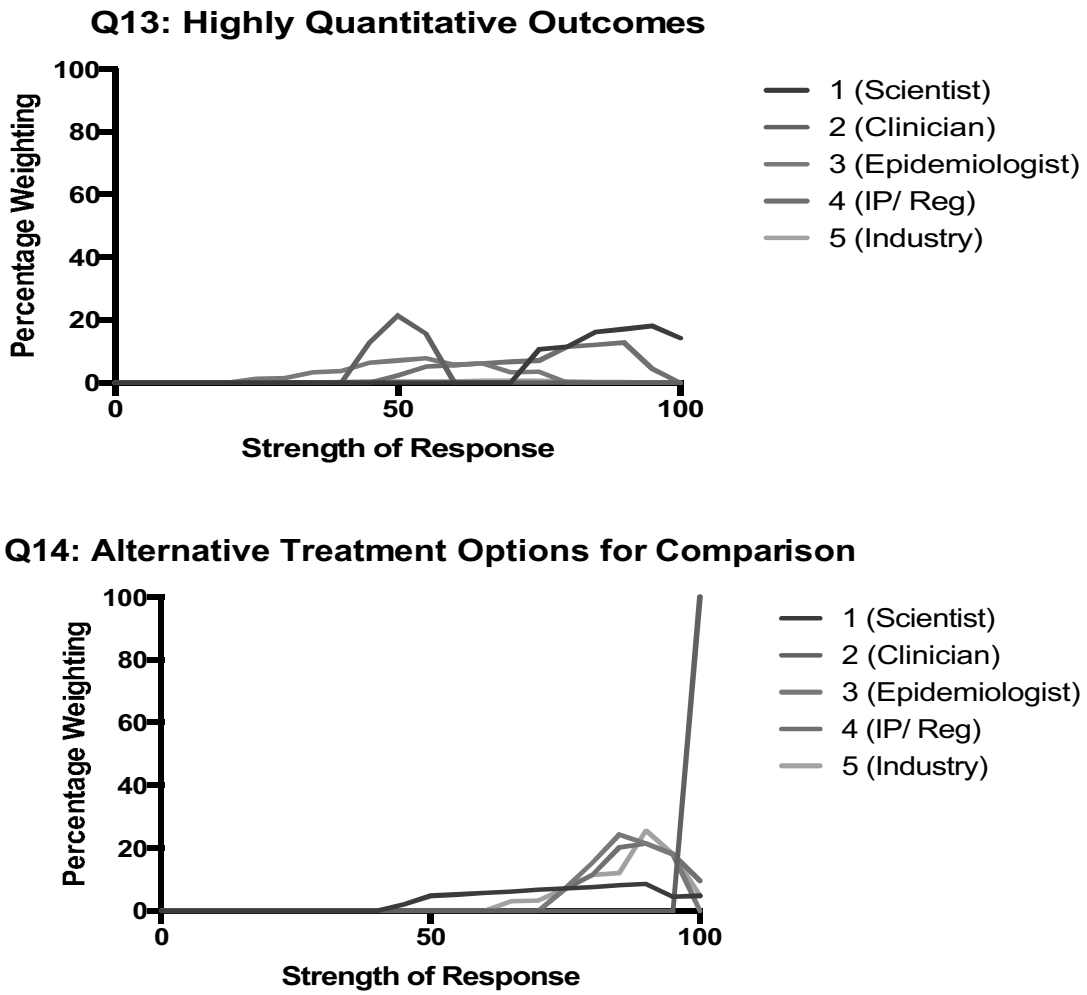


Figure 4.1: Inter-Stakeholder Pilot Expert Elicitation Probability Distributions

Expert Elicitation Question Number	Quality Factor Assessed	Discussion/Analysis
1	No. of Study Participants	Overall, a tight distribution in responses was observed amongst all stakeholders. However, the Epidemiologist surveyed, provided an outlier, stressing a strong desire for a large number of study participants in any risk:benefit analysis conducted.
2	Clear Indication of Risk:Benefit Appraisal	Minimal differences in stakeholder viewpoints were reported. Clinical respondents expressed their own desire to non-prescriptively assess the risk:benefit characteristics of given interventions which is reflected here.
3	Clear Scoring Criteria	A significant distribution of stakeholder opinions is represented. However, this limited sample is suggestive of a growing desire for the provision of clear scoring criteria throughout the development pathway – expressed strongest here by industry.
4	Highly Quantitative Methodology	A significant distribution in responses is observed. However, the least desire for high quantitative risk:benefit methodologies is expressed by regulators and the greatest desire by clinicians.
5	No. of Stakeholder Viewpoints Assessed	With the exception of the minor outlying result provided by an epidemiology respondent, there is strong agreement that a range of stakeholder viewpoints should be assessed in any robust risk:benefit appraisal.
6	No. of Statistical Techniques Utilised	There is a wide distribution in respondents' attitudes towards the number of statistical techniques applied in risk:benefit analysis. Further, analysis – including a larger sample – is required to derive practicable conclusions.
7	Frequency of Risk:Benefit Assessment	Similar results are observed from all stakeholders, indicating a desire for extensive patient follow-up and frequent risk:benefit assessments. This is stressed particularly by clinical respondents.
8	Missing Data Strategy	For all respondents there is strong agreement that a robust missing data strategy is an important feature of any risk:benefit analysis methodology.
9	Consistency of Risk:Benefit	For all respondents there is strong agreement that, where possible, consistent units of

	Units Utilised	risk:benefit are utilised to permit comparison of alternate treatment options.
10	Provision for Risk:Benefit Appraisal in Study Design	Similar results are observed from all stakeholders, indicating preference for the ex ante provision of risk:benefit appraisal strategies.
11	Patient Risk Stratification	Overall there is a strong preference towards the integration of patient stratification in risk:benefit appraisal methodologies. However, the uncertainty expressed by clinical respondents will require further analysis.
12	Hierarchical Description of Risk:Benefit Appraisal Methodology Utilised	For all respondents there is strong agreement that, where possible, a hierarchal description of risk:benefit assessment techniques utilised is described.
13	Utilisation of Highly Quantitative Outcome Measures	Significant heterogeneity is observed in attitudes towards the provision of highly quantitative outcomes in risk:benefit appraisal. Particularly, uncertainty is expressed by industrial respondents. Consequently, additional analysis is required.
14	Presence of Alternative Treatment Options to Permit Comparision	Despite a strong positive skew, significant heterogeneity is observed in attitudes towards the provision of risk:benefit appraisals of comparators. Interestingly, industrial respondents are strongly against, and clinicians strongly for the inclusion of such data, Consequently, additional analysis is required.

Table 4.2: Overview of Inter-Stakeholder Pilot Expert Elicitation Probability Distributions

4.3.3 Pilot Expert Elicitation Evaluation

4.3.3.1 Section A

Respondent	*Clarity of Techniques*	*Clarity of Questions*	*Relevance of Questions*	*Context*	*Timing*
Basic Scientist	5.00	5.00	4.00	5.00	5.00
Clinician	5.00	5.00	5.00	5.00	5.00
Statistician	5.00	5.00	4.00	5.00	5.00
Regulator	2.00	3.00	5.00	5.00	2.00
Industry	4.00	5.00	5.00	5.00	5.00
Average	*4.20*	*4.60*	*4.60*	*5.00*	*4.40*

Table 4.3: Results of Pilot Expert Elicitation Evaluation

Overall all respondents assessed the exercise positively. In particular, the unanimous appreciation of the context, and thus importance of the investigations is encouraging. However, a number of protocol weaknesses were highlighted by regulators – a key stakeholder. Consequently, modifications will be integrated into the final full expert elicitation protocol, including a paralinguistic analysis to evaluate any differences between cognitive and non-cognitive indicators of uncertainty.

4.3.3.2 Section B

All respondents indicated that:
(1) The exercise had increased the likelihood that they would conduct further individual research into risk:benefit analysis
(2) Increased the likelihood that they may seek to integrate risk:benefit analysis techniques into their own research
(3) That further training in risk:benefit analysis would be appreciated

Figure 4.2: Future Risk:Benefit Training Respondent Evaluation Overview

4.3.3.3 Section C

Key changes suggested to improve clarity of presentation used in pilot study:
(1) Integration of paralinguistic analysis (2) Randomise slide order (3) 'Familiarisation' slide (4) Terminology changes e.g. removal of National Competent Authority (NCA) as not essential to completion of task (5) Additional description of "uncertainty" (6) Add 'working definitions' of risk and benefit (7) Question refinements (8) Additional slide on technological complexity and necessary regulatory changes

Figure 4.3: Future Risk:Benefit Training Respondent Evaluation Overview

4.3.3.4 Record Re-Ranking Based on Pilot Expert Elicitation Study

Reference Number	No. of Participants	Prominence of R/B Analysis	Predefined R/B Index	Methodology	Scope of R/B Analysis	Statistical Tools	Frequency of Follow-Up	Missing Data Strategy	Consistency of R/B Units	Provision made for R/B in Study Design	Patient Risk Stratification	Hierarchical Approach to R/B	Outome Measures	Comparators			
MEDLINE	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	TOTAL (/70)	% TOTAL	%Change (Final-Original)
103 (Embase)	2.75	1.94	5.56	4.32	5.65	0.00	5.27	5.90	5.58	5.42	5.03	0.00	4.00	4.26	55.68	80	2.39
115	0.92	4.85	5.56	4.32	5.65	0.00	5.27	0.00	5.58	5.42	2.01	0.00	4.00	4.26	47.83	68	1.18
10	2.75	0.97	5.56	4.32	2.26	0.50	1.05	0.00	5.58	5.42	5.03	0.00	4.00	1.06	38.50	55	-0.72
1	3.67	4.85	0.00	2.59	2.26	2.48	5.27	0.00	0.00	5.42	5.03	0.00	2.40	0.00	33.96	49	-4.34
9	1.83	1.94	0.00	4.32	5.65	0.50	2.11	0.00	5.58	5.42	0.00	0.00	4.00	4.26	35.60	51	-0.57
35	4.58	0.97	0.00	4.32	5.65	2.48	5.27	0.00	0.00	0.00	5.03	0.00	4.00	0.00	32.30	46	-5.28
95 (Embase)	4.58	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	28.83	41	-1.67
2	1.83	1.94	0.00	2.59	2.26	0.50	2.11	0.00	5.58	5.42	0.00	0.00	2.40	4.26	28.88	41	-0.17
3	3.67	1.94	0.00	4.32	5.65	0.50	5.27	0.00	0.00	0.00	2.01	0.00	4.00	0.00	27.35	39	-2.36
57	4.58	0.97	0.00	2.59	2.26	2.48	2.11	0.00	0.00	0.00	2.01	6.04	2.40	1.06	26.51	38	-3.56
40 (Embase)	1.83	1.94	0.00	4.32	5.65	0.50	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	26.58	38	-2.03
144 (Embase)	2.75	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	27.00	39	-1.43
61	2.75	0.97	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	26.03	37	-1.38
112	4.58	0.97	0.00	4.32	2.26	0.50	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	24.97	36	-2.90
46	2.75	0.97	0.00	4.32	5.65	0.50	5.27	0.00	0.00	0.00	0.00	0.00	4.00	1.06	24.51	35	-2.12
50	0.92	0.97	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	0.00	0.00	4.00	4.26	25.38	36	-0.86
68	4.58	1.94	0.00	4.32	2.26	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	0.00	24.38	35	-2.32
73	0.92	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	25.17	36	-1.19
72 (Embase)	1.83	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	0.00	25.02	36	-1.40
55	0.00	0.97	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	0.00	0.00	4.00	4.26	24.46	35	-0.77
63	1.83	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	0.00	0.00	4.00	1.06	24.07	34	-1.33
72	2.75	1.94	0.00	4.32	2.26	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	23.61	34	-1.99
37	1.83	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	0.00	0.00	4.00	0.00	23.00	33	-1.42
51	1.83	0.97	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	0.00	0.00	4.00	1.06	23.10	33	-1.29
77	0.00	1.94	0.00	4.32	5.65	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	0.00	23.18	33	-1.17
75	1.83	0.97	0.00	4.32	2.26	0.00	5.27	0.00	0.00	0.00	2.01	0.00	4.00	1.06	21.72	31	-1.83
20	2.75	1.94	0.00	4.32	5.65	0.50	0.00	0.00	0.00	0.00	0.00	0.00	4.00	1.06	20.22	29	-2.55

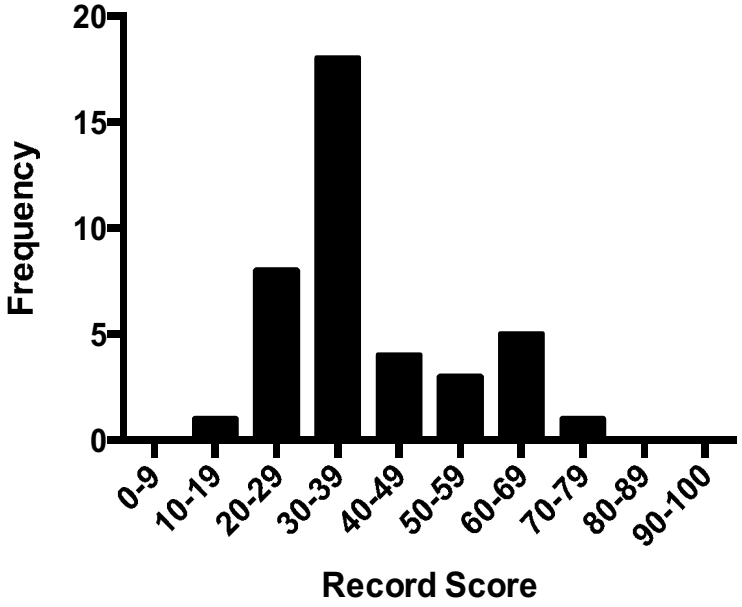
Figure 4.4.: Updated Ranking of Eligible Studies Based on Externally Generated Quality Factors

Despite significant changes in the relative weightings of quality factors assessed in selected studies, the quality ranking was entirely unaffected. However, a major observation is the increase in the percentage score of the highest ranked studies, and decreases for lower scoring studies. Consequently, the difference between higher quality and lesser quality studies is highlighted.

	Original	Pilot	Change
103 (Embase)	1	1	0
115	2	2	0
10	3	3	0
1	4	4	0
9	5	5	0
35	6	6	0
95 (Embase)	7	7	0
2	8	8	0
3	9	9	0
57	10	11	-1
40 (Embase)	11	12	-1
144 (Embase)	12	10	2
61	13	13	0
112	14	14	0
46	15	19	-4
50	16	16	0
68	17	18	-1
73	18	15	3
72 (Embase)	19	17	2
55	20	20	0
63	21	22	-1
72	22	21	1
37	23	25	-2
51	24	23	1
77	25	24	1
75	26	26	0
20	27	28	-1
42	28	27	1
65	29	30	-1
104	30	29	1
66	31	31	0
93	32	32	0
88	33	33	0
30	34	34	0
60	35	35	0
59	36	36	0

Table 4.4: Comparison of Record Rankings Unweighted Prototype Scorecard Versus Weighted Expert Elicitation Pilot

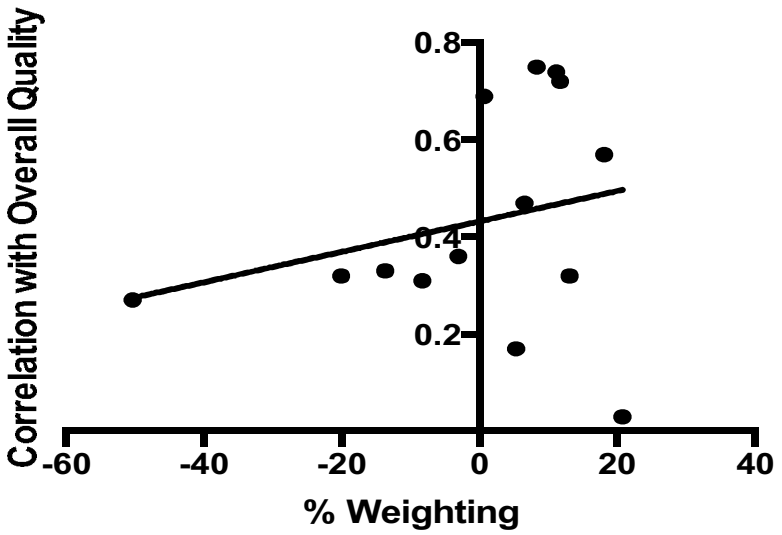
4.3.3.5 Distribution of Record Initial Ranking: Assessed Using Pilot Externally Generated Quality Factors



Skewness	1.949
Kurtosis	4.152

Figure 4.5: Distribution of Record Scores Based Upon Unweighted Scoring

The distribution of record scores assessing the quality factors identified in Section 4.3.2. generated an approximately bi-modal distribution with dominant left-tail. Overall, this analysis supports previous observations [Section 2.6] pertaining to the overall poor quality of risk:benefit appraisal methodologies utilised. There was a small decrease in the number of records scoring greater than 50% (n=5).



	% Weighting vs. Correlation with Overall Quality
Pearson r	
r	0.2562
95% confidence interval	-0.3176 to 0.6926
R squared	0.06562
P value	
P (two-tailed)	0.3767
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	14

Figure 4.6: Evaluating the Correlation between Individual Quality Factors and Overall Record Scores

There was a positive, but not statistically significant, correlation between the impact of specific individual quality factors on the overall score generated. The extent of the positive correlation between specific quality factors weighted using cumulative stakeholder pilot data was higher than that of the previous unweighted data [FIGURE 3.8] .

The greatest correlation between specific factors and the overall record score generated remained, as per Figure 3.10., the presence of a pre-defined risk:benefit index. However, a disparity to the previous data was the significant importance attributed to consistent units of risk and benefit respectively.

4.4 Discussion

The expert elicitation pilot study was designed to provisionally assess inter- and intra-stakeholder attitudes towards the relative importance of quality factors impacting the effectiveness of risk:benefit appraisal methodologies. Where possible, the study also aimed to evaluate response uncertainty.

Overall, the technique was executed effectively and not problematically, increasing the specificity and relevance of the prototype scorecard by more effectively weighting the quality factors assessed. Consequently despite the modest number of respondents (n=5), the quality factor weightings generated changes the overall distribution of risk:benefit appraisal assessments conducted, including in some cases changes in the ranking of individual studies.

4.4.1 Pilot Expert Elicitation Study: Cumulative Externally Generated Quality Factor Weightings

The cumulative quality factor weightings – equally representing the views of all stakeholders surveyed – generated a range of outcomes, and clearly indicate inter-stakeholder heterogeneity in the relative importance of the quality factors assessed. The greatest vector difference generated [-50.37%] was for the relative importance of the “Number of Statistical Techniques” utilised in the evaluation of risk:benefit.

Superficially this is unsurprising, as the number of statistical methods is axiomatically not equivalent to the quality of the overall outcome – and in some cases can contribute to the diminished quality and accessibility of the outcome. However, a number of public consultations evaluating risk:benefit appraisal best practices concluded the need for multiple statistical techniques to support mixed methods analysis and validation. Therefore, based upon this pilot study, some public guidance is not fully representative of inter-stakeholder attitudes (Guyatt et al., 1999).

The need for a clear “Hierarchal Description of Risk:Benefit Appraisal Techniques” utilised received strong endorsement [+20.73%], indicating cross stakeholder need - and potentially frustration – with the range of appraisal methodologies available and limitations in the accessibility of their reporting and thus utility to support decision making. During the earlier systematic review of eligible records [Section 3.0], it was apparent that the majority of records did not provide a clear graphic, analogous to a process flow in engineering, or a PRISMA record flow in systematic reviews (Liberati et al., 2009). Therefore, evaluating the quality and suitability of individual studies was challenging and in some cases simply impossible to reproduce and/or validate.

Some findings were equivocal, for example, the relative importance of a “Clear Indication of Risk:Benefit Analysis” in reported publications and the desire to integrate “Patient Stratification” into Risk:Benefit analysis. Based on the small sample size of respondents it is difficult to draw any substantive conclusions from these particular data points; however given that the quality factor weighting are on a relativistic scale, even equivocal data is important to the validity and representativeness of the final data generated.

The forest plot generated [Figure 4.0.] indicates that a small majority of factors were subject to a positive ‘over-weighting’ by the scorecard based upon the responses of expert stakeholders. No significant decay – or other trend – was detected in responses, such as changes in uncertainty as familiarity with the methodology increased throughout the data collection process.

4.4.2 Pilot Expert Elicitation Study: Externally Generated Quality Factor Weightings Inter-Stakeholder Variance

For ease of reference, brief analysis and discussion of the expert elicitation curves generated to represent inter-stakeholder variance is included in Figure 4.2.

Overall, the expert elicitation curves generated, despite the small sample size (n=5) demonstrated consistency in the grouping of inter-stakeholder responses, in terms of both

the relative importance and uncertainty assessed. The most consistent outlier was the clinical respondent who responded consistently with minimal uncertainty, and attributing a very high importance to a number of factors – in excess of that expressed by other respondents. For example, “Need for Clear Scoring Criteria”, “Highly Quantitative Techniques”, “High Number of Statistical Techniques Utilised”, “Frequency of Risk:Benefit Appraisal”, “Provision for Risk:Benefit Analysis”, “Need for a Hierarchical Description”, and the “Provision of Alternative Treatment Options”.

Given that only a single clinician was surveyed in the pilot it is difficult to draw any firm conclusions from these individual responses, as they may be substantially idiosyncratic. However, clear judgements to overweight particular factors, with minimal uncertainty are apparent trends for this respondent. Further analysis with multiple clinical respondents, followed by the pooling of responses (Minelli et al., 2004), is necessary to more effectively evaluate the impact of these observations.

Other outliers appeared to be more understandably specialism-specific. For example, the epidemiology respondent, whose work would revolve around big data sets in order to elucidate small relative changes, indicating the relative importance of a “Large Number of Study Participants” and “Patient Risk Stratification”. The most consistent inter-stakeholder uncertainty pertained to the requirement for “Highly Quantitative Outcome Measures”. Participants’ verbal observations during responses to this question were centered around most stakeholders acknowledging the ideality, but impracticality, of purely quantitative patient outcome measures, in particular with regard to patient reported outcomes (PROMS) (Kushner et al., 2008).

In all responses the regulatory subject exhibited a high degree of uncertainty, and provided the only absolutely uncertain response in the entire pilot – all twenty one counters placed horizontally across the x-axis, describing no relative weighting to the factor presented. The response in question pertained to the “Consistency of Risk:Benefit Units,” with significant

uncertainty also represented for clinicians and industrialists. Conversely, minimal uncertainty was present for epidemiologist and basic scientists.

Therefore, based upon the data captured, it would appear that the stakeholders 'closest' to and most deeply involved in the development and adoption of healthcare innovations note their inherent heterogeneity, both in terms of technicality and target patient populations, and thus impracticality of consistent units of risk and benefit. "Patient Risk Stratification" also elicited substantial respondent uncertainty, again most notable amongst stakeholders with the greatest engagement in the product development process.

4.4.3 Pilot Expert Elicitation Evaluation

For all stakeholders and evaluation questions, the majority of responses, quantitative and qualitative, were positive. However, one respondent, the regulator, expressed some confusion with respect to the clarity of the technique. From the responses elicited and in-person observations, this does not appear to have impacted the quality of responses obtained.

The most significant learning from the pilot study evaluation was the differences in verbal responses – both linguistic and paralinguistic. For example, some respondents indicated minimal uncertainty in their non-verbal responses using the expert elicitation data collection grid and counters. Conversely, other respondents, in particular regulators, spent substantial time verbalising and rationalising their responses. In future, it may be valuable to capture this data using a well validated technique to compare versus the non-verbal uncertainty elicited if possible (Presser, 2004).

4.4.4 Record Re-Ranking and Distribution Based on Pilot Expert Elicitation Study

The addition of quality factor weightings to the scorecard reflecting inter-stakeholder attitudes contributed to changes in the distribution of scores obtained. Principally, the

distribution of the quality of risk:benefit appraisal methodologies increased, with the net difference in scores between higher and poorer quality studies increasing.

One unexpected observation is the bimodal nature of the distribution of record scores generated [Figure 4.5]. Statistical analysis confirms that the curve is not the product of two normal distributions [Ray and Lindsay Test: $d \leq 1$]. The reason(s) for this observation are unclear. However, in the absence of significant differences in the structure and/or content of studies comprising the two groups, the phenomenon can most likely be attributed to a large number of studies scoring towards the lower bound of the 40-49% interval in the unweighted scorecard, now being moved into the upper bound of the 30-39% interval in the weighted scorecard Further investigation with a larger sample size of expert stakeholders will be required to evaluate and understand these differences more fully.

The correlation between the relative importance attributed to quality factors by participants in the pilot study increased in significance [Figure 4.6] compared to the unweighted scorecard [Figure 3.10]. Again while the data set is not amenable to demonstrating a statistically significant correlation, the finding does indicate that the precision of the scorecard – the specificity of individual quality factor assessment metrics to overall quality outcomes – is superior in the weighted versus unweighted scorecard.

4.5 Limitations

The principal limitation of this pilot expert elicitation study is the small sample size of stakeholders (n=5). This limitation is not significant in the context of the pilot which successfully validated the suitability of expert elicitation as a technique to systematically determine relative quality factor weightings that are representative of inter-stakeholder viewpoints. However, a larger study with a greater number of stakeholder types and individual stakeholders within those groups is required.

Expert elicitation typically only requires n~5 respondents to generate a statistically significant curve. This is principally due to each question response representing twenty one mutually relative data points. Thus an n~5 represents in excess of one hundred inter-dependent data points, however to elicit statistically significant intra-stakeholder trends, n~5 of each stakeholder type must be recruited for the expanded study.

A major challenge identified was related to data blinding. It became apparent that if the data from previous respondents was analysed prior to conducting the assessment with future respondents there was a potential for the interviewer to 'lead' respondents and thus bias the data obtained. Consequently, all data in the final study will be blinded until all responses have been obtained.

As the familiarity of the interviewer with the data collection technique and experimental protocol increased there is likely to have been a difference in the quality of protocol description and conduct to participants. No major problems were identified by the participant evaluation. It is hoped that this learning curve did not substantially compromise the data obtained. However, in either instance, the interviewer acquired a robust and consistent baseline competency level through this exercise prior to the larger study.

4.6 Conclusion

The pilot study confirmed that expert elicitation is an appropriate technique to evaluate inter- and intra-stakeholder heterogeneity pertaining to the relative importance of quality factors in the risk:benefit appraisal of healthcare innovations. This is supported by a significant difference between the unweighted and weighted scorecard rankings.

A larger study with a greater range of stakeholder groups represented and an increased number of individual stakeholders per group, is required to robustly validate the scorecard quality factor weightings. Additionally, if possible, an assessment of the effect of non-verbal

versus verbal [paralinguistic] uncertainty would be of academic interest to further validate the tool's usefulness.

These findings support the initial hypothesis, and contribute to the overall research question: "Can we make risk:benefit assessment objective, transparent and broadly representative of all stakeholder requirements?" This early pilot evidence leads towards the affirmative, yet a more thorough study will confirm and further tune the practicability of the technique.

Chapter 5

Assessing the Relative Importance of Risk:Benefit Appraisal Quality Factors

5.1 Introduction

The expert elicitation pilot study successfully validated the prototype risk:benefit appraisal scorecard; and contributed provisional improvements to the weighting of specific quality factors to maximise its specificity and the accuracy to which it represents the consensus viewpoint of multiple stakeholders in healthcare translation. A larger study was conducted to robustly validate the quality factor weightings obtained (Sutton et al., 2005).

Expert elicitation curves exhibit a smoothing effect after approximately n=5 responses (Powell, 2011). Therefore, strict respondent inclusion criteria were applied to ensue that the quality of all respondents was maximised. Given the relatively modest intra-stakeholder sample size required to generate statistically significant data, breadth and greater representativeness was contributed to the study by increasing the number of stakeholders surveyed from n=5 in the pilot to n=10 in the full study. Therefore, n=6 respondents were sought per stakeholder group, with an additional respondent to add richness to the data set and mitigate against the risk of significant anomalies. Thus the total number of respondents across all stakeholder groups in the full study was n=60.

5.1.1 Hypothesis

There is significant inter and intra-stakeholder heterogeneity in the relative importance of quality attributes in the risk:benefit appraisal methodologies as demonstrated a though an full expert elicitation pilot study assessing the criticality of defined quality factors in risk:benefit appraisal methodologies.

5.1.2 Aims and Goals

i. To evaluate a representative selection of inter and intra stakeholder attitudes to critical quality factors impacting the effectiveness of individual risk:benefit appraisal methodologies
ii. Evaluate and refine quality factor weighting generated by the expert elicitation pilot
iii. Assess inter and intra stakeholder response strength and uncertainty

5.2 Materials and Methods

Full details of the expert elicitation materials and methods are reported in Section 4.2 Herein, to avoid duplication, only modifications to the pilot protocol are stated.

5.2.1 Stakeholder Selection

The following stakeholders were selected for assessment Table 5.0 subject to the strict inclusion and exclusion criteria outlined Table 5.1.

Pilot and Full Study	Full Study Only
Regulator	Healthcare Risk Management Experts
Clinician	Engineer
Statistician	Lay
Industrialist	Clinical Trial Co-Ordinator
Basic Scientist	Epidemiologist

Table 5.0: Stakeholders Assessed in Full Expert Elicitation Study

Stakeholder	Inclusion Criteria	Exclusion Criteria
Basic Scientist	- Educated to at least a PhD level in a basic science discipline - Actively engaged in laboratory based basic science research and/or has responsibility for managing a team of basic scientists	- Clinician- scientists - Non-'pure' and/or non-biomedical PhD holders - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools - Those with past and/or current significant involvement in clinical trial design and/or management
Clinician	- Completed a recognised medical degree - Has at least a basic level of experience in clinical trial design and/or management - Currently practicing in a recognised healthcare organisation	- Clinician- scientists - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools
Statistician	- Holders of a recognised regulatory and/or educational certification	- Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools - Individuals who have significant experience in developing and/or operating (bio)medical risk:benefit tools
Regulator	- Current and/or past holders of positions in international national competent authorities - Holders of a	- Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing

	recognised regulatory certification e.g. RAC, FTOPRA	risk:benefit analysis tools - Individuals with experience solely in cost-effectiveness assessment(s) e.g. NICE
Industrialist	- Actively involved in investment and/or development of biomedical technologies - Private 'financially orientated' organisations e.g. venture capital and/or with experience in developing and managing corporate strategic partnerships e.g. at a major (bio)pharmaceutical company - Basic understanding of drug and/or device development pathways	- Purely academic practitioners - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications - Individuals engaged solely in assessing regulatory compliance e.g. maintaining statutory capital requirements
Epidemiologist	- Holders of a recognised regulatory and/or educational certification in public health and/or epidemiology e.g. MPH	- Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications - Individuals who have significant experience in developing and/or operating (bio)medical risk:benefit tools
Healthcare Risk Management 'Experts'	- Published biomedical risk:benefit related	- Practitioners focused solely in non-systematic

	research recognised academic journals - And/or holder of an existing academic and/or industrial position in (bio)medical risk:benefit analysis - Basic understanding of drug and/or device development pathways	and/or non-quantitative risk perception research - Practitioners focused exclusively on cost-benefit/ effectiveness and/or benefit: harm research. - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications
Engineer	- Completed a recognised engineered degree, accredited by the appropriate professional body e.g. Institution of Chemical Engineers (IChemE) - Basic understanding of drug and/or device development pathways	- Practitioners focused solely in non-systematic and/or non-quantitative risk perception research - Practitioners focused exclusively on cost-benefit/ effectiveness and/or benefit: harm research. - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications
Statistican	- Published biomedical risk:benefit related research recognised academic journals - Recognised statistical training e.g. degree and/or	- Practitioners focused solely in non-systematic and/or non-quantitative risk perception research - Practitioners focused exclusively

	professional designation e.g. CStat - understanding of drug and/or device development pathways	on cost-benefit/ effectiveness and/or benefit: harm research. - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications
Clinical Trial Co-Ordinator	- Lead co-ordinator of a recognised clinical trial within the past three years. - Basic understanding of drug and/or device development pathways	- Practitioners focused solely in non-systematic and/or non-quantitative risk perception research - Practitioners focused exclusively on cost-benefit/ effectiveness and/or benefit: harm research. - Practitioners who have a financial stake of greater than $10,0000 in entities developing and/or providing risk:benefit analysis tools –with significant (bio)medical applications

Table 5.1.: Proposed Respondents in Full Expert Elicitation Study and Proposed Inclusion and Exclusion Criteria

5.2.2 Changes to Pilot Study Design

a. The order of questions presented to respondents was randomised.

b. Additional background information pertaining to the risk:benefit appraisal of healthcare innovations was included in presentation.

c. All responses were blinded until the full sample (all stakeholder groups) had been assessed.
d. Minor grammatical amendments were made to the presentation to improve clarity
e. To avoid demographic biases an equal number of male and female respondents were recruited in each stakeholder group
f. The type of counters used in the study were changed to increase the ease of response making
g. Where practicable, intra-stakeholder response environments were controlled
h. All responses were given a unique and anonymous identification code

5.2.3 Synthesis of Collected Data

Full details of techniques used to synthesise the collected data are reported in Section 4.2.2.1. Only modifications to the pilot protocol are stated herein.

5.2.3.1 Combining Intra and Inter Stakeholder Probability Distributions and Weightings

$$Cumulative\ Adjusted\ Average\ ([z]) = \sum_{n+1}^{n} Adjusted\ Intra-Stakeholder\ Adjusted\ Averages\ (z)$$

Equation 5.1

5.2.3.2 Inter-stakeholder Variance Probability Distribution and Weightings

$$Cumulative\ Weighted\ Average\ ([\phi]) = \sum_{n+1}^{n} Adjusted\ Intra-Stakeholder\ Cumulative\ Weighted\ Averages\ (\phi)$$

Equation 5.2

$$Cumulative\ Weighting\ ([b]) = \sum_{n+1}^{n} \%\ Weighting\ (b)$$

Equation 5.3

$$\%\ Net\ Weighting\ (\omega) = \left[\%\ Weighting\ (b) - \left(\frac{100}{\text{No. of Factors Assessed } (\upsilon)}\right)\right]$$

$$Cumulative\ Net\ \%\ Weighting\ ([\omega]) = \sum_{n+1}^{n} \%\ Net\ Weighting\ (\omega)$$

Equation 5.4

$$Net\ Weighting\ \%\ Difference\ (\tau) = \left[\left(\frac{\%\ Net\ Weighting\ (\omega)}{\left(\frac{100}{\text{No.of Factors Assessed } (\upsilon)}\right)}\right).\ \frac{100}{1}\right]$$

$$Cumulative\ Net\ Weighting\ \%\ Weighting\ ([\tau]) = \sum_{n+1}^{n} Net\ Weighting\ \%\ Difference\ (\tau)$$

Equation 5.5

5.2.3.3 Inter-stakeholder Variance Impact on Record Ranking

$$Cumulative\ Weighted\ Record\ Ranking\ ([\mu]) = \sum_{n+1}^{n} Cumulative\ Weighted\ Record\ Ranking\ (\mu)$$

Equation 5.6

5.3 Results

5.3.1 Expert Elicitation Study: Externally Generated Quality Factor Weightings Intra-Stakeholder Variance

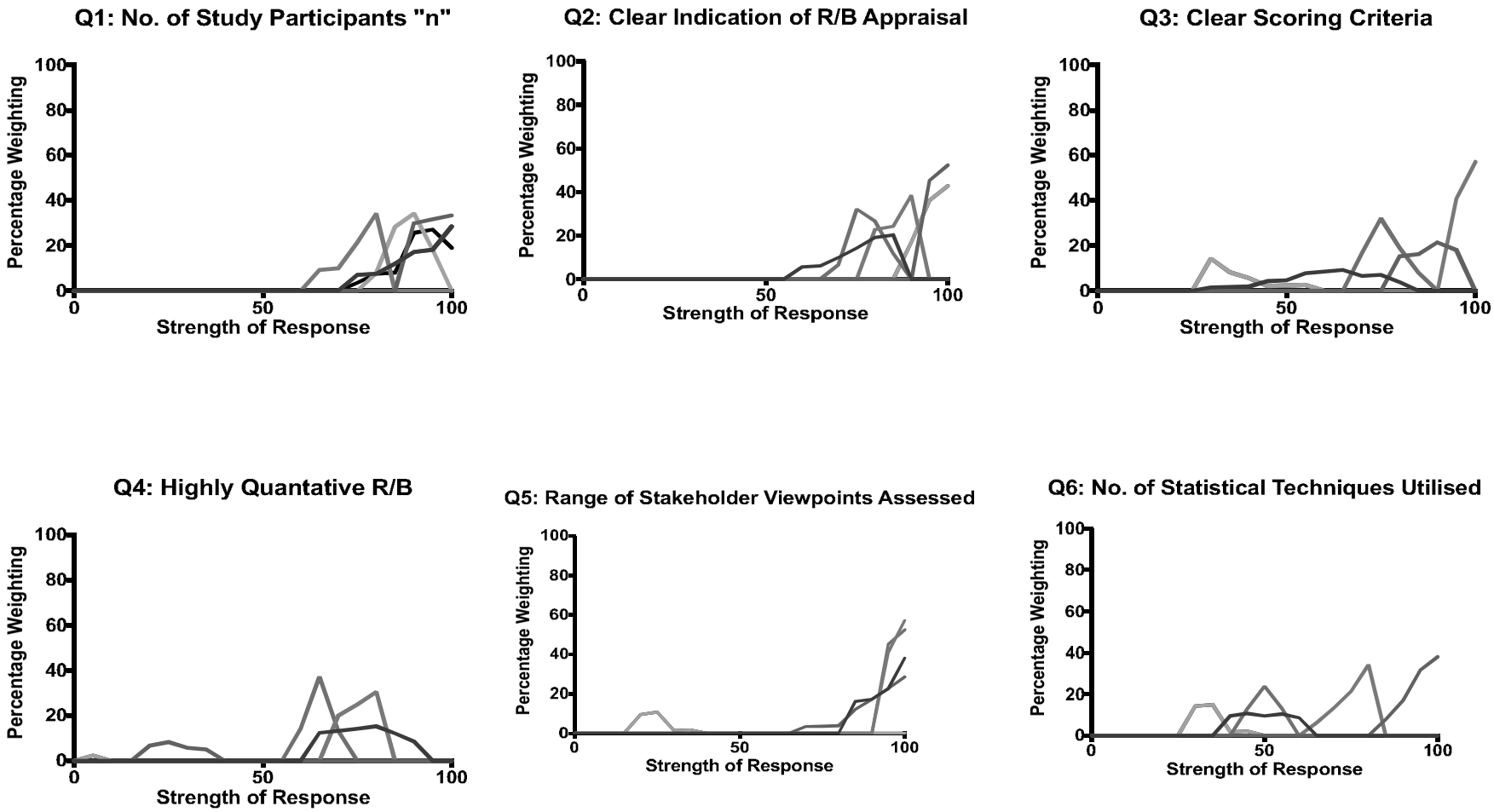
5.3.1.1 Lay Respondents

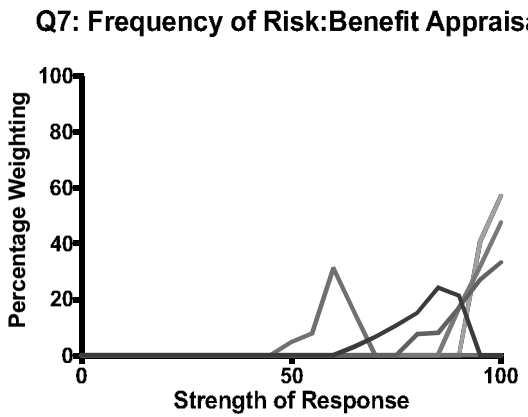
Overall, for all questions, the lay respondents showed excellent grouping; particularly, given the heterogeneous backgrounds of the group. Uncertainty expressed was consistent amongst respondents. However, Respondent 3 [blue] consistently responded with greater uncertainty than his peers.

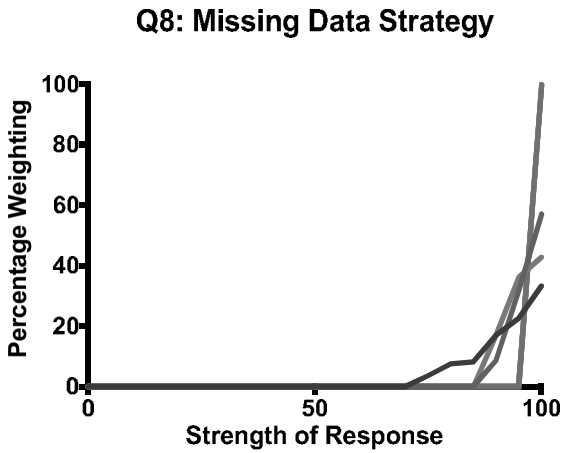
Some technical nuances of questions; for example, pertaining to statistical analysis techniques utilised in RCTs were obviously unfamiliar to some respondents. This is reflected in said question with responses grouped around 50% with high uncertainty.

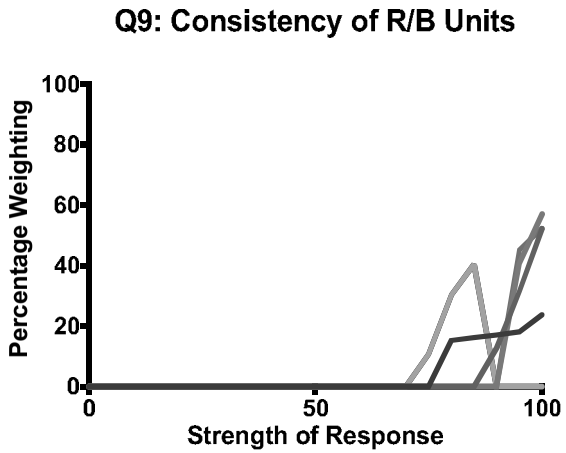
The clearest trend observed, shared by all respondents was the need for a clear hierarchal description of the risk:benefit appraisal methodology utilised to aid potential patients in assessing treatment options. The “impenetrability” of clinical studies published in open access journals, and thus freely available, was referenced verbally by one respondent.

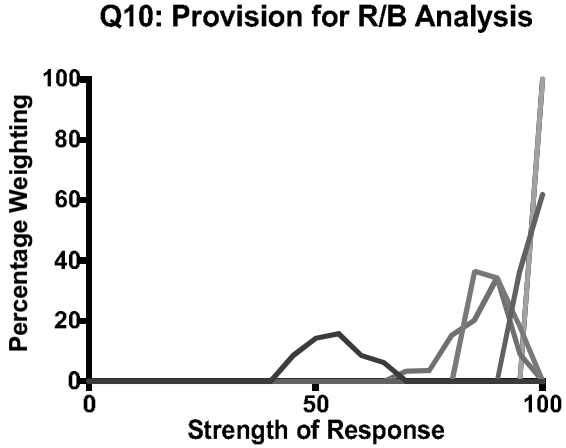
Figure 5.0: Lay Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

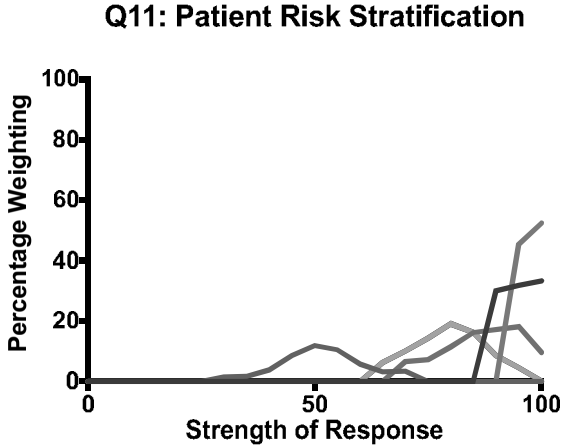


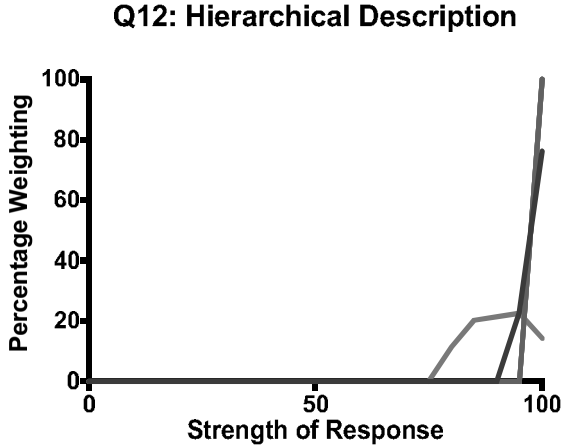

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

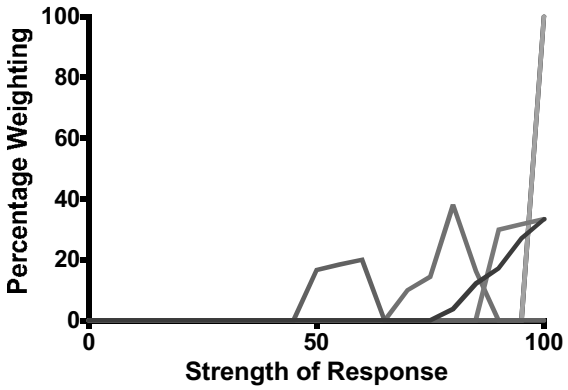

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

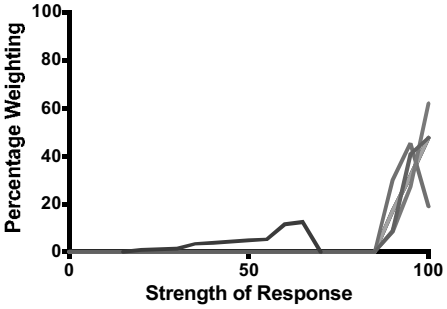

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



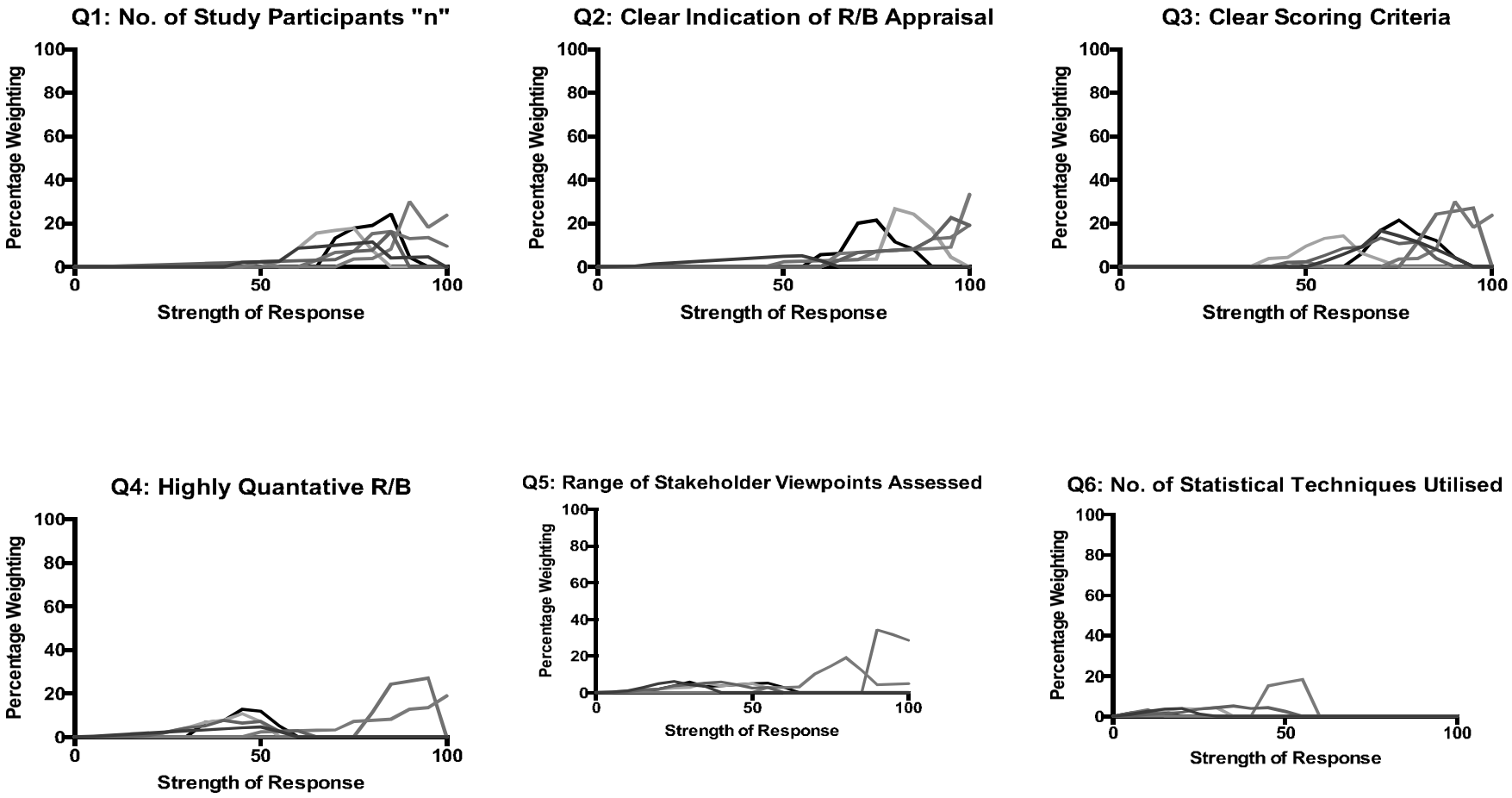
5.3.1.2 Regulatory Respondents

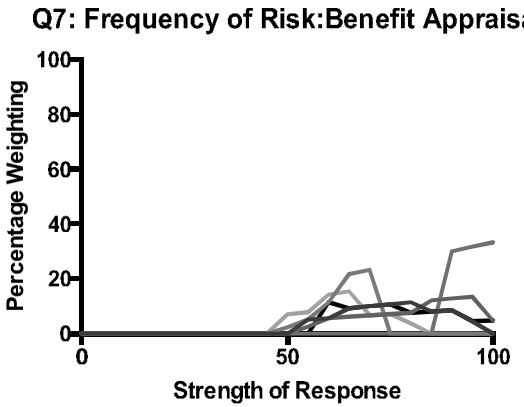
Regulatory respondents exhibited extraordinarily good grouping in most questions. In particular, for questions evaluating structural aspects of clinical trials, from which data is generated to support risk:benefit appraisal. Two respondents, Respondent 2 [purple] and Respondent 4 [green] represented occasional outliers. In both cases, neither respondent exhibited significant uncertainty; however, simply had differing opinion(s) on the relative importance of specific quality factors to their peers.

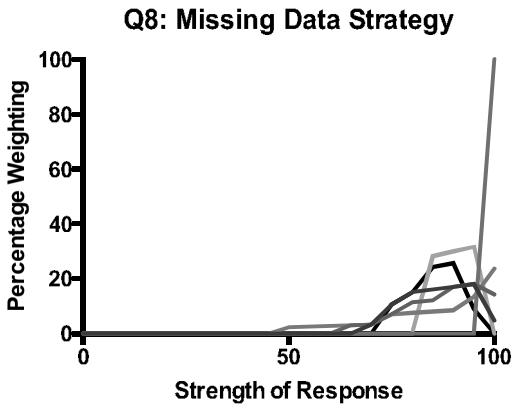
A proportion of increased consistency intra-stakeholder responses for regulators versus the lay control group can be attributed to greater homogeneity in the technical understanding and experience of respondents. However, the stakeholders were sourced from a range of jurisdictions (UK, Germany, US and South Korea); specialities (device, therapeutic and transplant); and academic training (law, medicine, basic science and history).

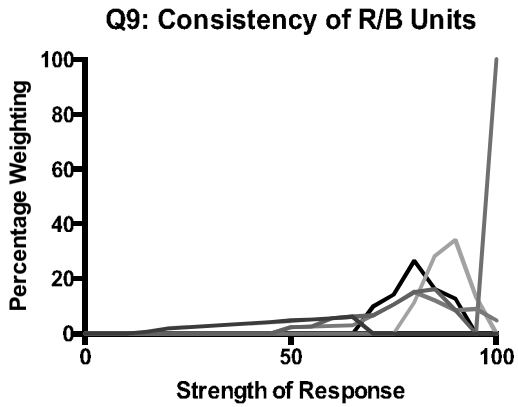
The clear trend is that while the regulatory sample represented similar views with respect to the relative importance of specific quality factors, these were accompanied with a high degree of uncertainty in decision-making. Equivocal responses were obtained pertaining to the “assessment of a range of stakeholder views;” use of highly quantitative outcome measures;” and provision of the risk:benefit profiles of alternative treatment options to permit comparison. One respondent commented that they had not previously considered the publication of comparators alongside recommendations for new interventions.

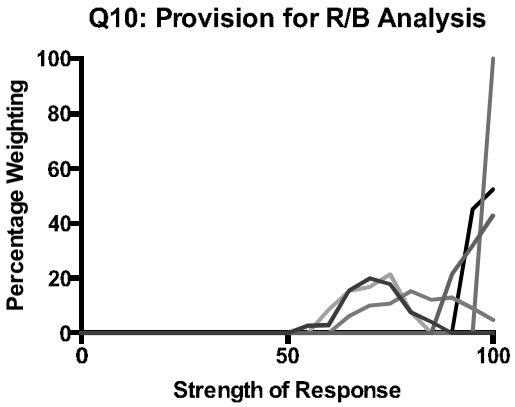
Figure 5.1: Regulatory Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

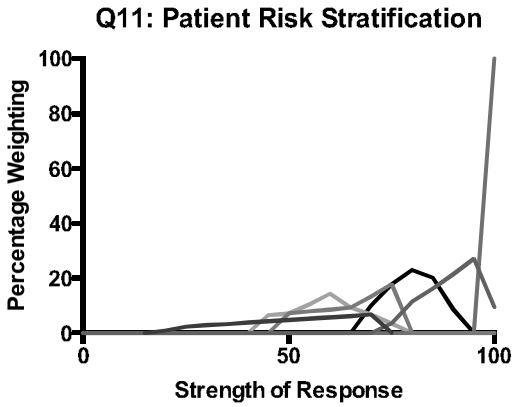


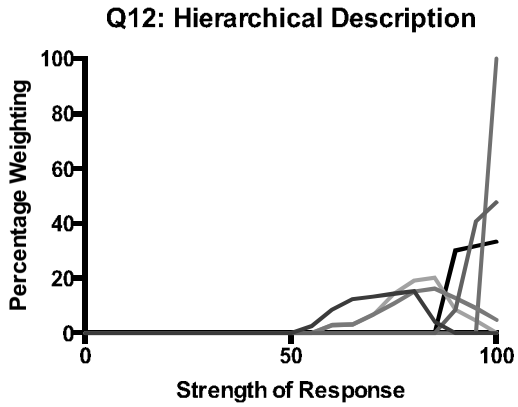

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

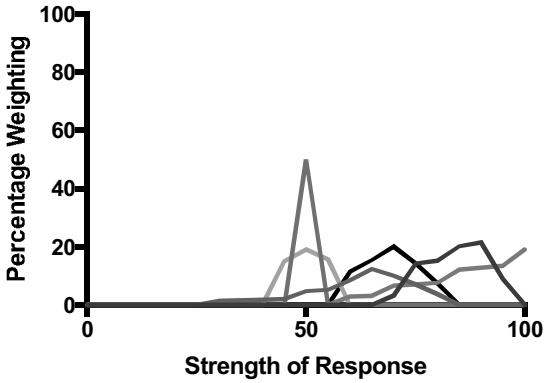

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

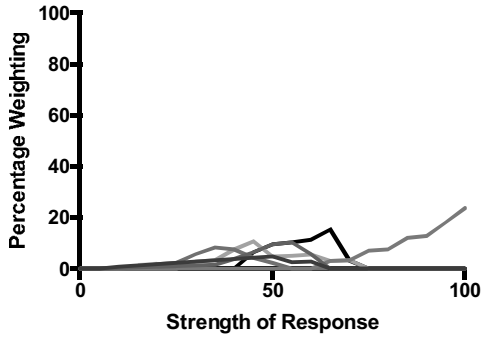

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



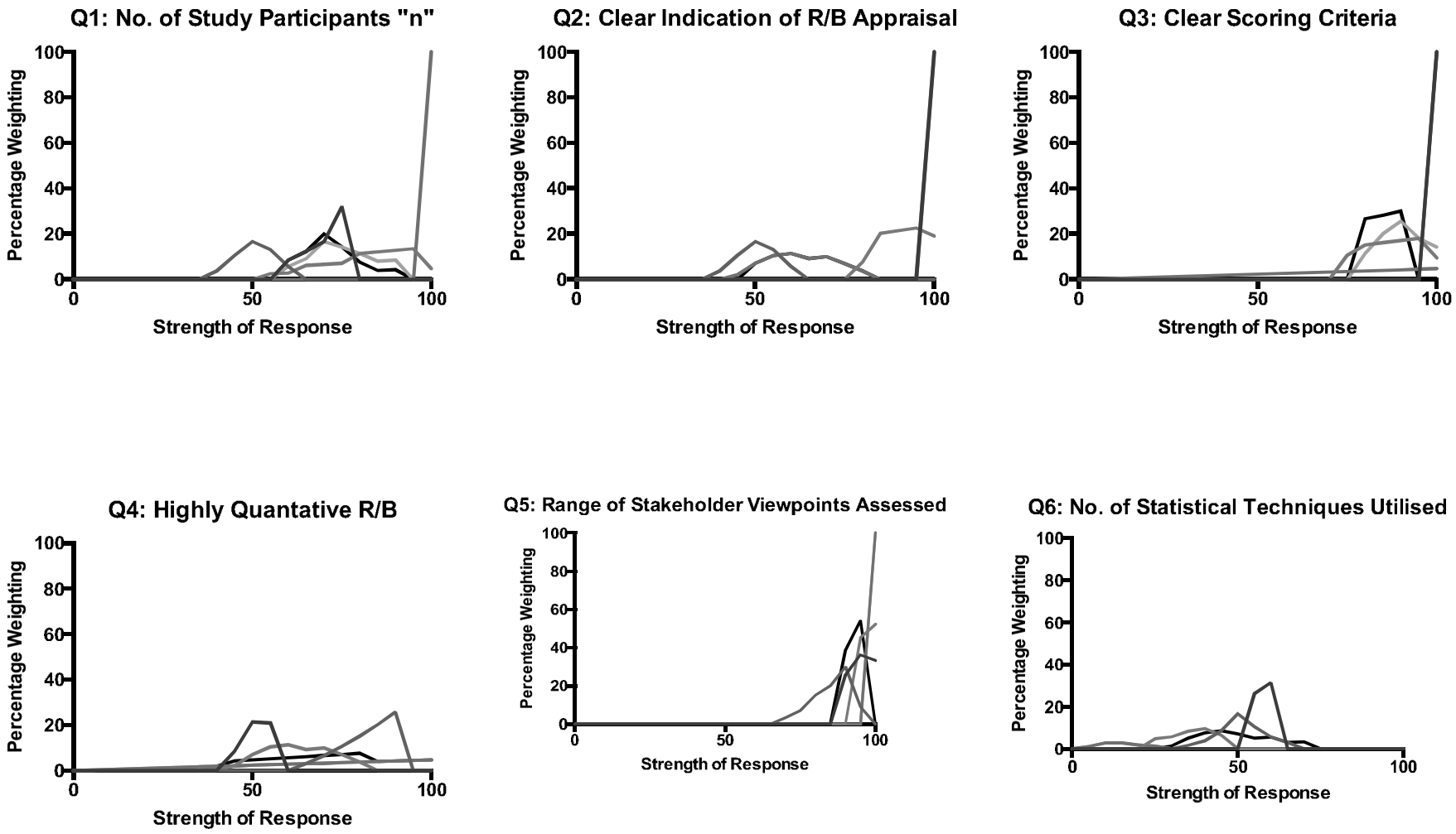
5.3.1.3 Healthcare Risk Management Respondents

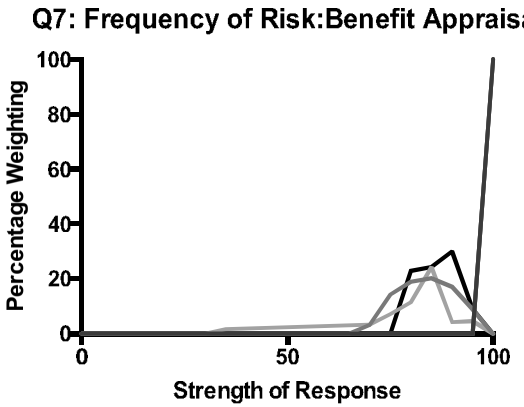
Reasonable; but not excellent grouping was obtained for most respondents. However, response styles varied within the group, with Respondent 3 [blue] exhibiting a high degree of certainty, mostly associated with highly weighted responses. Possible explanation for heterogeneity within this stakeholder group is that unlike for most other respondents, some healthcare risk management respondents were familiar with the technique of expert elicitation and as such were answering in a different style – “Type 1” versus “Type 2.”

Significant uncertainty and heterogeneity was exhibited in responses regarding the presence of “Missing data strategies.” One respondent, Respondent 1 [Red] demonstrated absolute uncertainty when assessing the importance of “consistent risk:benefit units.”

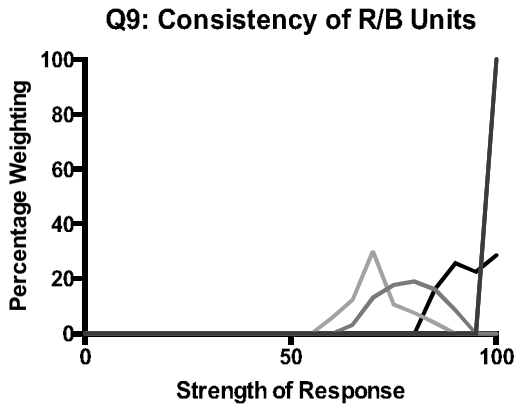
A clear and uniform preference was observed for methodologies that assess a range of stakeholder viewpoints, with multiple respondents referring directly and/or indirectly to the importance of assessing “systems risks” [Section 1.2].

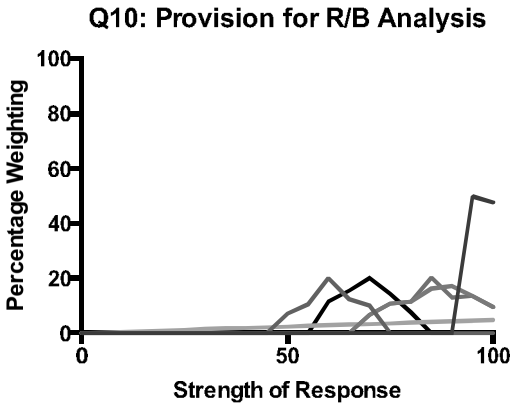
Figure 5.2: Healthcare Risk Management Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

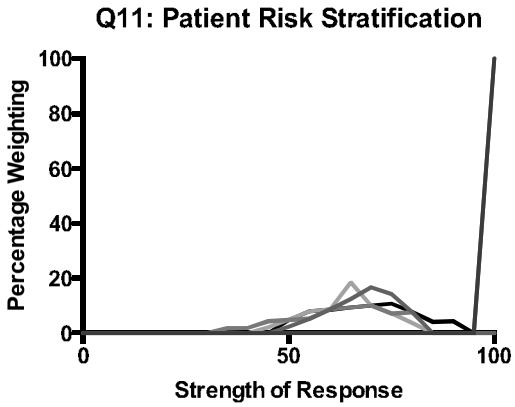


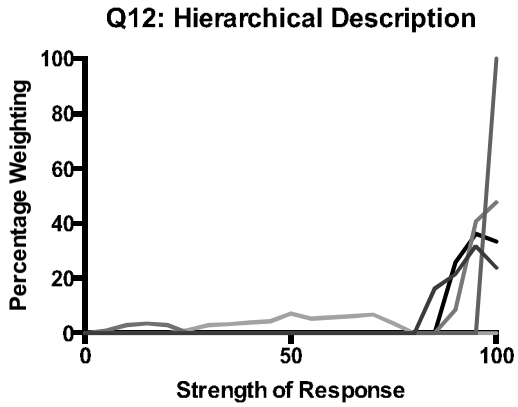

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

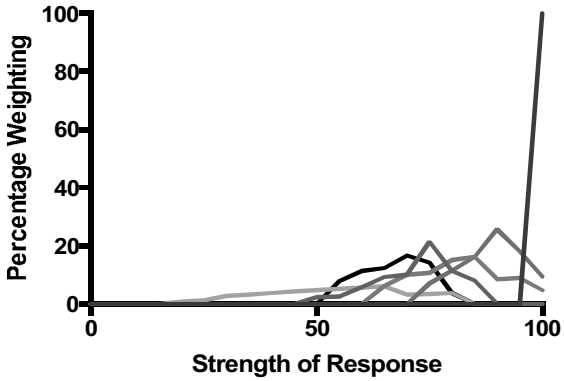

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

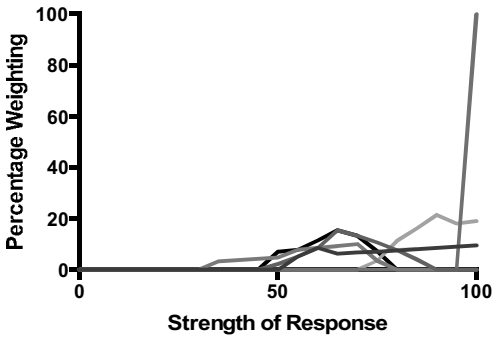

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



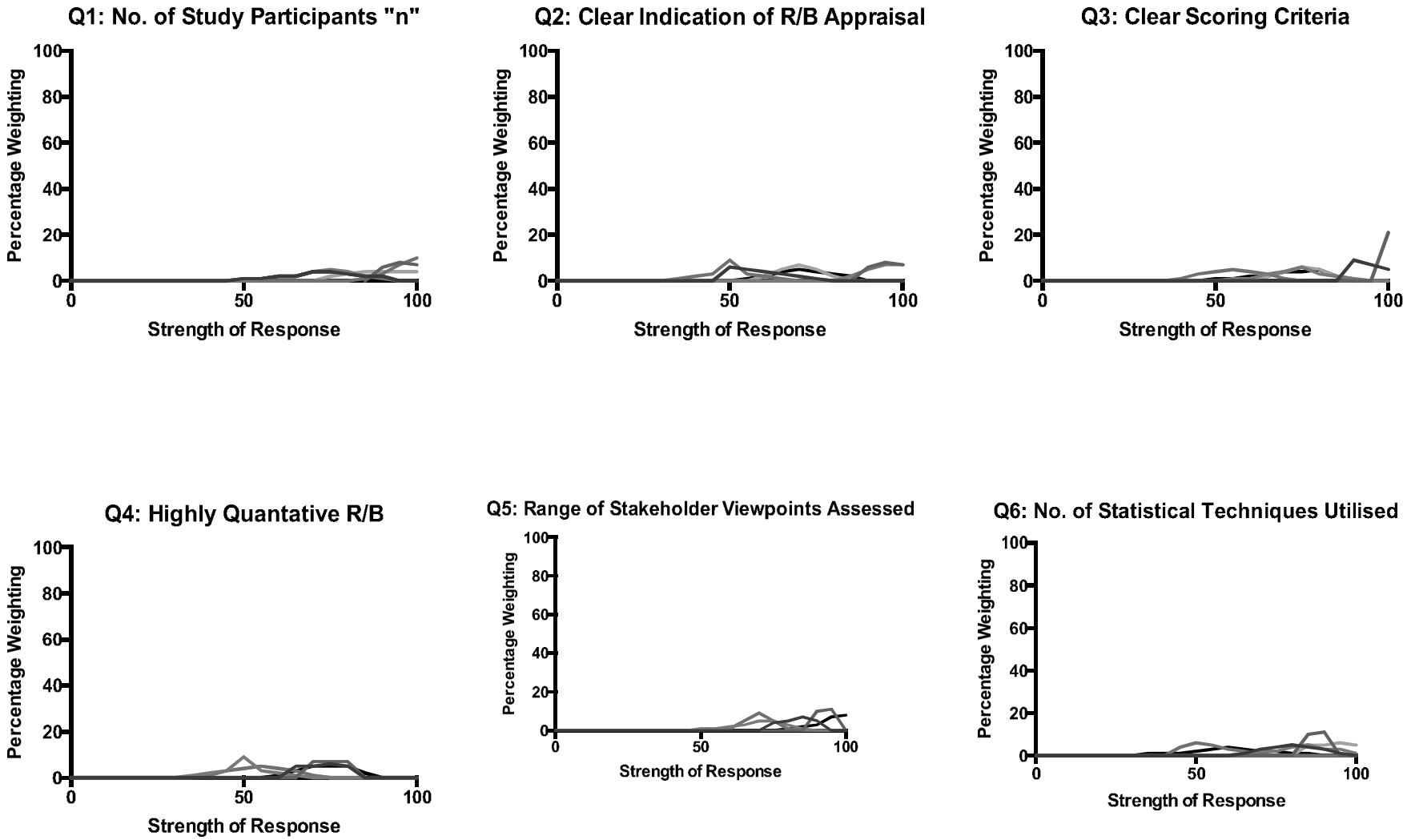
5.3.1.4 Basic Scientist Respondents

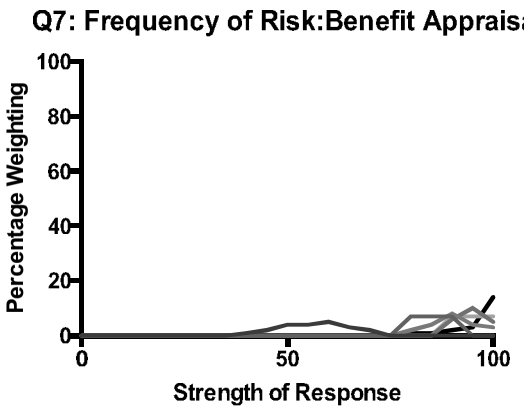
Basic scientists were one of the most significant and consistent outliers of stakeholders surveyed, exhibiting high uncertainty in the assessment of every quality factor. Respondent 1 [red] occasionally demonstrated more certainty than his peers; however, this was not significant.

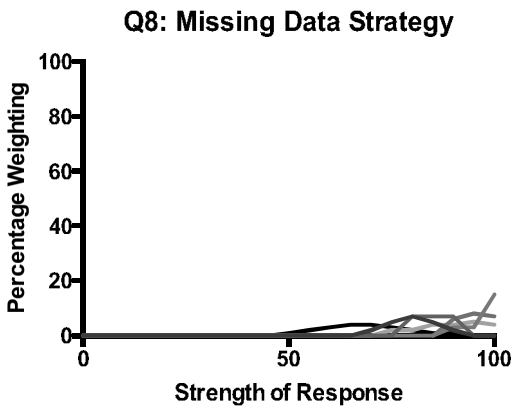
While not immediately obvious from the data collection process, given the consistently high uncertainty and equivocal trend in responses, it is possible that the basic scientists had a limited and/or uniformly biased understanding of risk:benefit appraisal and/or clinical trials.

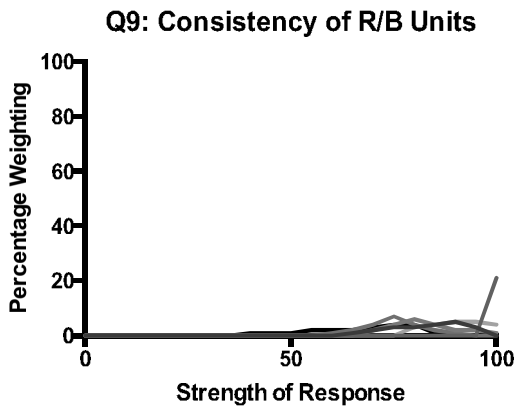
Perhaps unsurprisingly, basic scientists showed a strong desire for statistical features of risk:benefit analyses, including the “number of study participants,” number of statistical techniques used” and the “frequency of risk:benefit appraisal.” Significant verbal uncertainty was also observed amongst basic scientist respondents.

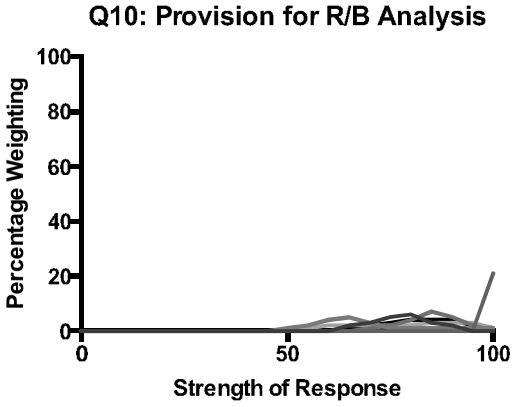
Figure 5.3: Basic Scientist Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

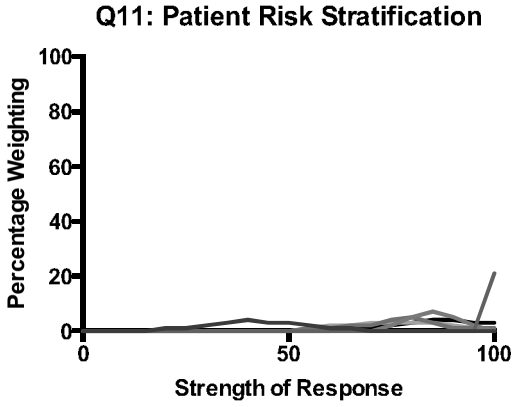


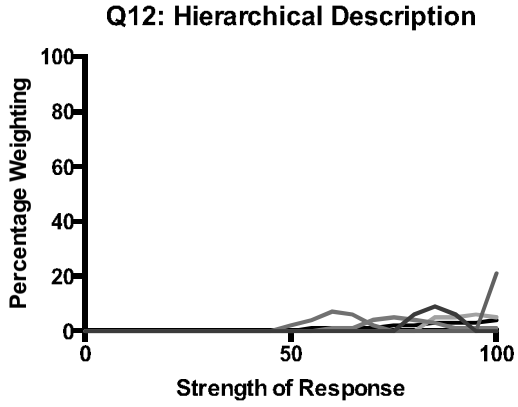

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

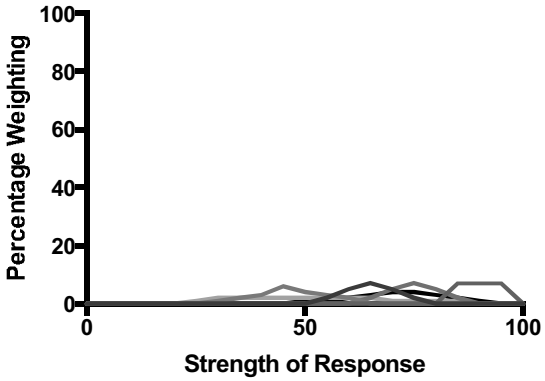

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

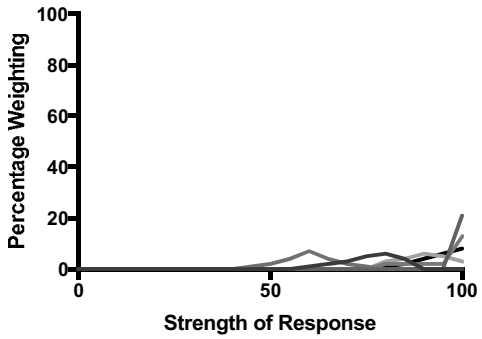

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



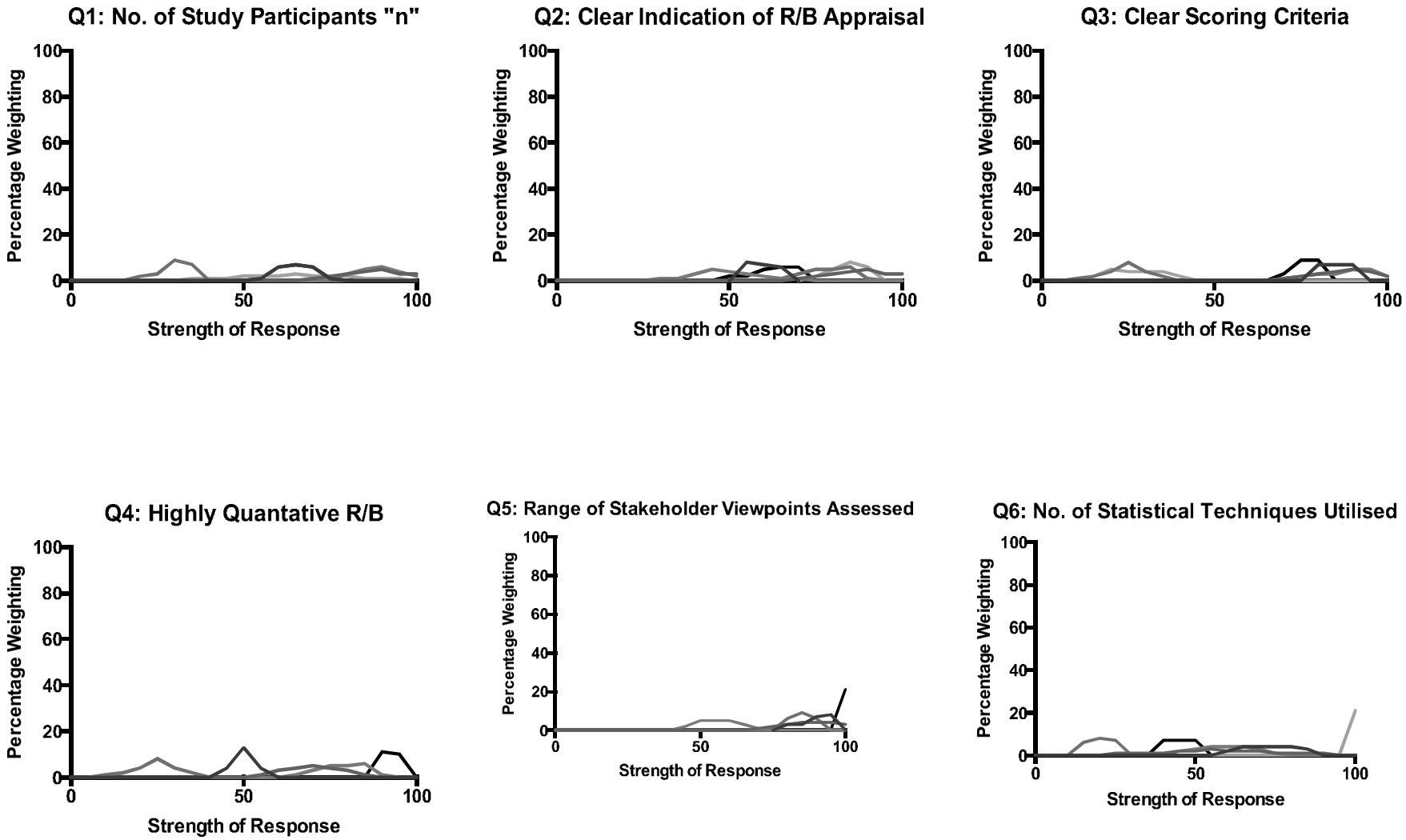
5.3.1.5 Engineering Respondents

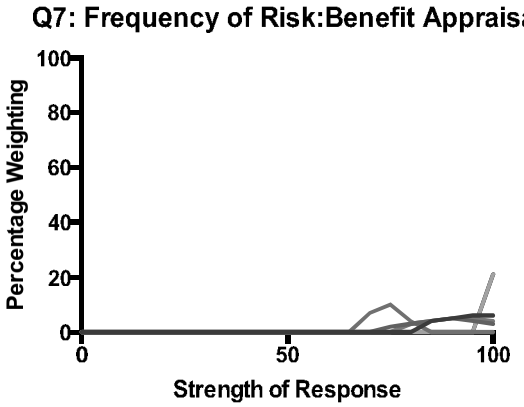
As expected, given the breadth of engineering as an academic discipline and professional practice, significant heterogeneity and uncertainty was present in some responses. However, this was not uniform for all quality factors assessed. For example, some types of statistical analysis skills are common to all types of engineering training and the evaluation of clinical trials.

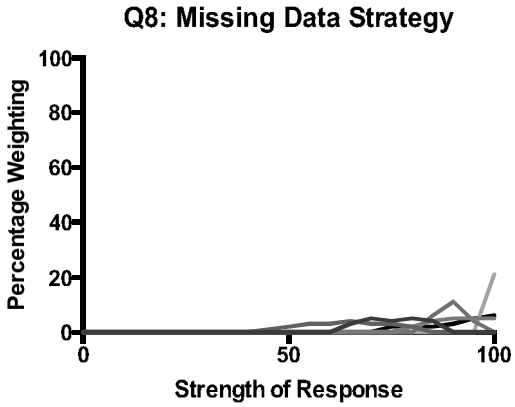
Technical details pertaining to patient as opposed to process outcomes measures were unfamiliar to respondents, contributing to high uncertainty and a distribution of response weightings for questions assessing “clear scoring criteria;” highly quantitative assessment methods;” and “patient risk stratification.

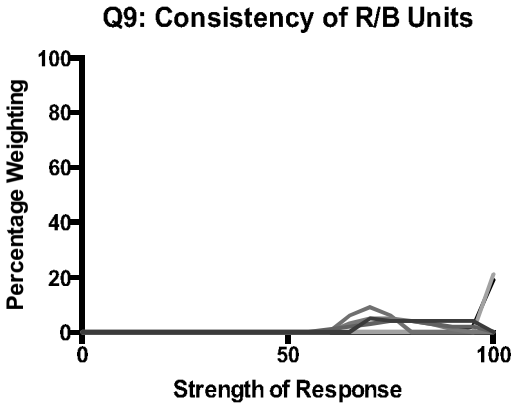
The most conclusive, consistent and tight grouping demonstrated strong preferences for a high “Frequency of Risk Benefit Appraisal” and the *ex ante* “provision for risk:benefit analysis” in the study design. Surprisingly, there was only a modest positive preference for a “hierarchal description” of the risk:benefit appraisal utilised. When I did an engineering degree everything was presented in a hierarchical process flow!

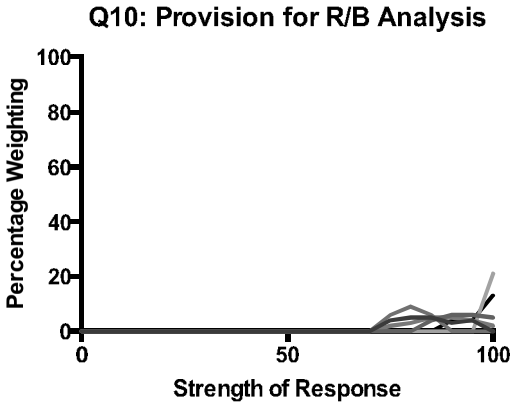
Figure 5.4: Engineering Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

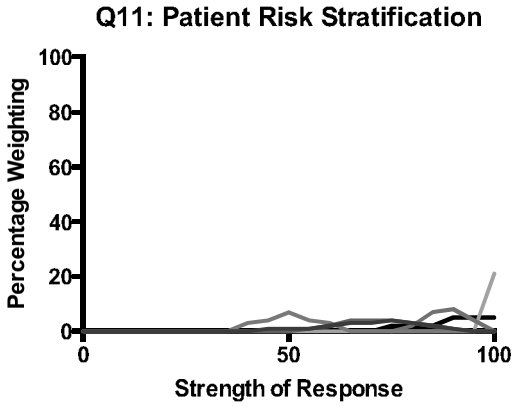


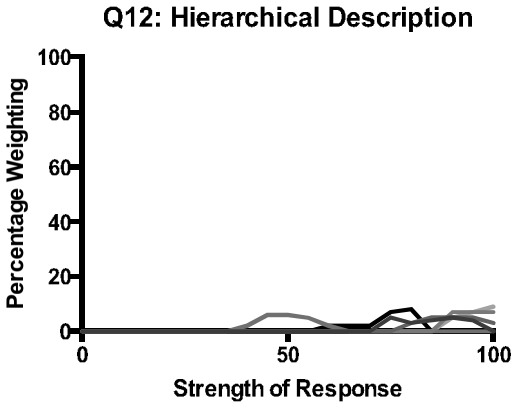

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

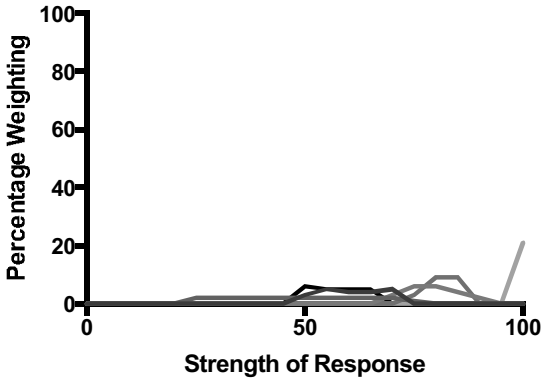

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

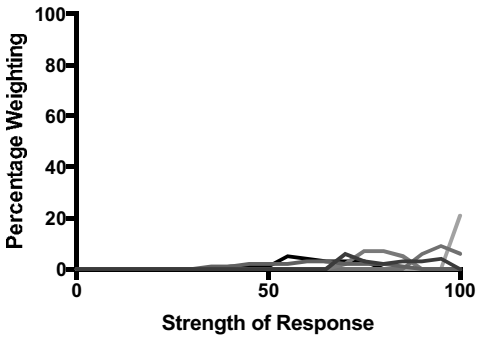

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison

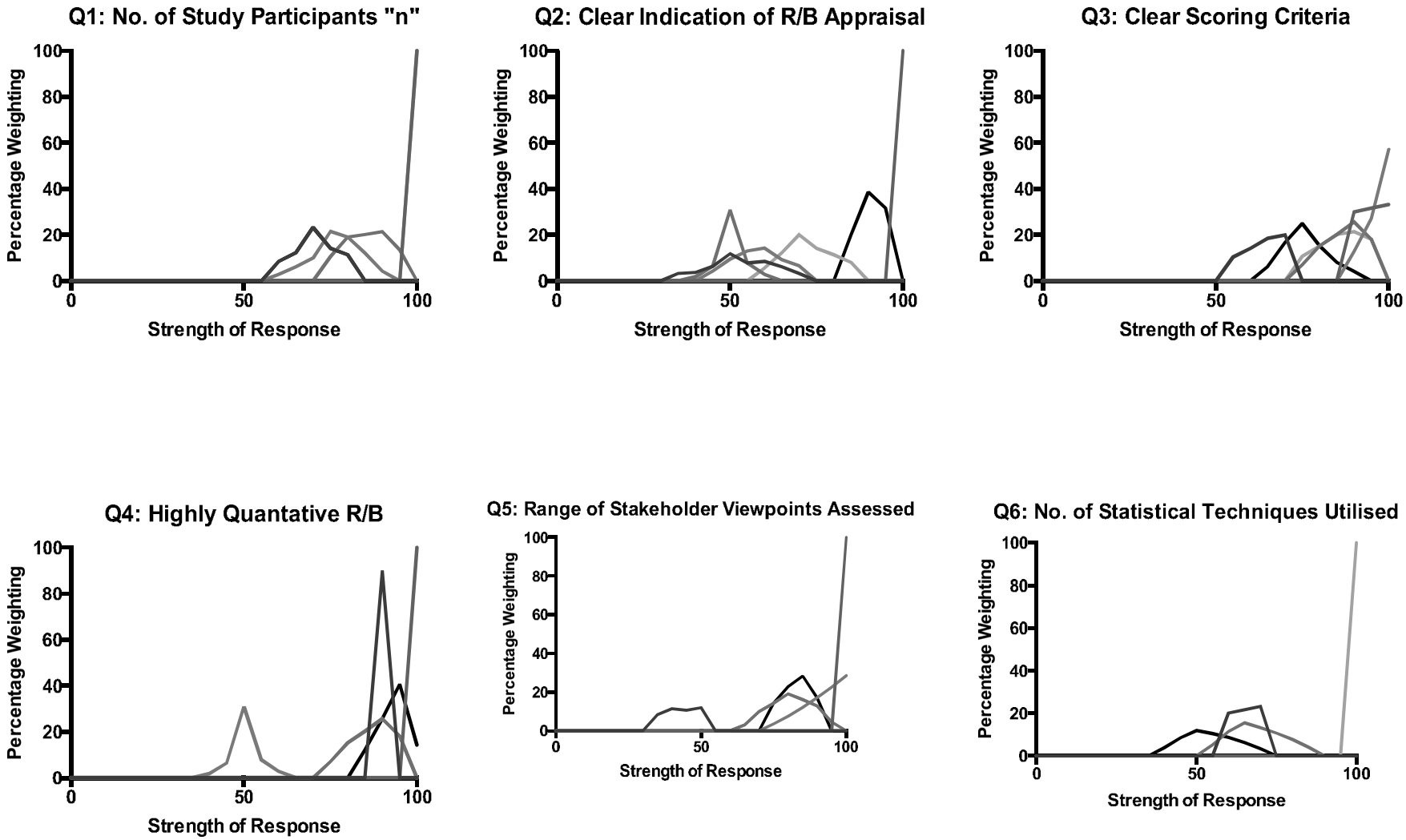


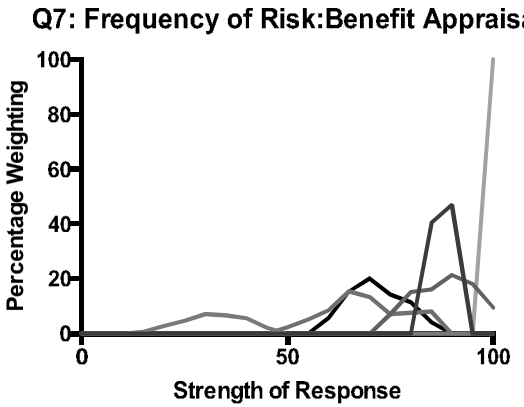
5.3.1.6 Statistician Respondents

Statistical stakeholders assessed had yielded data with a number of unique attributes compared to other stakeholders; principally, responses with high variability in strength and consistent uncertainty. Additionally, every statistical expert surveyed represented an outlier versus their peers for at least one of the quality factors assessed.

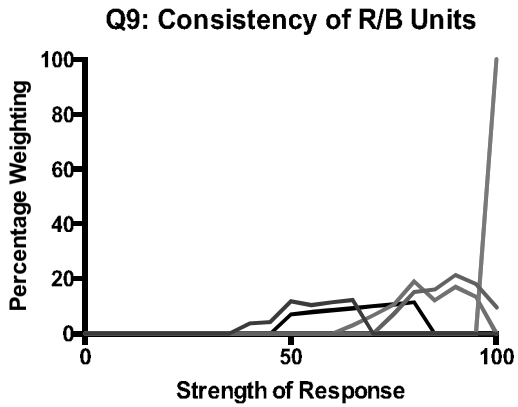
In all cases, the direction of the preferred relative importance – positive or negative – was uniform amongst the group. However, the only quality factors assessed with significant consistency in the strength of responses obtained expressed a strong positive preference for the publication of “comparators” alongside risk:benefit appraisal of candidate healthcare innovations and a “hierarchical description” of the method applied.

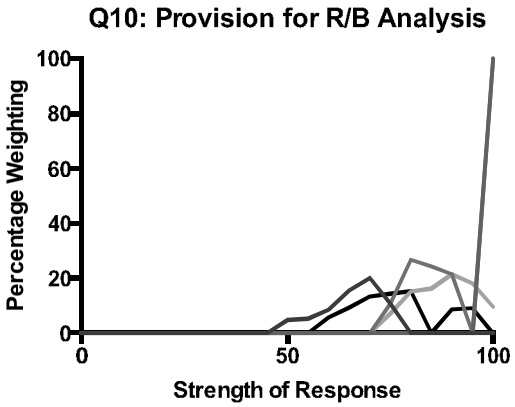
Figure 5.5: Statistician Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

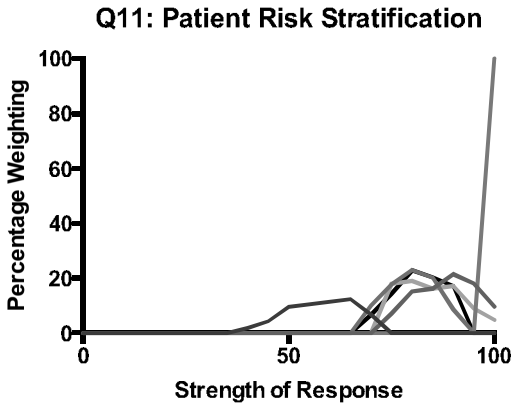


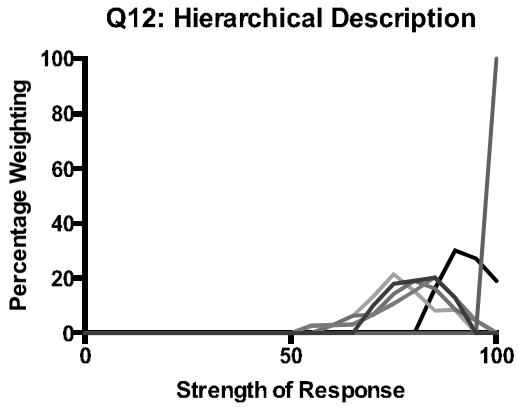

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

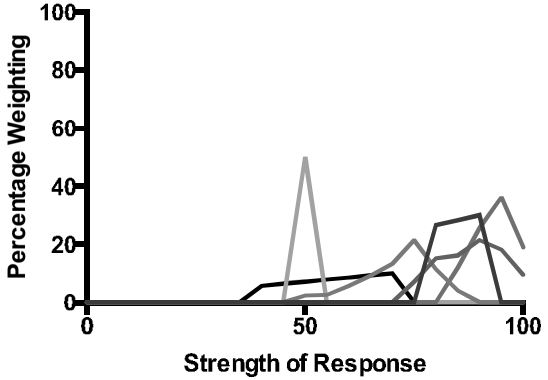

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

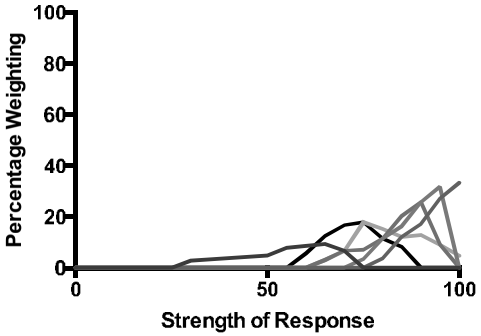

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



5.3.1.7 Clinical Respondents

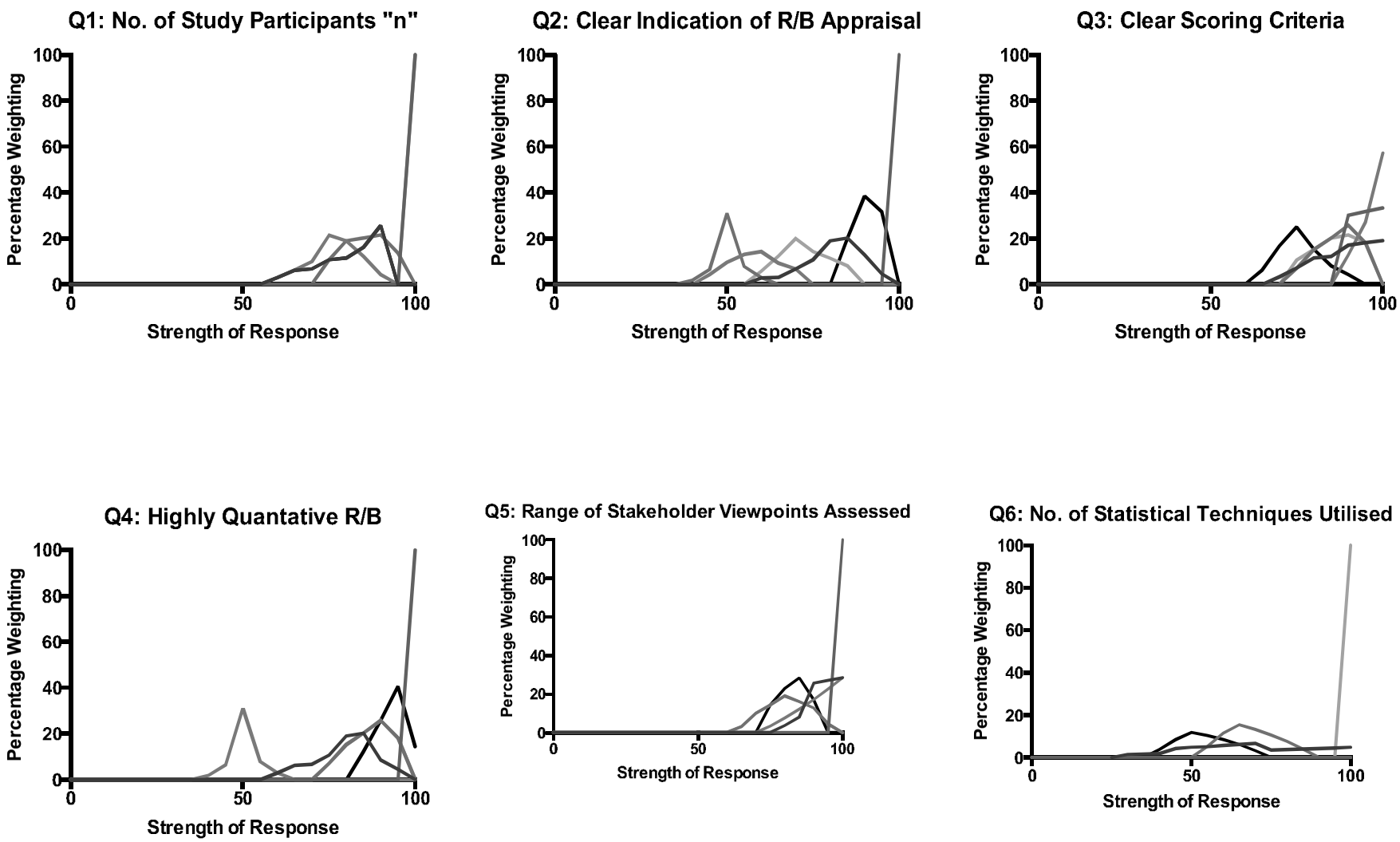
Clinical participants in the study demonstrated consistent intra-stakeholder trends in both response strength and associated uncertainty. In all cases the stakeholder group exhibited uniform agreement in the direction of the quality factor weighting – positive or negative.

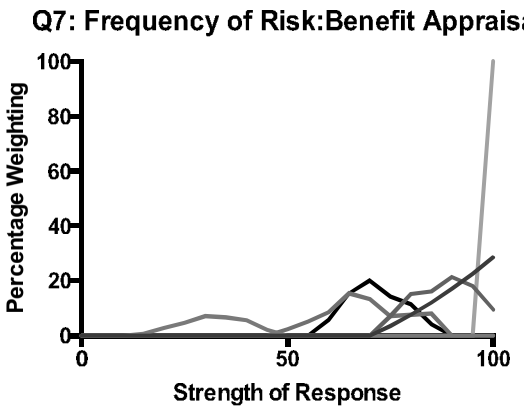
Throughout clinicians responded with high strength and conviction in their responses; but typically a high degree of uncertainty. Given the time constraints of clinical practice, high consistency in response styles is unsurprising.

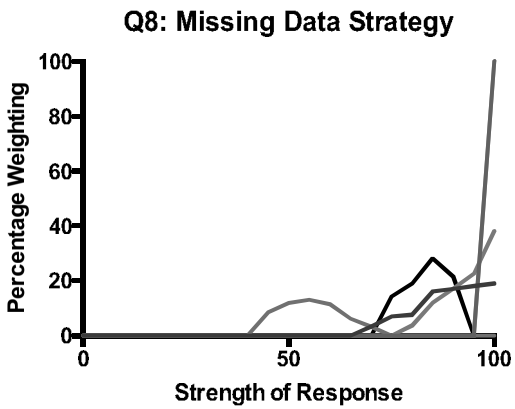
Verbal comments and the expert elicitation data collected indicated a strong preference amongst clinician for transparent and accessible statistical analysis. Additionally, 'clinical considerations' including patient stratification and outcome measures were of importance to this stakeholder group.

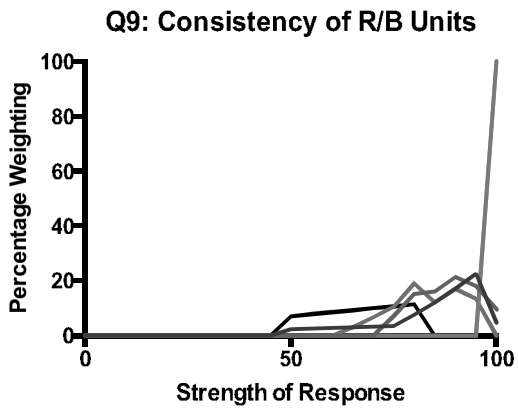
Clinicians also expressed a strong preference, with a high degree of certainty for the integration of a range of stakeholder viewpoints into risk:benefit appraisal

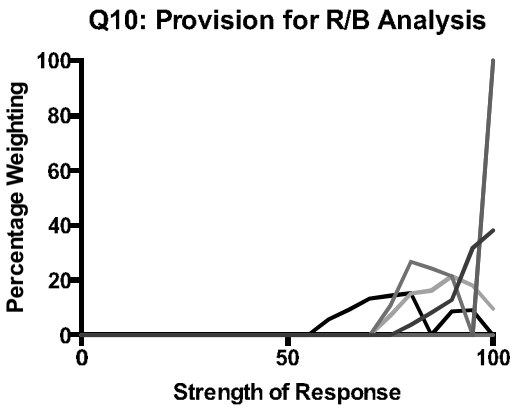
Figure 5.6: Statistician Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions




Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
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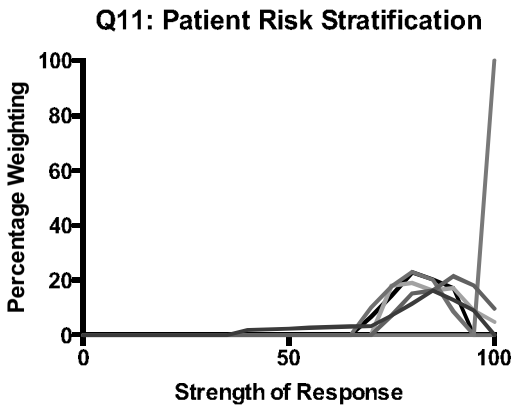
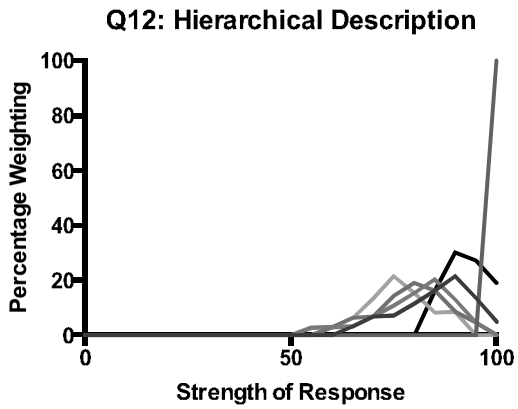
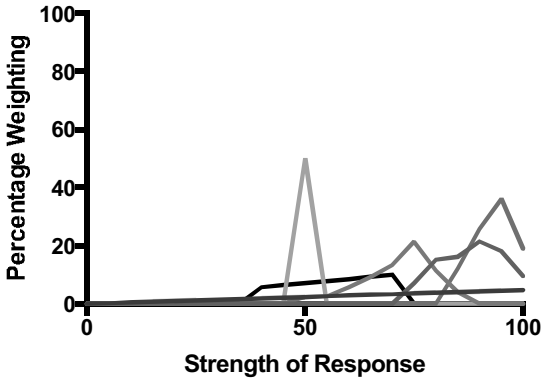
80
60
40
20
0
0
50
100
Strength of Response

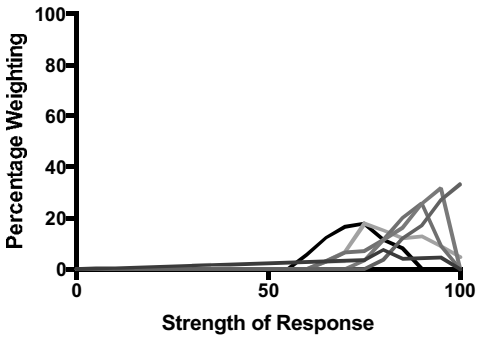

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



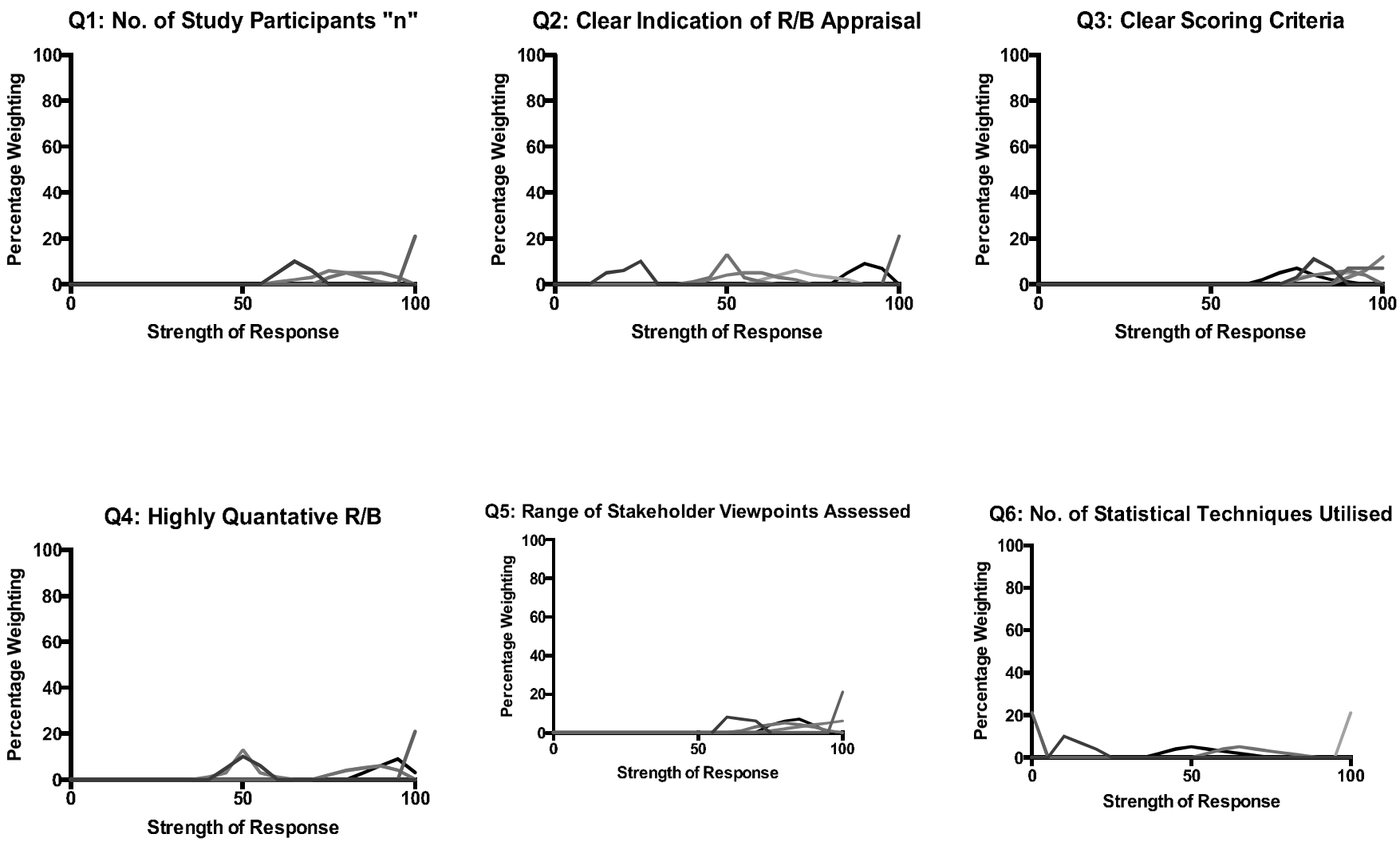
5.3.1.8 Clinical Trial Co-Ordinator Respondents

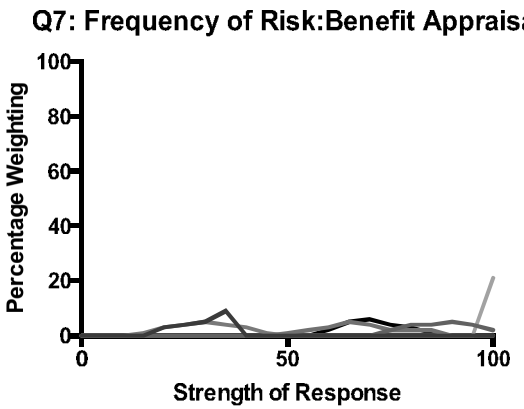
Clinical trial co-ordinators responded consistently with high uncertainty and low response strength. Generally, the direction of responses were consistent with the exception of heterogeneous views pertaining to the importance attributed to a “clear indication that risk:benefit appraisal” is conducted in a reported study.

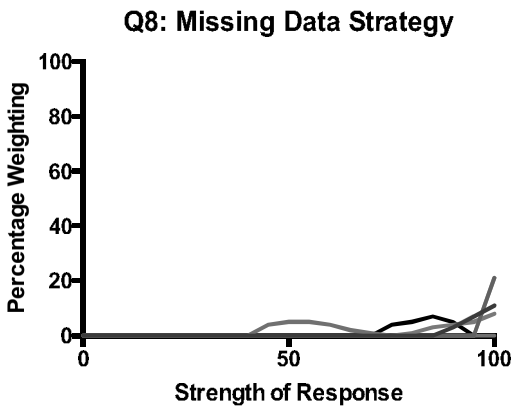
Minimal limitations in technical knowledge were observed verbally, or in the expert elicitation data obtained. However, similar to clinicians, a strong preference for ‘statistically’ transparent techniques was determined.

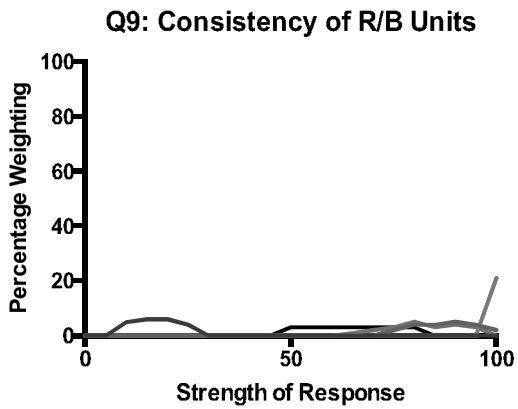
No responses obtained were particularly strong, with the exception of a strong desire with modest uncertainty for the publication of risk:benefit profiles of comparators alongside the intervention under investigation.

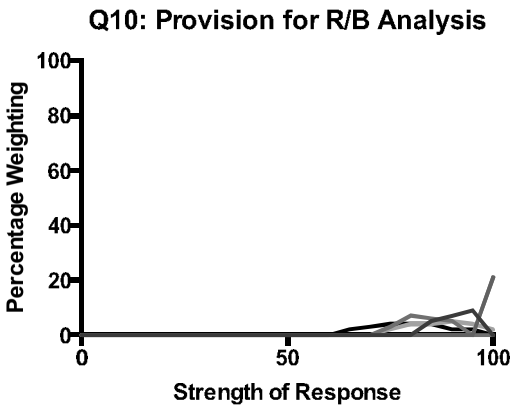
Figure 5.7: Clinical Trial Co-ordinator Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

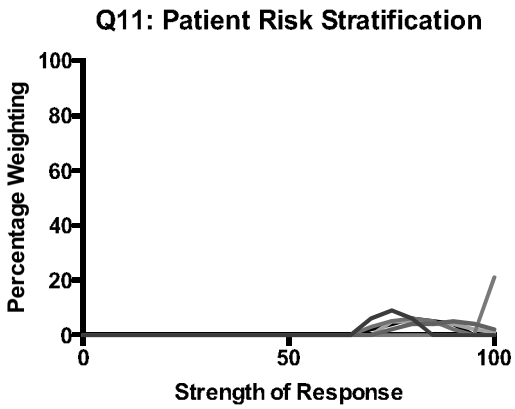


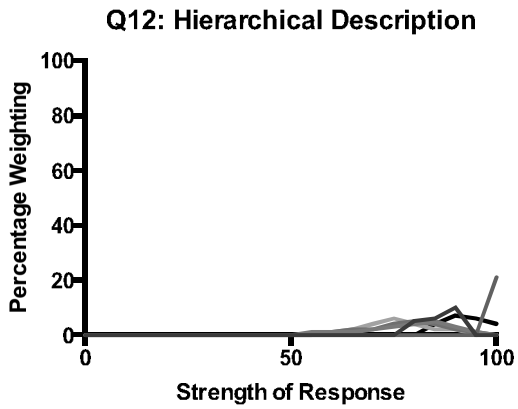

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

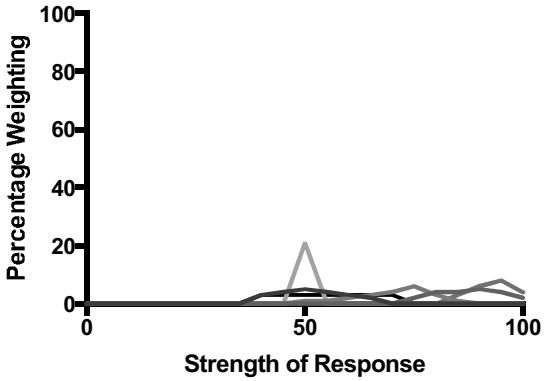

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

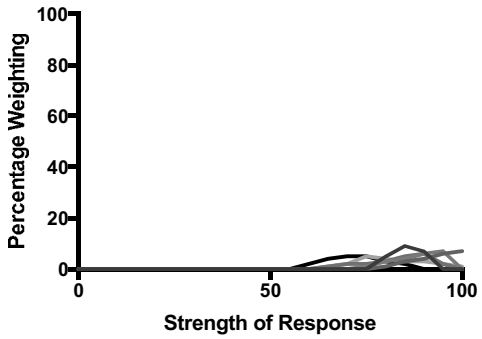

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison

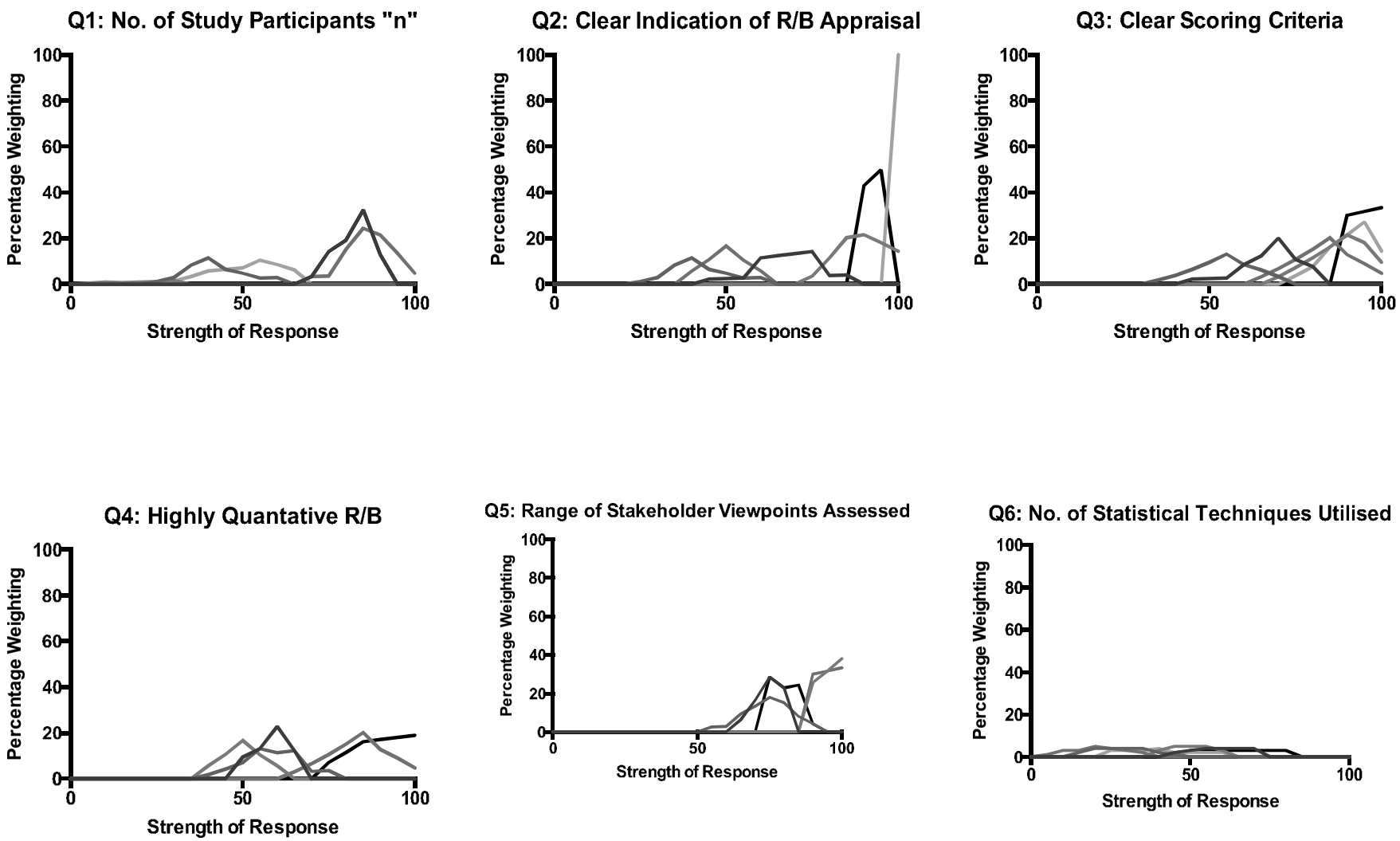


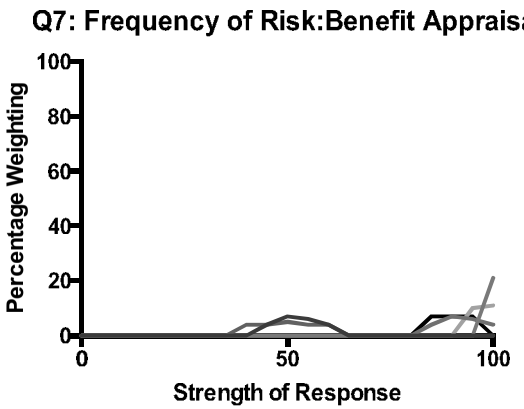
5.3.1.9 Epidemiology Respondents

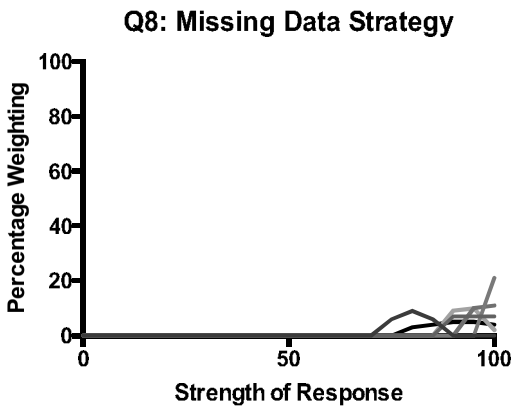
Epidemiology experts surveyed consistently as a stakeholder group, with significant variation in both response strength and uncertainty. No major outliers were observed.

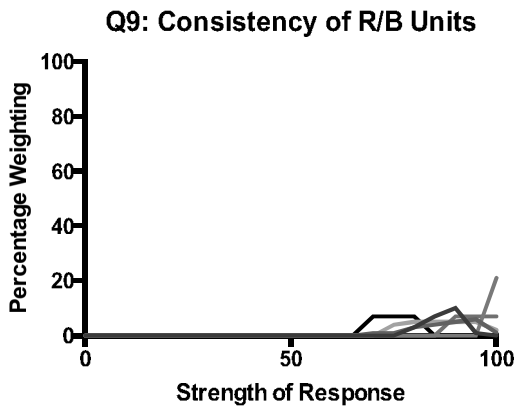
Responses pertaining to patient and intervention specific quality factors elicited responses of high strength and low uncertainty. Conversely, assessments of quality factors related to clinical trial strictures and statistical techniques exhibited high levels of uncertainty.

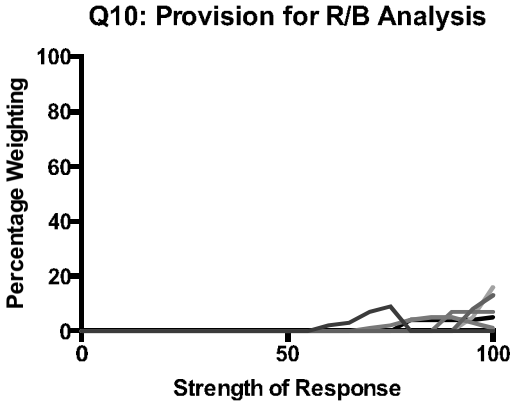
Figure 5.8: Epidemiology Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions

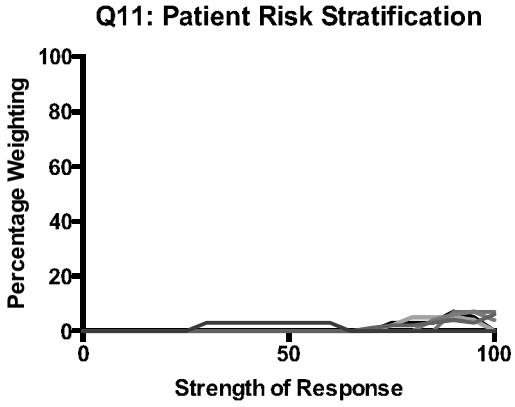


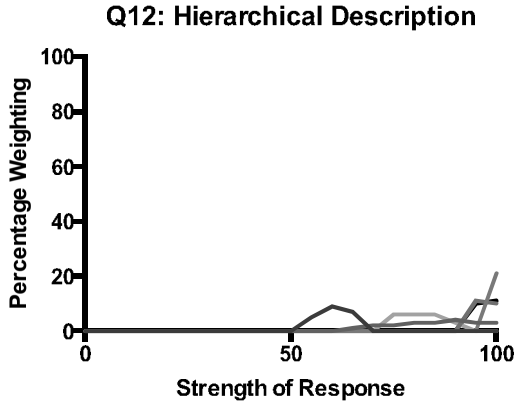

Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

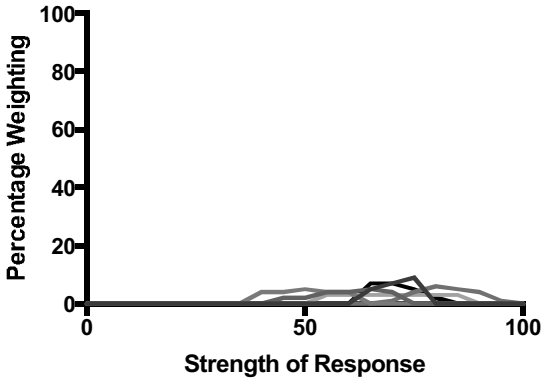

Q9: Consistency of R/B Units
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

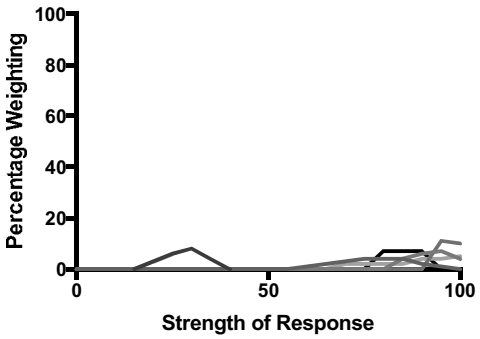

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes



Q14: Alternative Treatment Options for Comparison



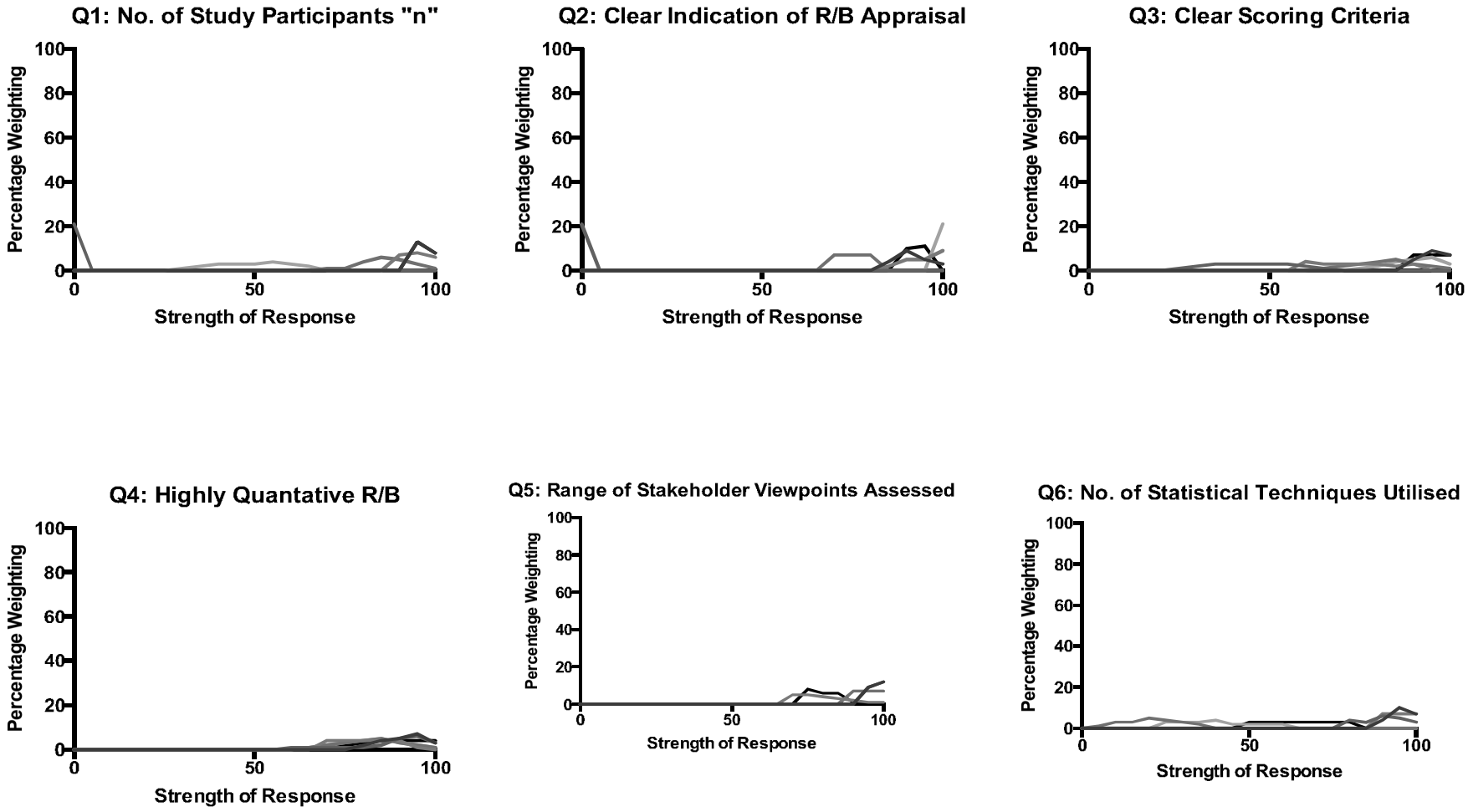
5.3.1.10 Industry Respondents

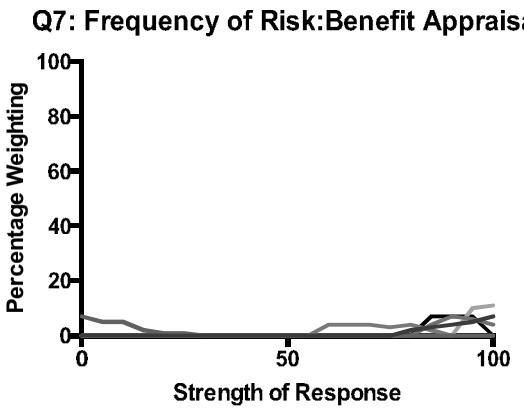
Industrialists surveyed represented amongst the highest uncertainty of any stakeholder group surveyed, with low response strength. With the exception of Respondent 4 [orange] that represented an occasional outlier, all respondents offered a similar direction and magnitude of observations.

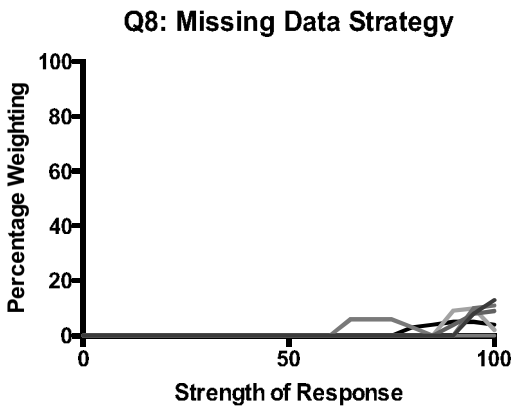
Significant variation in responses were observed for a number of questions relating to statistical methods, including “number of study participants;” frequency of risk:benefit appraisal;” and “number of statistical techniques used.” These were complemented by verbal responses – which were not mutually exclusive - indicating limited familiarity with statistical techniques and/or comments relating to the cost and practicality of extensive investigation.

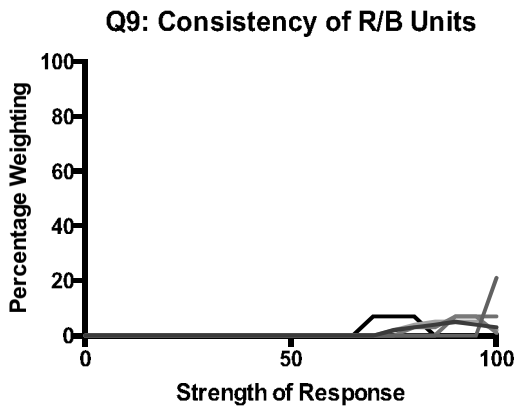
The most consistent trend amongst all respondents was broad agreement as to tbe importance of *ex ante* provision for risk:benefit appraisal in RCTs.

Figure 5.10: Industry Respondents: Intra-Stakeholder Pilot Expert Elicitation Probability Distributions




Q7: Frequency of Risk:Benefit Appraisal
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q8: Missing Data Strategy
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q9: Consistency of R/B Units
Percentage Weighting
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60
40
20
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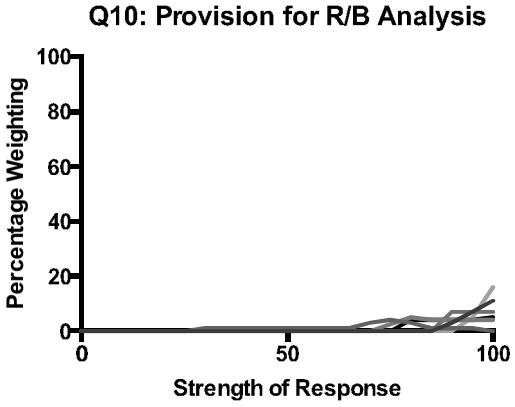
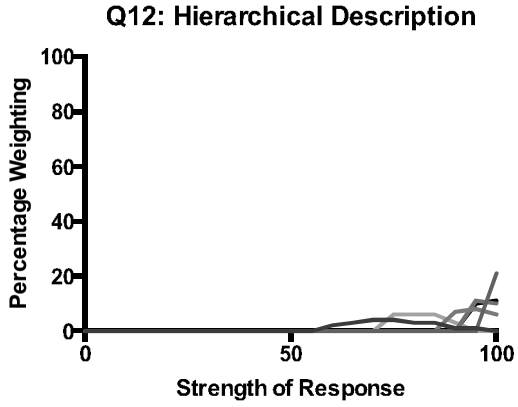
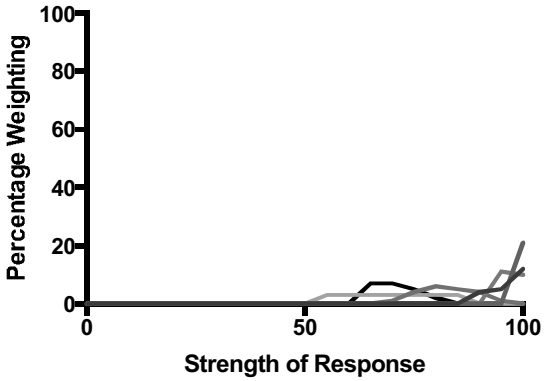
0
50
100
Strength of Response


Q10: Provision for R/B Analysis
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

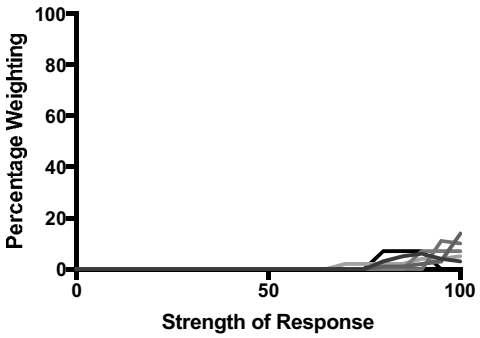

Q11: Patient Risk Stratification
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response


Q12: Hierarchical Description
Percentage Weighting
100
80
60
40
20
0
0
50
100
Strength of Response

Q13: Highly Quantitative Outcomes

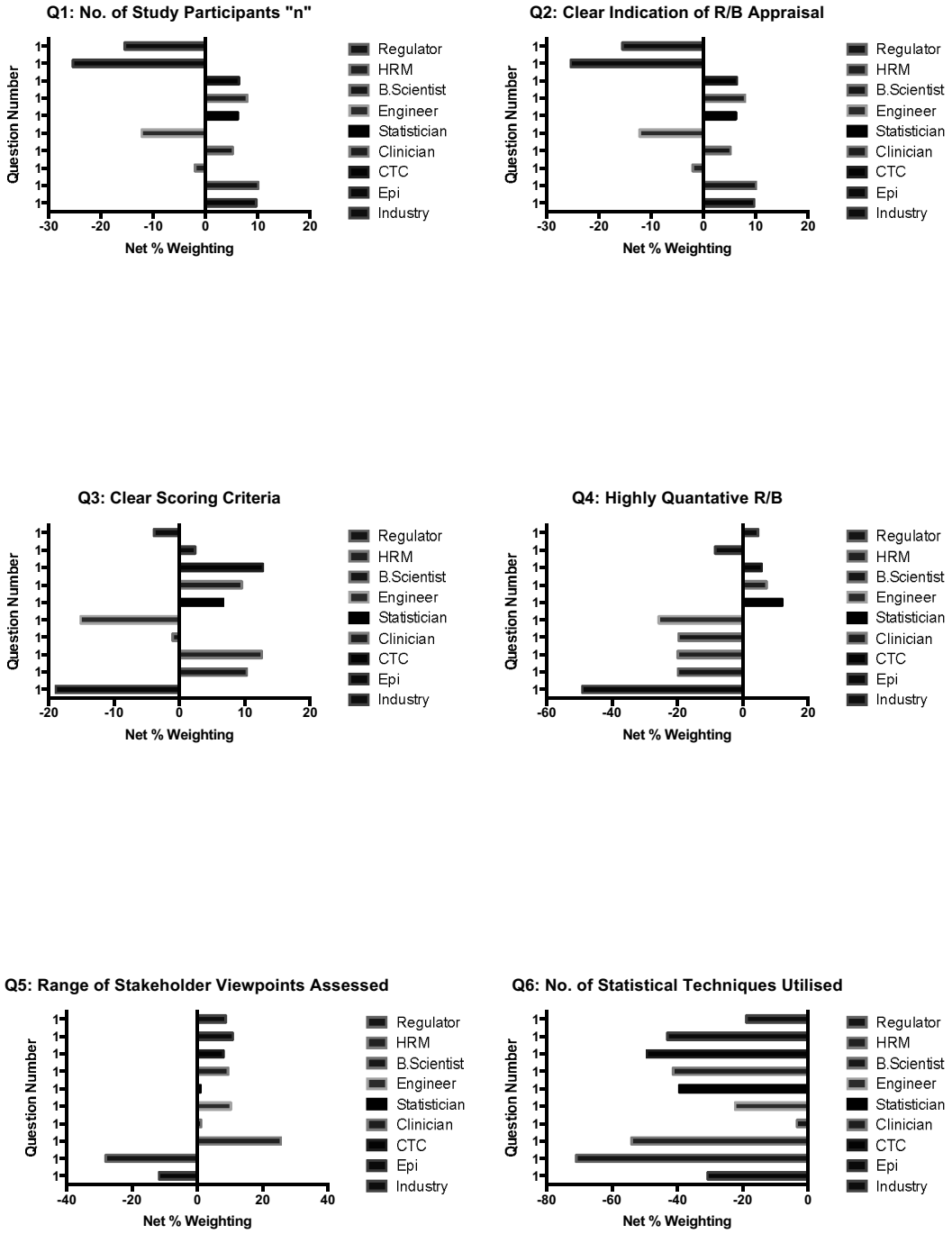


Q14: Alternative Treatment Options for Comparison



5.3.2 Quality Factor Net Weightings

5.3.2.1 Inter-Stakeholder Quality Factor Net Weightings



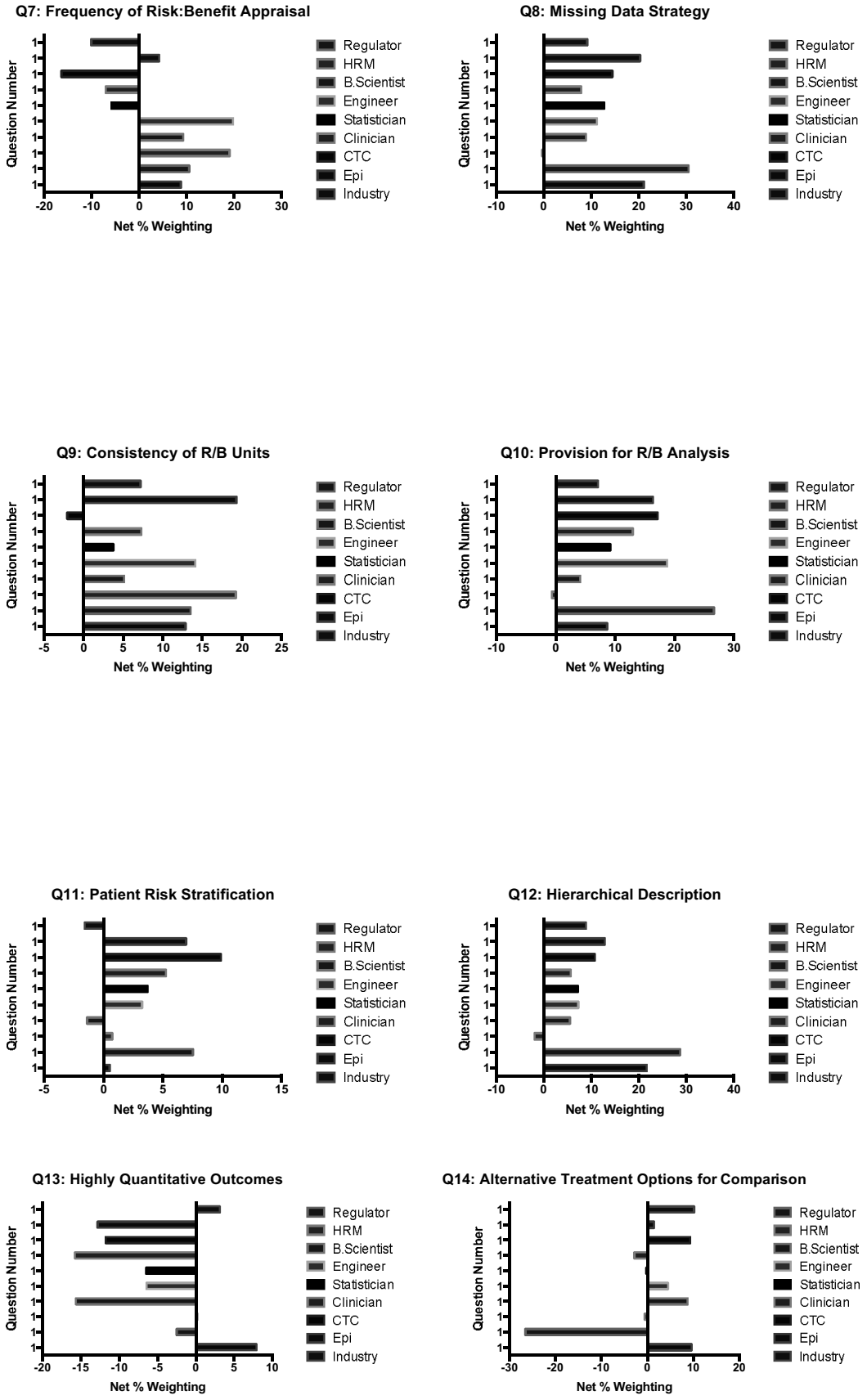


Figure 5.10: Cumulative Inter-stakeholder Quality Factor Weightings

5.4 Discussion

5.4.1 Expert Elicitation Study: Externally Generated Quality Factor Weightings Intra-Stakeholder Variance

For ease of reference, detailed discussion of the intra-stakeholder variance is provided alongside the results obtained [Section 5.3.1]. Herein, additional observations are presented, pertaining principally to similarities and differences between the response styles and trends of stakeholder respondents.

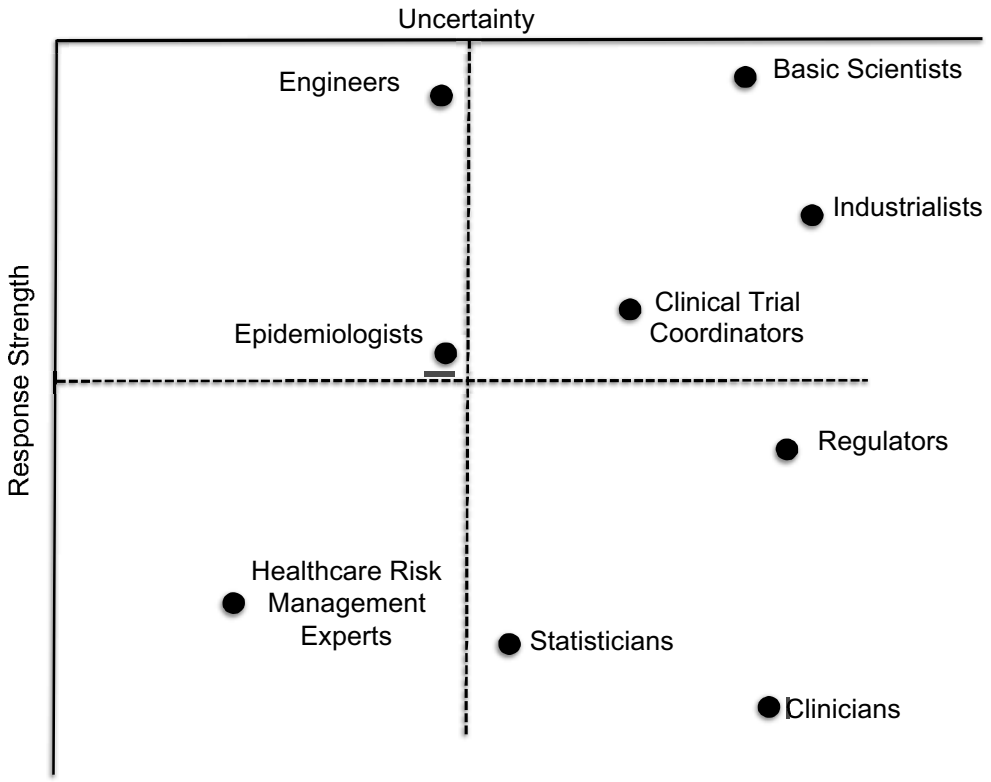


Figure 5.11: Inter-Stakeholder Response Strength and Uncertainty Distribution

Therefore, the intra-stakeholder analysis is indicative of cumulative inter-stakeholder uncertainty and response strength. As in [section 4.3] those stakeholders 'closest' to the end stage translation of biomedical innovations exhibit the greatest uncertainty in decision making, namely industrialists, regulators and clinicians.

5.4.2 Inter-Stakeholder Quality Factor Net Weightings

Given the heterogeneity of respondents, the inter-stakeholder quality factor net weightings generated exhibit relatively clear trends for quality factors assessed. Substantial

heterogeneity was only present for questions pertaining to the “number of study participants;” clear indication of risk:”benefit appraisal;” frequency of risk:benefit appraisal;” and the provision of “alternative treatment options to permit comparison.”

Inter-stakeholder responses regarding the “number of statistical techniques utilised;” missing data strategy;” and “provision for risk:benefit appraisal in study design” generated unanimous responses. Consequently, the cumulative net quality factor weightings [Figure 5.10] provided a robust and representative basis by which to re-rank the eligible studies generated in the earlier systematic review.

Positive Quality Factor Weighting	
Strong	**Weak**
(8) Missing Data Strategy	(5) No. of Stakeholder Viewpoints Assessed
(9) Consistency of Risk:Benefit Units Utilised	(7) Frequency of Risk:Benefit Assessment
(10) Provision for Risk:Benefit Appraisal in Study Design	(11) Patient Risk Stratification
(12) Hierarchical Description of Risk:Benefit Appraisal Methodology Utilised	

Table: 5.2: Positive Quality Factor Weightings Generated

Negative Quality Factor Weighting	
Strong	**Weak**
(4) Highly Quantitative Methodology	(2) Clear Indication of Risk:Benefit Appraisal
(6) No. of Statistical Techniques Utilised	(13) Utilisation of Highly Quantitative Outcome Measures

Table: 5.3: Positive Quality Factor Weightings Generated

Equivocal
(1) No. of Study Participants
(3) Clear Scoring Criteria
(14) Presence of Alternative Treatment Options to Permit Comparison

Table: 5.4: Equivocal Quality Factor Weightings Generated

5.5 Limitations

The full expert elicitation study demonstrated a number of significant improvements in structure delivery and the quality of data generated compared to the pilot study [Section 4.0]. However, it was not practicable to resolve some limitations present in the pilot and others were identified to inform future work.

Perhaps the greatest limitation of the study is that the decision was made to exclude patients and patient advocates. While unfortunate, given the extraordinary heterogeneity in clinical indications (chronic vs acute), the patient population (demographic variation) and the conflation of patient advocacy groups and disease specific organisations, the inclusion of an unhelpfully and unavoidably general patient stakeholder group would have yielded data with too many confounders to inform robust quality factor weightings (Wagner, 2000). It is hoped, however, that a patient stakeholder specific study can be conducted in the future to evaluate intra-patient and inter-stakeholder similarities and differences. For similar reasons, health economists, payers and (bio)ethicists were omitted from the study.

While every effort was made to ensure homogeneity in intra-stakeholder experience and skills, given the significant overlap and/or collaborative efforts between stakeholders in healthcare translation, some respondents may have ‘overlapped’ stakeholder categories; for example clinician-scientists, statistician-epidemiologists and engineer-industrialists. However, assuming that current and/or recent expertise is likely to influence subject responses most

significantly (Schrier, 1998), this is not believed to have significantly compromised the data obtained.

Regulators were a challenging group to both recruit and assess. Firstly, all regulators have previously trained in a different discipline before secondary training in regulation; typically, basic science, medicine and/or law. Similarly, most regulators specialise in a specific type of healthcare innovation; for example, therapeutic or device, which are organisationally separated within agencies (FDA CBER vs CDER).

Secondly, most general approaches to regulatory bodies to participate in the study – including the MHRA, EMA and FDA – either did not generate a response and/or a negative response. The most common reasons given were time constraints of assessors and/or agency policies not to engage in external research. Consequently, most regulatory respondents were sourced from existing professional networks.

Thirdly, during the study one regulator abstained from any participation after reviewing the introductory slides, due to concern that conclusions may be drawn pertaining to the risk perception of regulators. Most regulatory respondents expressed some verbal concern regarding how the data would be used. Counterpoint to this all with the exception of one abstainer, all regulatory respondents indicated that they would be happy to support a larger study which they believed would be of academic and practical importance.

The full expert elicitation study included provision for the collection of data pertaining to paralinguistic uncertainty, identified as a weakness of the pilot study [Section 4.5]. While data was collected for all respondents, with the exception of response latencies, due to respondent heterogeneity the data was not of sufficient quality to warrant additional analysis, nor inclusion in the final investigation [Section 6.0].

While from response styles a rich intellectual vein of work remains comparing verbal versus non-verbal indicators of risk perception and uncertainty, such techniques require a sample size orders of magnitude higher than for expert elicitation and the strict control of both

subject expertise and demographics. Electronic delivery tools would be helpful in the implementation of such a future study, in order to maximise achievable sample size and minimise assessment uncertainties present in manual delivery (Millard et al., 2012).

5.6 Conclusion

The full expert elicitation study confirmed that the intra and inter-stakeholder uncertainty pertaining to the relative importance of quality factors in the risk:benefit appraisal of healthcare innovations. The specificity of this finding was also improved compared to the pilot [Section 4.3], thereby increasing the representativeness and utility of the prototype scorecard.

Non-verbal indicators of response strength and uncertainty proved difficult to elicit using the same respondent cohort. Therefore, a separate larger and potentially remote electronic study may be required to evaluate verbal versus non-verbal indicators, and their impact on stakeholder quality factor weightings in the future (Presser, 2004).

The data generated may now be integrated into the prototype scorecard to evaluate any impact of the ranking of eligible studies identified in the systematic review [Sections 6.3 and 6.4.]. Additionally, organisation of the quality factors would aid the clarity and utility of the scorecard.

These findings support the initial hypothesis, and validate pilot study findings.

Chapter 6

Integration of Risk:Benefit Scorecard into Systematic Review

6.1 Introduction

This work has demonstrated both a limited and heterogeneous cohort of RCTs formally reporting risk:benefit appraisal [Section 3.0] and significant inter and intra-stakeholder heterogeneity in the relative importance in quality factors pertaining to the effectiveness of risk:benefit appraisal [Sections 4.0 and 5.0]. To date, no study has quantified these observations, nor criticality implemented them to inform and reduce uncertainty in the translation of healthcare innovations.

Therefore, this part of the investigation aims to apply the updated quality factor weightings generated to the prototype scorecard [Section 3.3] and apply the scorecard to systematically assess the quality of eligible studies. Where possible, partially attributed statistical trends identified in the implementation of the prototype scorecard [Section 5.3] will also be evaluated.

6.1.1 Hypothesis

The specificity and representativeness of the risk:benefit scorecard quality factors be improved through a full expert elicitation study as demonstrated through updates to the risk:benefit scorecard and its implementation in the assessment of eligible studies.

6.1.2 Aims and Goals

i. To (re)rank published attempts to deploy to risk:benefit appraisal methodologies to evaluate healthcare innovations, based upon key quality factors and the attitudes of multiple stakeholders to these factors
ii. To evaluate inter and intra-stakeholder response strength and uncertainty pertaining to risk:benefit appraisal quality factor weightings
iii. To determine if the bimodal distribution of the quality of risk:benefit appraisal methodologies in the sample is a persistent trend

6.2 Materials and Methods

Full details of the expert elicitation materials and methods are reported in Sections 4.3 and 5.3 Herein, to avoid duplication, only modifications to the pilot full protocols are stated.

6.2.1 Synthesis of Data

The intra-stakeholder quality factor weightings were pooled in order to generate inter-stakeholder quality factor weightings [Section 5.2.3] which were subsequently combined to yield overall multi-stakeholder weightings [Section 5.3]. The overall multi-stakeholder weightings were compared to those generated by the pilot study to ensure validity and identify any anomalies [Section 5.3 and 5.4].

6.2.2 Applying Updated Quality Factor Weightings to Prototype Risk:Benefit Scorecard

The overall multi-stakeholder weightings were integrated into the prototype scorecard to representatively weight the quality factors assessed based upon the multi-stakeholder viewpoints assessed [Section 5.3]. Thereafter, the scoring of all eligible risk:benefit appraisal studies identified in Section 3.3 were recalculated.

6.2.3 Re-Ranking of Eligible Records

Updated cumulative quality scores [Section 5.3.2.1] were used to re-rank eligible records identified in Section 3.3. and results compared to those generated by the pilot expert elicitation study [Sections 5.3 and 5.4].

6.2.4 Adjusting to Reflect Criticality of Quality Factors

A minimum acceptable quality threshold was integrated into the scorecard to ensure that 'unbalanced' studies – that is to say those which are not sufficiently thorough; but may attain an acceptable score due to high performance in a small number of areas, despite unacceptable deficiencies in others – were not included in the final sample. This was also intended to maximise the utility of the tool in the assessment of clinical trial quality; particularly, by clinicians and investors.

This 'minimum acceptable quality threshold' was integrated into the final scorecard and a final assessment of eligible records conducted [Section 5.4].

6.3 Results

6.3.1 Calculation of Cumulative Multi-Stakeholder Quality Factors

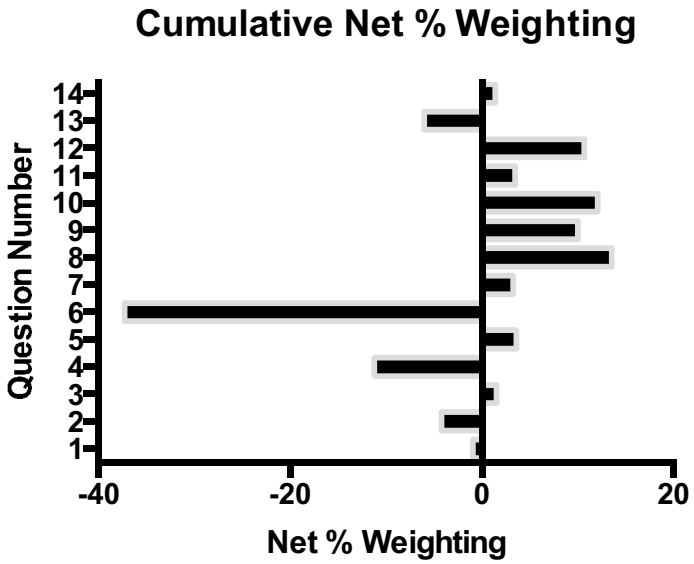


Figure 6.0: Cumulative Net Quality Factor Weightings

The cumulative weightings obtained support the findings of Figure 5.3.2.1 indicating statistically and practically significant inter-stakeholder attitudes towards critical quality factors in the risk:benefit appraisal of healthcare innovations.

6.3.2 Application of Updated Risk:Benefit Scorecard

Stakeholder Cumulative % Weighting												
Question Number	*Lay*	Regulator	HRM	B.Scientist	Engineer	Statistician	Clinician	CTC	Epi	Industry	Average % Weighting Full Study	Average % Weighting Pilot Study
1	9.73	10.11	-1.99	5.24	-12.18	6.24	7.98	6.44	-25.35	-15.45	-0.92	-8.32
2	9.29	9.64	1.63	-7.36	-7.64	-10.73	-6.74	-15.37	-5.39	-9.42	-4.21	-3.09
3	-18.91	10.34	12.64	-1.03	-15.10	6.69	9.57	12.79	2.43	-3.86	1.56	11.14
4	-49.02	-19.72	-19.86	-19.56	-25.63	12.09	7.34	5.88	-8.32	4.73	-11.21	-13.67
5	-11.67	-27.98	25.63	1.28	10.30	1.09	9.47	8.04	10.92	8.77	3.59	13.08
6	-30.67	-70.93	-53.88	-3.29	-22.24	-39.41	-41.17	-49.25	-43.00	-18.82	-37.27	-50.37
7	8.80	10.58	19.08	9.31	19.79	-5.83	-7.03	-16.35	4.23	-10.03	3.26	5.32
8	21.10	30.50	-0.31	8.91	11.19	12.70	7.89	14.44	20.29	9.15	13.59	18.08
9	12.88	13.51	19.24	5.09	14.11	3.76	7.29	-2.07	19.31	7.20	10.03	11.67
10	8.70	26.69	-0.63	4.14	18.80	9.21	13.02	17.22	16.38	7.15	12.07	8.32
11	0.53	7.53	0.74	-1.38	3.26	3.71	5.27	9.90	6.96	-1.58	3.49	0.68
12	21.69	28.74	-1.94	5.54	7.28	7.14	5.71	10.77	12.88	8.91	10.67	20.73
13	7.91	-2.49	0.21	-15.64	-6.44	-6.49	-15.78	-11.76	-12.80	3.12	-6.02	-20.08
14	9.63	-26.52	-0.57	8.76	4.51	-0.18	-2.83	9.33	1.46	10.14	1.37	6.50

Table 6.0: Inter-stakeholder Quality Factor Weightings and Variation versus Pilot Study

The updated inter-stakeholder quality rankings with the exception of two factors three [clear scoring criteria] and five [assessment of a range of stakeholder viewpoints] demonstrate the same direction – positive or negative - of stakeholder preference as in the pilot study. In most cases the magnitude of updated quality rankings are also comparable.

6.3.3 Evaluation of Pilot Versus Updated Scorecard Performance

Reference Number	No. of Participants	Prominence of R/B Analysis	Predefined R/B Index	Methodology	Scope of R/B Analysis	Statistical Tools	Frequency of Follow-Up	Missing Data Strategy	Consistency of R/B Units	Provision made for R/B in Study Design	Patient Risk Stratification	Hierarchical Approach to R/B	Outcome Measures	Comparators				
MEDLINE	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Score	Weighted TOTAL (/70)	Weighted % Total	Original % TOTAL	% Change Weighted - Unweighted
103 (Embase)	2.97	1.92	5.08	4.44	5.18	0.00	5.16	5.68	5.50	5.60	5.17	0.00	4.70	4.05	55.46	79.23	77	2.23
115	0.99	5.08	5.08	4.44	5.18	0.00	5.16	0.00	5.50	5.60	2.07	0.00	4.70	4.05	47.86	68.37	67	1.37
10	2.97	0.96	5.08	4.44	2.07	0.63	1.03	0.00	5.50	5.60	5.17	0.00	4.70	1.01	39.17	55.96	56	-0.04
9	1.98	1.92	0.00	4.44	5.18	0.63	2.07	0.00	5.50	5.60	0.00	0.00	4.70	4.05	36.07	51.53	51	0.53
1	3.96	5.08	0.00	2.66	2.07	3.14	5.16	0.00	0.00	5.60	5.17	0.00	2.82	0.00	35.67	50.96	53	-2.04
35	4.95	1.02	0.00	4.44	5.18	3.14	5.16	0.00	0.00	0.00	5.17	0.00	4.70	0.00	33.76	48.23	51	-2.77
95 (Embase)	4.95	1.92	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	29.43	42.05	43	-0.95
2	1.98	2.03	0.00	2.66	2.07	0.63	2.07	0.00	5.50	5.60	0.00	0.00	2.82	4.05	29.42	42.03	41	1.03
3	3.96	1.92	0.00	4.44	5.18	0.63	5.16	0.00	0.00	0.00	2.07	0.00	4.70	0.00	28.06	40.08	41	-0.92
144 (Embase)	2.97	2.03	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	27.57	39.38	40	-0.62
57	4.95	1.02	0.00	2.66	2.07	3.14	2.07	0.00	0.00	0.00	2.07	5.53	2.82	1.01	27.34	39.06	41	-1.94
40 (Embase)	1.98	1.92	0.00	4.44	5.18	0.63	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	27.09	38.70	40	-1.30
61	2.97	0.96	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	26.49	37.85	39	-1.15
112	4.95	1.02	0.00	4.44	2.07	0.63	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	26.05	37.22	39	-1.78
73	0.99	2.03	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	25.59	36.55	37	-0.45
50	0.99	1.02	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	4.05	25.54	36.49	37	-0.51
72 (Embase)	1.98	1.92	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	0.00	25.45	36.35	37	-0.65
68	4.95	1.92	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	0.00	25.31	36.16	37	-0.84
46	2.97	0.96	0.00	4.44	5.18	0.63	5.16	0.00	0.00	0.00	0.00	0.00	4.70	1.01	25.05	35.79	37	-1.21
55	0.00	1.02	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	4.05	24.55	35.07	36	-0.93
72	2.97	2.03	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	24.46	34.94	36	1.06
63	1.98	1.92	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	1.01	24.39	34.85	36	-1.15
51	1.98	1.02	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	1.01	23.49	33.56	34	-0.44
77	0.00	1.92	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	0.00	23.47	33.52	34	-0.48
37	1.98	1.92	0.00	4.44	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	0.00	23.38	33.40	34	-0.60
75	1.98	1.02	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	2.07	0.00	4.70	1.01	22.45	32.08	33	-0.92
42	3.96	2.03	0.00	2.66	2.07	0.00	2.07	0.00	0.00	0.00	0.00	0.00	4.70	4.05	21.55	30.78	31	-0.22
20	2.97	1.92	0.00	4.44	5.18	0.63	0.00	0.00	0.00	0.00	0.00	0.00	4.70	1.01	20.85	29.78	31	-1.22
104	1.98	1.02	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	1.01	20.38	29.12	30	-0.88
65	0.99	1.92	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	1.01	20.29	28.99	30	-1.01
66	1.98	0.96	0.00	4.44	2.07	0.00	5.16	0.00	0.00	0.00	0.00	0.00	4.70	0.00	19.31	27.59	29	-1.41
93	0.00	2.03	0.00	2.66	5.18	0.00	5.16	0.00	0.00	0.00	0.00	0.00	2.82	0.00	17.86	25.51	26	-0.49
88	0.99	1.92	0.00	2.66	2.07	0.00	5.16	0.00	0.00	0.00	0.00	0.00	2.82	1.01	16.64	23.77	24	-0.23
60	1.98	1.92	0.00	2.66	2.07	0.00	5.16	0.00	0.00	0.00	0.00	0.00	1.88	0.00	15.68	22.39	23	-0.61
30	1.98	1.02	0.00	4.44	2.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.70	1.01	15.22	21.74	23	-1.26
59	0.00	2.03	0.00	1.78	2.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.88	0.00	7.76	11.08	11	0.08

Table 6.1: Evaluation of Pilot Versus Updated Scorecard Performance

The comparability in quality factor weightings in Table 6.0 is verified when applied to re-rank eligible studies, with the specificity and sensitivity of the updated questionnaire improved.

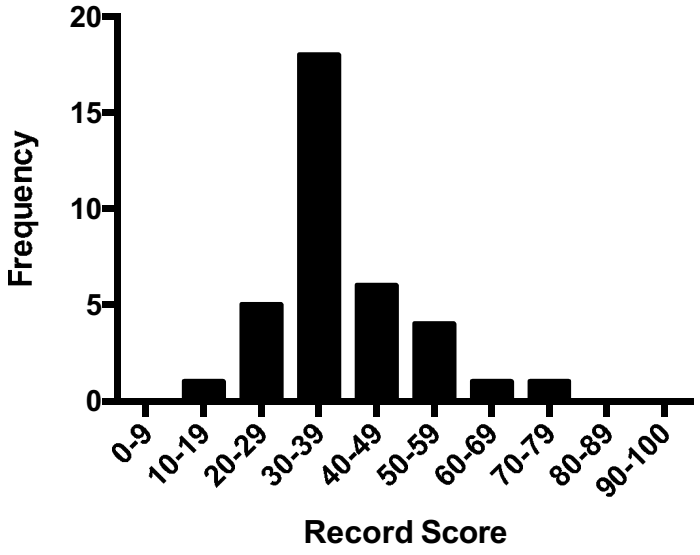
6.3.4 Record Rankings Pilot Versus Updated Scorecard Performance

	Unweighted Ranking	Weighted Ranking	Change
103 (Embase)	1	1	0
115	2	2	0
10	3	3	0
1	4	5	-1
9	5	4	1
35	6	6	0
95 (Embase)	7	7	0
2	8	8	0
3	9	9	0
57	10	11	-1
40 (Embase)	11	12	-1
144 (Embase)	12	10	2
61	13	13	0
112	14	14	0
46	15	19	-4
50	16	16	0
68	17	18	-1
73	18	15	3
72 (Embase)	19	17	2
55	20	20	0
63	21	22	-1
72	22	21	1
37	23	25	-2
51	24	23	1
77	25	24	1
75	26	26	0
20	27	28	-1
42	28	27	1
65	29	30	-1
104	30	29	1
66	31	31	0
93	32	32	0
88	33	33	0
30	34	34	0
60	35	35	0
59	36	36	0

Table 6.2: Record Rankings Pilot Versus Updated Scorecard Performance

The majority of studies re-ranked using updated quality factor rankings were subject to minor or no changes in their relative rankings. However, there was a concentration of ranking changes for studies approximately within the middle of the distribution.

6.3.5 Updated Scorecard Distribution of Results

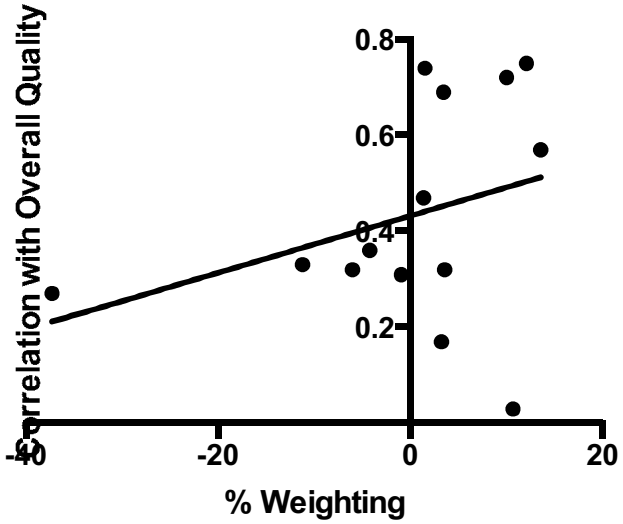


Skewness	2.318
Kurtosis	5.915

Figure 6.1: Updated Scorecard Distribution of Results

Compared to previous scorecards, the updated scorecard has greater negative kurtosis and a dominant left tail. Therefore, the refined multi-stakeholder quality factor rankings have reproduced the trend seen in Figure 4.6, whereby the scorecard increases the distribution of results; particularly, those in the lowest and highest quartiles.

6.3.6 Updated Scorecard Distribution of Results



	% Weighting vs. Correlation with Overall Quality
Pearson r	
r	0.3339
95% confidence interval	-0.2391 to 0.7344
R squared	0.1115
P value	
P (two-tailed)	0.2434
P value summary	ns
Significant? (alpha = 0.05)	No
Number of XY Pairs	14

Figure 6.2: Correlation of Quality Factors and Final Record Scores Assessed with Updated Scorecard

6.3.7 Minimum Acceptable Quality Threshold (MAQT) Implementation

	STRUCTURE								REPORTING								
	Study Quality, T_Q				Study Effectiveness, T_E				Reporting Quality, R_Q			Reporting Effectiveness, R_E					
Refrence Number	No. of Participants	Prominence of R/B Analysis	Predefined R/B Index	Methodology	Scope of R/B Analysis	Statistical Tools	Frequency of Follow-Up		Missing Data Strategy	Consistency of R/B Units	Provision made for R/B in Study Design	Patient Risk Stratification	Hierarchical Approach to R/B	Outcome Measures	Comparators		
MEDLINE	Score	Score	Score	Score	Score	Score	Score		Score	Score	Score	Score	Score	Score	Score		Weighted TOTAL (/70)
103 (Embase)	2.97	1.92	5.08	4.44	5.18	0.00	5.16		5.68	5.50	5.60	5.17	0.00	4.70	4.05		55.46
115	0.99	5.08	5.08	4.44	5.18	0.00	5.16		0.00	5.50	5.60	2.07	0.00	4.70	4.05		47.86
10	2.97	0.96	5.08	4.44	2.07	0.63	1.03		0.00	5.50	5.60	5.17	0.00	4.70	1.01		39.17
9	1.98	1.92	0.00	4.44	5.18	0.63	2.07		0.00	5.50	5.60	0.00	0.00	4.70	4.05		36.07
1	3.96	5.08	0.00	2.66	2.07	3.14	5.16		0.00	0.00	5.60	5.17	0.00	2.82	0.00		35.67
35	4.95	1.02	0.00	4.44	5.18	3.14	5.16		0.00	0.00	0.00	5.17	0.00	4.70	0.00		33.76
95 (Embase)	4.95	1.92	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		29.43
2	1.98	2.03	0.00	2.66	2.07	0.63	2.07		0.00	5.50	5.60	0.00	0.00	2.82	4.05		29.42
3	3.96	1.92	0.00	4.44	5.18	0.63	5.16		0.00	0.00	0.00	2.07	0.00	4.70	0.00		28.06
144 (Embase)	2.97	2.03	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		27.57
57	4.95	1.02	0.00	2.66	2.07	3.14	2.07		0.00	0.00	0.00	2.07	5.53	2.82	1.01		27.34
40 (Embase)	1.98	1.92	0.00	4.44	5.18	0.63	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		27.09
61	2.97	0.96	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		26.49
112	4.95	1.02	0.00	4.44	2.07	0.63	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		26.05
73	0.99	2.03	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		25.59
50	0.99	1.02	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	4.05		25.54
72 (Embase)	1.98	1.92	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	0.00		25.45
68	4.95	1.92	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	0.00		25.31
46	2.97	0.96	0.00	4.44	5.18	0.63	5.16		0.00	0.00	0.00	0.00	0.00	4.70	1.01		25.05
55	0.00	1.02	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	4.05		24.55
72	2.97	2.03	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		24.46
63	1.98	1.92	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	1.01		24.39
51	1.98	1.02	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	1.01		23.49
77	0.00	1.92	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	0.00		23.47
37	1.98	1.92	0.00	4.44	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	0.00		23.38
75	1.98	1.02	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	2.07	0.00	4.70	1.01		22.45
42	3.96	2.03	0.00	2.66	2.07	0.00	2.07		0.00	0.00	0.00	0.00	0.00	4.70	4.05		21.55
20	2.97	1.92	0.00	4.44	5.18	0.63	0.00		0.00	0.00	0.00	0.00	0.00	4.70	1.01		20.85
104	1.98	1.02	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	1.01		20.38
65	0.99	1.92	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	1.01		20.29
66	1.98	0.96	0.00	4.44	2.07	0.00	5.16		0.00	0.00	0.00	0.00	0.00	4.70	0.00		19.31
93	0.00	2.03	0.00	2.66	5.18	0.00	5.16		0.00	0.00	0.00	0.00	0.00	2.82	0.00		17.86
88	0.99	1.92	0.00	2.66	2.07	0.00	5.16		0.00	0.00	0.00	0.00	0.00	2.82	1.01		16.64
60	1.98	1.92	0.00	2.66	2.07	0.00	5.16		0.00	0.00	0.00	0.00	0.00	1.88	0.00		15.68
30	1.98	1.02	0.00	4.44	2.07	0.00	0.00		0.00	0.00	0.00	0.00	0.00	4.70	1.01		15.22
59	0.00	2.03	0.00	1.78	2.07	0.00	0.00		0.00	0.00	0.00	0.00	0.00	1.88	0.00		7.76

Table 6.3: Impact of MAQT on Record Scores Assessed Using Updated Scorecard

Applying the MAQT eliminated n=30 of n=36 eligible records, with structure quality factors [T_Q and T_E] demonstrating significant and consistent superiority to reporting quality factors [R_Q and R_E].

6.3.8 Final QUORUM Figure

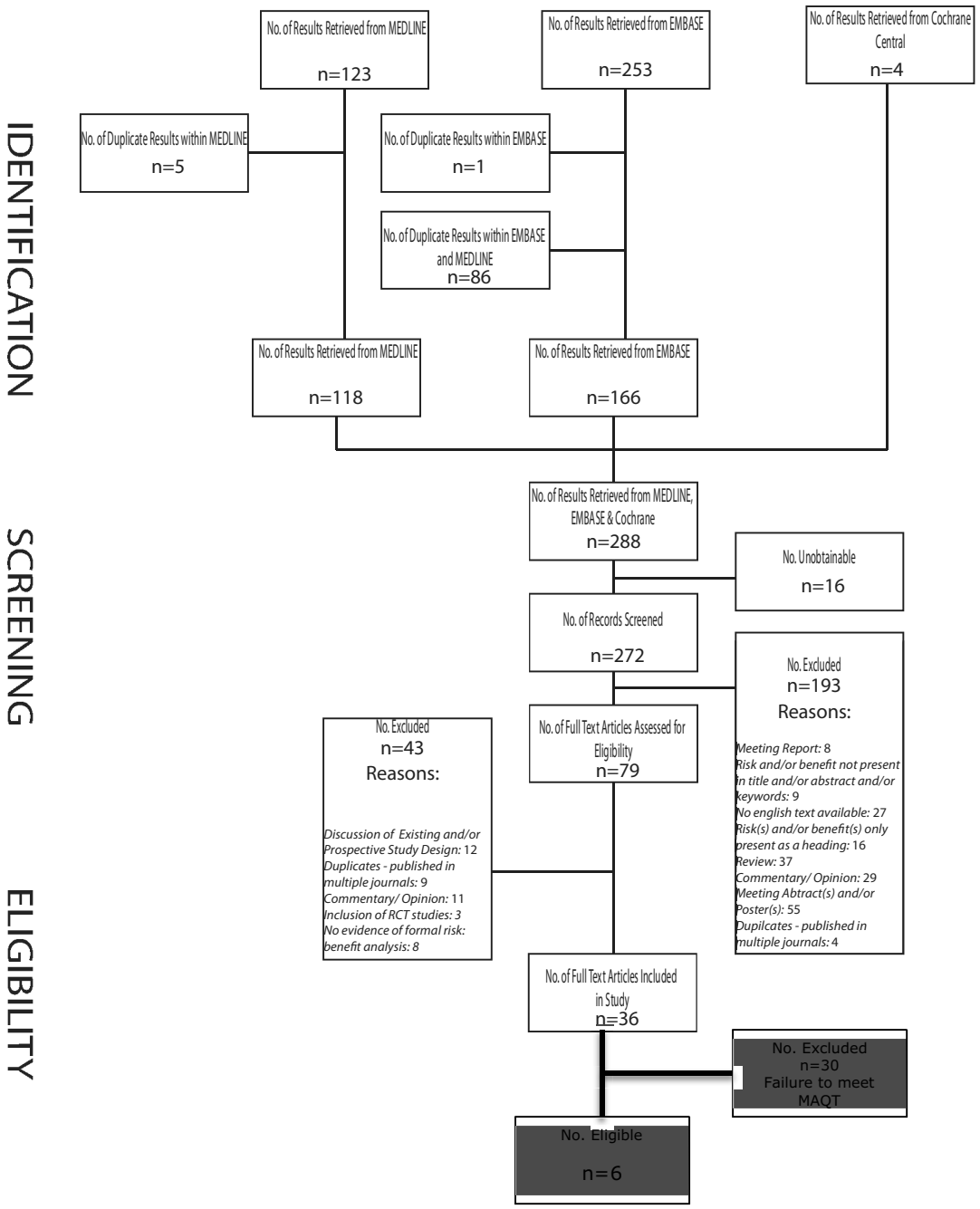


Figure 6.3: Final QUORUM Figure Integrating MAQT

6.3.9 Final Assessment of Eligible Studies

	STRUCTURE								REPORTING										
	Study Quality, T_Q					Study Effectiveness, T_E			Reporting Quality, R_Q				Reporting Effectiveness, R_E						
Reference Number	*No. of Participants*	*Prominence of R/B Analysis*	*Predefined R/B Index*	*Methodology*		*Scope of R/B Analysis*	*Statistical Tools*	*Frequency of Follow-Up*	*Missing Data Strategy*	*Consistency of R/B Units*	*Provision made for R/B in Study Design*		*Patient Risk Stratification*	*Hierarchical Approach to R/B*	*Outome Measures*	*Comparators*		*Weighted TOTAL (/70)*	*Weighted % Total*	*Original % TOTAL*
MEDLINE	*Score*	*Score*	*Score*	*Score*		*Score*	*Score*	*Score*	*Score*	*Score*	*Score*		*Score*	*Score*	*Score*	*Score*				
103 (Embase)	*2.97*	*1.92*	5.08	4.44		5.18	0.00	5.16	5.68	5.50	5.60		5.17	0.00	4.70	4.05		55.46	79.23	77
115	*0.99*	*5.08*	5.08	4.44		5.18	0.00	5.16	0.00	5.50	5.60		2.07	0.00	4.70	4.05		47.86	68.37	67
10	*2.97*	*0.96*	5.08	4.44		2.07	0.63	1.03	0.00	5.50	5.60		5.17	0.00	4.70	1.01		39.17	55.96	56
9	*1.98*	*1.92*	0.00	4.44		5.18	0.63	2.07	0.00	5.50	5.60		0.00	0.00	4.70	4.05		36.07	51.53	51
1	*3.96*	*5.08*	0.00	2.66		2.07	3.14	5.16	0.00	0.00	5.60		5.17	0.00	2.82	0.00		35.67	50.96	53
2	*1.98*	*2.03*	0.00	2.66		2.07	0.63	2.07	0.00	5.50	5.60		0.00	0.00	2.82	4.05		29.42	42.03	41

Table 6.4: Final Ranking of Eligible Records Exceeding MAQT

6.3.10 Eligible Records Exceeding MAQT

Reference Number	*Citation*	*Database Source*
1	1991. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. American Journal of Medicine, 90, 450-9.	Medline
2	AGUSTI, A., BONET, S., ARNAU, J. M., VIDAL, X. & LAPORTE, J.-R. 2003. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction : meta-analysis of randomised clinical trials. Drug Safety, 26, 895-908.	Medline
9	BAI, W., HENNEICKE-VON ZEPELIN, H.-H., WANG, S., ZHENG, S., LIU, J., ZHANG, Z., GENG, L., HU, L., JIAO, C. & LISKE, E. 2007. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas, 58, 31-41.	Medline
115	WOHLRAB, J., BECK, G. M., NEUBERT, R. H. H., SISCHKA, U. & KREFT, B. 2010. Hydrocortisone aceponate activity and benefit/risk ratio in relation to reference topical glucocorticoids. Skin Pharmacology & Physiology, 23, 177-82.	Medline
103 (Embase)	LEHERT, P., POIRIER-LITTRE, M. F., PRINGUEY, D. & GALINOWSKI, A. 1998. New statistical proposals to evaluate the benefit/risk ratio of long-term treatment of depression. Application to a one-year double-blind study comparing medifoxamine with fluoxetine. Clinical Drug Investigation, 15, 285-295.	Embase

Table 6.5: References of Eligible Records Exceeding MAQT

6.4 Discussion

6.4.1 Calculation of Cumulative Multi-Stakeholder Quality Factors

The cumulative quality factor weightings obtained [Figure 6.0.] are comparable to those obtained in the expert elicitation pilot study [Section 4.0 and Figure 4.0]. Encouragingly the overall weightings seem rationale and the need for a large ‘number of statistical techniques” employed to evaluate risk:benefit is dismissed. Axiomatically, the use of the correct technique(s) is more important than the number of techniques – which can increase net uncertainty in the analysis.

Perhaps surprisingly, the need for a “clear indication that risk:benefit appraisal is conducted in a given study” and the “utilisation of high quantitative outcome measures” were given weak negative weightings. This is principally due to some stakeholders, particularly those engaged in the design and delivery of clinical trials, strongly and certainly dismissing these factors as impractical, tempered by other stakeholders responding positively; but with high uncertainty regarding the practicality of the approach(es).

6.4.2 Application of Updated Risk:Benefit Scorecard

The updated risk:benefit scorecard was successfully implemented [Figure 6.1] While some outliers were present in terms of response direction – positive versus negative – the magnitude of any difference observed was generally modest. Therefore, the quality of the overall weightings was not compromised significantly.

Notably regulators responded strongly, certainly and positively to questions relating to the importance of a "missing data strategy;" provision for risk:benefit analysis in study designs;" and the inclusion of a "hierarchical description of the methodology utilised." This is encouraging and suggests that regulators are supportive of increased transparency in the assessment of healthcare innovations. However, subject to caveats relating to technological complexity and heterogeneity – and thus the feasibility of such approaches.

6.4.3 Evaluation of Pilot Versus Updated Scorecard Performance

The majority of studies re-ranked using updated quality factor rankings were subject to minor or no changes in their relative rankings. However, there was a concentration of ranking changes for studies approximately within the middle of the distribution [Figure 6.1]. This is a typical observation when seeking to improve the specificity of assessment methodologies in a range of applications where the arithmetic separation between outliers increases, while data points in areas of high density the arithmetic separation decreases (Millard et al., 2012).

Consequently, the distribution of study scores [Figure 6.1] is more negatively skewed than previous iterations of the scorecard and quality factor weighting methodology [Sections 4.0 and 5.0]. Similarly, the correlation of specific quality factors with overall record quality increased [Figure 6.2] versus previous analyses [Figure 4.6]. This observation supports improvements in the specificity and representativeness of the scorecard generated.

6.4.4 Minimum Acceptable Quality Threshold (MAQT) Implementation

A MAQT was implemented to ensure that all records included in the final meta-analysis exceed a minimum level of quality and effectiveness in terms of their structure and reporting. Thereby, preventing studies with exceptionally high scores in a small number of quality factors; but entirely deficient in all other quality factors receiving a score representative of a methodology of overall high-quality.

The impact of the MAQT, requiring the presence of at least one quality factor in of each of the four categories defined [Table 6.3], was significant, and based upon manually reviewing and producing a meta-analysis of all eligible records [Figure 6.3], unsurprising. The final six eligible records, represent n=6 of n=288 (~2%) of all records identified by the literature database search terms [Section 3.3]. However, all six studies clearly meet the inclusion and exclusion criteria outlined, and represent good examples of the risk:benefit appraisal of healthcare innovations; and a useful starting point for future research.

Nevertheless, it is of significant disappointment and concern that despite the *en vogue* nature of risk:benefit appraisal in public consultations by regulators, and a range of academic literature – principally commentaries and perspectives – that the frequency and quality of implementation in RCTs to date has been so poor.

6.5 Limitations

The scope of the initial literature search terms – all RCTs, in all clinical indications since the inception of all databases – despite being extraordinarily broad retrieved a modest number of records (n=288). Thereby indicating the infrequent application and reporting of risk:benefit appraisal RCTs. However, future increases to the size of the dataset may be achieved by increasing the number of data sources to include conference presentations and/or posters; and evaluating clinical trial protocols available on clinicialtrials.gov.

Perhaps the greatest confounder in the entire study, and one which is regrettable in an age of 'big data' and increasing transparency in healthcare translation, is that the study only assessed publically available risk:benefit analyses, while the majority may be held confidentially with regulators worldwide. An extraordinarily valuable, albeit logistically (and potentially politically) challenging future study would be to obtain access to a small subject of these in collaboration with worldwide NCAs – and obtain a more holistic view of the 'state of the art.'

If the study were to be repeated electronically to assess paralinguistic uncertainty (Presser, 2004) is would also be helpful to use the platform to regularly validate, using a large sample size, the quality factors assessed in the scorecard versus potential candidate that may result as from further investigation, multi-stakeholder consultation and/or unique attributes of future healthcare innovations. Additionally, it may be possible to adapt and validate the scorecard for use in more specific applications; for example, cost-effectiveness assessment methodologies and/or specific clinical situations – including permitting the experimental or off-label use of interventions in the cases of unmet medical needs and/or pandemics (Fry et al., 2011).

6.6 Conclusions

6.6.1 Conclusions: Chapter 6

The multi-stakeholder quality factor weightings were successfully integrated into the prototype scorecard and a minimum acceptable quality threshold (MAQT) devised in order to maximise consistency and utility of the final scorecard, while also maintaining its specificity.

Of the initial records identified by the systematic review literature search terms, only n=6 of n=288 met the minimum quality threshold and were suitable for inclusion in further analysis. A manual review confirmed the final studies identified meet all inclusion and exclusion criteria defined previously, and as such, the protocol was both appropriate and implemented successfully.

6.6.1 Conclusions: PART II

A scorecard to assess the quality and effectiveness of risk:benefit appraisal methodologies utilised in RCTs was successfully developed, validated and implemented.

It is hoped that the long-term academic and ‘real world’ impact of the tools is to assist all stakeholders engaged in healthcare translation make risk:benefit appraisal more objective, transparent and reflective of stakeholder requirements.

PART III

APPLICATION OF RISK:BENEFIT APPRAISAL: EMERGING STAKEHOLDERS AND TECHNOLOGIES

Chapter 7

Assessment of Pharmacists' Attitudes to Risk:Benefit Appraisal

7.1 Introduction

A persistent and growing theme throughout this investigation was not simply the changing nature and interaction of system and technology risks in healthcare translation; but also the subsequently changing role of stakeholders within these systems (Fernandez et al., 2012). Within academic literature and participant feedback during expert elicitation data collection a clear need was established to assess the attitudes of pharmacists' to the risk:benefit appraisal of healthcare innovations, in view of their rapidly changing role in healthcare innovation and delivery (Fevang, 1994, Muijrers et al., 2003).

Historically, the formal (continuous) assessment and utilisation of healthcare risk management methods have been applied towards the end of the translation pathway (Mt-Isa et al., 2014). For example, in the case of interventions that have traversed a clinical trial and are seeking and/or have successfully sought marketing authorisation. The management of such risks typically falls under the scope of post-market surveillance and pharmacovigilance (Xiang et al., 2011). However, for a number of reasons, this status quo is changing.

Adaptive clinical trial structures, permitting conditional marketing approval subject to augmented pharmacovigilance, are stimulating the implementation in explicit risk:benefit

appraisal for pre-licensure therapeutics. Additionally, for novel therapeutic platforms subject to hospital exemptions and/or accelerated access schemes – including cell, gene and immunotherapies – pharmacists are required to perform final fill and finish stages for cryopreserved therapies (Banfi et al., 2000). Thus the system and technological scope of any risk:benefit analysis conducted is expanded. A similar trend can be observed for established therapies.

The powerful convergence of the increasing scope of pharmacy based product and care delivery – including prescription only to over the counter (POM – OTC) transitions (Bond and Hannaford, 2003); growth in online pharmacies; and assessment of informed consent for specific products, notably anti-malarials and emergency contraception – with increasing regulatory oversight enforced in the EU by the incumbent Falsified Medicines Directive (Taaffe, 2012) is may be contributing to an increasingly active participation in risk:benefit assessment and communication by pharmacists. This is the basis of the central research question(s) addressed herein.

7.1.1 Hypothesis

Pharmacists believe they have an important role in evaluating risk:benefit appraisal in RCTs and communicating this to patients as demonstrated by a pilot and a full study assessing their attitudes to risk:benefit appraisal in RCTs and implications for patient care and communication.

7.1.2 Aims and Goals

i. To assess if pharmacists believe they have an important role in helping patients understand the relative risks and benefits of medicines
ii. To evaluate the relative importance of a sample of risk:benefit critical quality factors assessed in the scorecard developed [Section 6.0] to pharmacists.
iii. To determine the whether formal risk:benefit appraisals in RCTs should be communicated directly to the patient *and* pharmacist

7.2 Materials and Methods

7.2.1 Questionnaire Design

The questionnaire subject matter was derived partly from prior research into the expert elicitation scorecard [Sections 4.0-6.0] and through discussion with regulators and pharmacists to ascertain key areas where pharmacists had an existing, changing and/or growing role in risk:benefit appraisal. The final factors for assessment were determined by consensus in collaboration with the University College London Centre for Behavioural Medicine, School of Pharmacy (London, UK); Oxford University Hospitals, Pharmacy Services (Oxford, UK); and the software provider Aegate Ltd (Royston, UK).

In order to minimise the time inconvenience to pharmacists completing the questionnaire, a short format with seven questions were devised. All answers were provided in the form of a qualitative Likert scale. Minimisation of behavioural responses biases was sought through the use of an equal number of response intervals.

The questionnaire was translated into respondent languages – Italian, Dutch and English – by specialist technical translators. All translations were verified by a second reader for clarity and technical accuracy.

7.2.2 Questionnaire Delivery

The questionnaire was delivered in both the pilot and full studies direct to pharmacists through existing patient medication record (PMR) systems in which Aegate medicines authentication software [Figure 7.0.] was embedded, and operational. Consistency in display and delivery was ensured by existing Aegate calibration and security protocols.

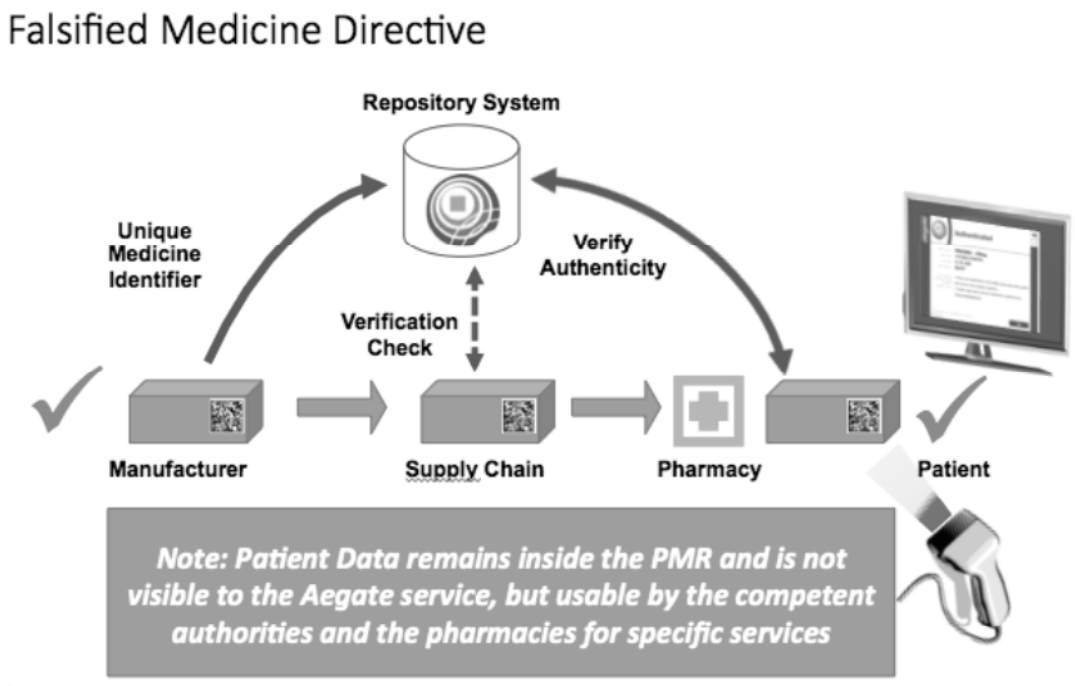


Figure 7.0: Overview of EU Falsified Medicines directive and Authentication Software

As the questionnaire was delivered through existing software and in a format to which users were familiar with, the risk to patients and pharmacy operations was deemed minimal and therefore ethical approval was not required.

Patient level data was not utilised in the study, and as such, patient confidentially was not compromised at any point.

7.2.4 Pilot Study

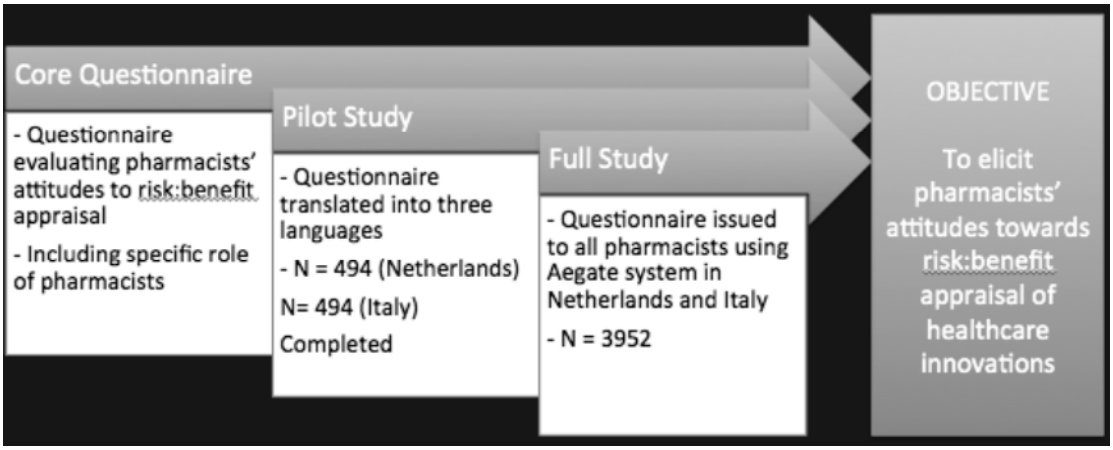


Figure 7.1: Overview of Pilot and Full Study Structures

In order to validate the readability and effectiveness of the provisional questionnaire the n = 988 pharmacists in the Netherlands and Italy were randomly selected. The questionnaire was delivered to pharmacies on 3rd November 2014, with one reminder for pharmacists that elected not to respond to the first prompt on 5th November 2014.

The option for respondents to offer feedback and/or seek clarification was provided via the 'Live Help' function of the Aegate software and a contact e-mail address at the end of the questionnaire.

7.2.5 Full Study

Following the satisfactory evaluation of responses from the pilot study, a full study was conducted in the same markets to n = 3952 randomly selected pharmacies in the Netherlands and Italy. The questionnaire was delivered to pharmacies on 10th November 2014, with one reminder for pharmacists that elected not to respond to the first prompt on 12th November 2014.

The option for respondents to offer feedback and/or seek clarification was provided via the 'Live Help' function of the Aegate software and a contact e-mail address at the end of the questionnaire.

7.2.6 Synthesis of Data

Data for all markets surveyed was pooled in order to maintain the anonymity of respondents. Additionally, this was required to maintain regulatory compliance of the electronic authentication system.

Respondent data for all questions was analysed using Microsoft Excel (Seattle, WA, USA) and GraphPad Prism (San Diego, CA, USA).

7.3 Results

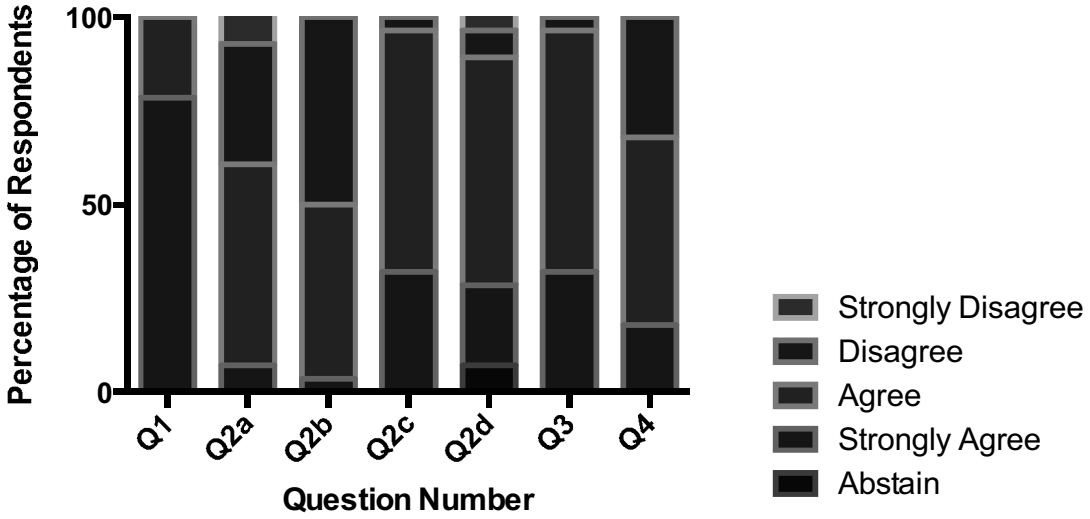
7.3.1 Response Rates

Study Type	Number of Questionnaires Issued	Number of Responses Received	Response Rate (%)
Pilot	988	**30**	**3.04**
Full	3952	**124**	**3.14**

Table 7.0: Pilot and Full Study Response Rates

The response rates received were consistent between the pilot and full studies. Typical response rates for a randomised survey using the software platform are ~ 5%. Therefore, both the pilot and full studies were subject to a modest decrease compared to previous studies.

7.3.2 Pilot Study



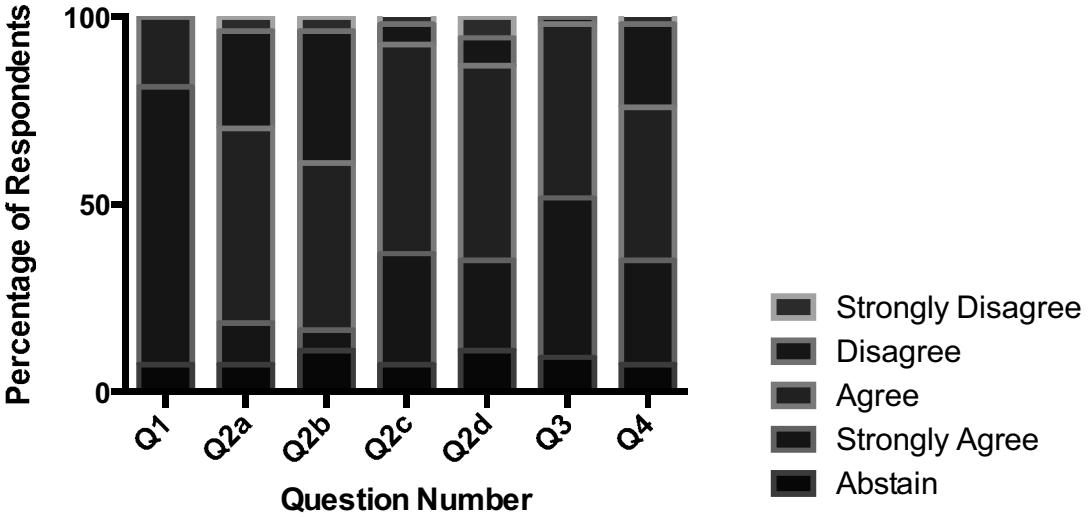
	Abstain	Strongly Agree	Agree	Disagree	Strongly Disagree
Minimum	0.0	3.571	21.43	0.0	0.0
25% Percentile	0.0	7.143	46.43	3.571	0.0
Median	0.0	21.43	53.57	7.143	0.0
75% Percentile	0.0	32.14	64.29	32.14	3.571
Maximum	7.143	78.57	64.29	50.00	7.143
Mean	1.020	27.55	51.53	18.37	1.531
Std. Deviation	2.700	25.06	14.99	19.50	2.810
Std. Error of Mean	1.020	9.472	5.666	7.370	1.062
Lower 95% CI of mean	-1.476	4.374	37.67	0.3335	-1.068
Upper 95% CI of mean	3.517	50.73	65.40	36.40	4.129

Figure 7.2: Pilot Study Cumulative Results

Responses for all questions indicated a consistent positive preference for pharmacist engagement in the risk:benefit appraisal of healthcare innovations. Minimal abstentions were observed.

Responses pertaining to the “number of statistical techniques utilised” and the presence of a “clear hierarchal description of the methodology utilised” received weaker positive support than the other factors assessed.

7.3.3 Full Study



	Abstain	Strongly Agree	Agree	Disagree	Strongly Disagree
Minimum	7.407	5.556	18.52	0.0	0.0
25% Percentile	7.407	11.11	40.74	1.852	0.0
Median	7.407	27.78	46.30	7.407	1.852
75% Percentile	11.11	42.59	51.85	25.93	3.704
Maximum	11.11	74.07	55.56	35.19	5.556
Mean	8.730	30.69	44.18	14.02	2.381
Std. Deviation	1.761	22.70	12.40	13.64	2.061
Std. Error of Mean	0.6658	8.581	4.685	5.157	0.7788
Lower 95% CI of mean	7.101	9.692	32.72	1.402	0.4753
Upper 95% CI of mean	10.36	51.68	55.64	26.64	4.287

Figure 7.3: Full Study Cumulative Results

Responses for all questions indicated a consistent positive preference for pharmacist engagement in the risk:benefit appraisal of healthcare innovations. However, a small increase in abstentions was observed compared to the pilot study [Figure 7.2].

As observed in the pilot study [Section 7.4.2] responses pertaining to the “number of statistical techniques utilised” and the presence of a “clear hierarchal description of the methodology utilised” received weaker positive support than the other factors assessed. However, the extent of any disparity of these two factors versus other assessed was lower than in the pilot study [Section 7.4.2].

7.3.4 Comparison of Pilot and Full Studies

	Response % Difference Final vs Pilot						
Response Categories	Q1	Q2a	Q2b	Q2c	Q2d	Q3	Q4
Abstain	7.41	7.41	11.11	7.41	3.97	9.26	7.41
Strongly Disagee	0.00	-3.44	3.70	1.85	1.98	0.00	1.85
Disagree	0.00	-6.22	-14.81	1.98	0.26	-1.72	-9.92
Agree	-2.91	-1.72	-1.98	-8.73	-8.86	-17.99	-9.26
Strongly Agree	-4.50	3.97	1.98	-2.51	2.65	10.45	9.92

Table 7.1: Comparison of Full and Pilot Studies

The tabular assessment of differences between the pilot and full studies supports visual assessments of Figures 7.2 and 7.3. However, perhaps in part due to the increased sample size, the frequency the “Strongly Disagree” category increased significantly for a number of questions in the full study compared to the pilot.

Due to the pooling and anonymisation of collected data is it not possible to discern if this observation can be attributed to an increase in the number of respondents offering consistently stronger responses – that is to say at either extreme of the Likert scale provided.

7.4 Discussion

Overall the use of this novel research platform, principally a regulatory compliance tool, yielded clear results in all areas, indicating pharmacists’ strong desire for greater engagement in the assessment and communication of risk:benefit of healthcare innovations. There were, however, some unexpected trends in the data generated.

7.4.1 Response Rates

Usually the platform is used to deliver single questions with a binary Likert scale. Therefore, the delivery of a larger number of questions with more complex scales was subject to significant uncertainty in research outcomes; in particular, with respect to response rates.

For both the pilot and full studies, the response rate was ~3% [Table 7.0], comparable to previous simpler studies, and sufficient to generate statistically significant data. However,

clearly in future studies it would be advantageous to simplify the questions posed and/or incentive pharmacists' to respond to yield richer outcomes.

7.4.2 Pilot Study

All pilot study results provided clear insights into pharmacists' attitudes to risk:benefit appraisal, most of which were positive. 78.60% of respondents indicated that they "strongly agreed" and 21.43% "agreed" that pharmacists have an important role in "helping patients understand the relative risks and benefit of medicines." This is an important finding as patient care delivery pathways increasingly engage pharmacists, who often may not have access to the same data and/or targeted training provided by product developers as clinicians.

Responses to selected risk:benefit appraisal critical quality factors assessed and validated in the risk:benefit scorecard were broadly; but not exclusively positive. Questions pertaining to the use of "consistent units to communicate risk:benefit of medicines" and "use of a clear hierarchal description of the calculation methodology" generated some negative "(strongly) disagree" responses, 39.28% and 50.00% respectively. The reasons for this are unclear and offer an opportunity for future investigation; however, it is possible that pharmacists wish to access simple, high-level and consistent product specific risk:benefit messages, and as such do not desire tremendous statistical depth and/or explanation.

Conversely, questions evaluating the need for "consistent units of risk:benefit" and the "evaluation of comparator risk:benefit" generated clear positive responses, "(strongly) agree" 96.43% and 82.14% respectively. This supports pharmacist attitudes towards the type of data they desire most highly being overtly functional, as opposed to detailed research interest.

One respondent abstained from question 2d; however responded to all other questions. Therefore, in the absence of a failure to understand the question sufficiently to offer a

response – unlikely given the strong responses of their peers – this may simply represent a data input error due to the respondents' limited familiarity with the system.

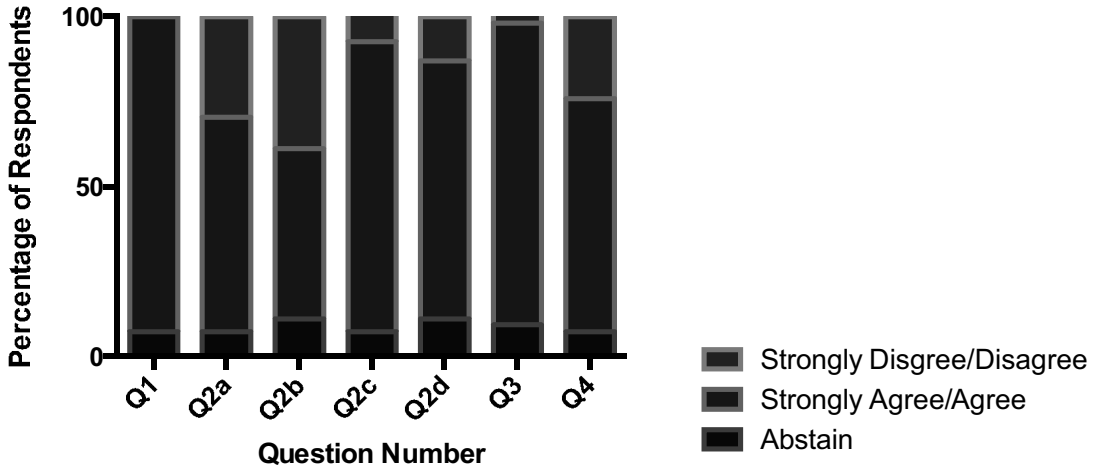
96.43% of respondents believed that a "formal risk:benefit analysis should be integrated into all clinical trials" – which given the limited number of good quality examples [Section 6.6] of such assessments in RCTs is of concern. 67.86% of respondents "(strongly) agreed" that "product risk:benefit should be integrated into patient information leaflets (PILs)." It is possible that the 32.14% of respondents that "[disagreed]" with this proposal believed that it would be confusing for the patient. However, one confounder is poor overall pharmacist beliefs in PILs.

7.4.3 Full Study

The results of the full study were comparable with those of the pilot. However, there was an unexplained increase in the number abstentions. In the context of the entire sample this was minimal. However, for some questions such as question 2d relating to the "evaluation of comparator risk:benefit" abstentions were modest (11.11%). If one is to assume that the abstention in question 2d in the pilot was not in fact data entry error; but a problem with the question causing confusion amongst respondents, it would suggest that questions 2b and 2d should be rewritten in future studies.

Additionally, there was a modest increase in the number of "strongly disagree" responses, the maximum being 5.56% in question 2d. However, in order to maintain regulatory compliance and respondent anonymisation, it is not possible to determine if these minor differences were idiosyncratic or a statistically significant of the larger stakeholder sample.

7.4.4 Comparison of Pilot and Full Studies



	Abstain	Strongly Agree/Agree	Strongly Disgree/Disagree
Minimum	7.407	50.00	0.0
25% Percentile	7.407	62.96	1.852
Median	7.407	75.93	12.96
75% Percentile	11.11	88.89	29.63
Maximum	11.11	92.59	38.89
Mean	8.730	74.87	16.40
Std. Deviation	1.761	15.38	14.79
Std. Error of Mean	0.6658	5.812	5.591
Lower 95% CI of mean	7.101	60.65	2.721
Upper 95% CI of mean	10.36	89.09	30.08

Figure 7.4: Comparison of Pilot and Full Studies (Abridged Response Categories)

As indicated by Figure 7.4 excellent consistency was demonstrated between the pilot and full studies, for all questions. Consequently, in the absence of statistical differences, the combined pilot and full study data [Figure 7.4] indicated overwhelmingly pharmacists' strong beliefs pertaining to the importance of risk:benefit appraisal, and their substantial role in its operationalization.

Therefore, in light of current and forthcoming changes in the role of pharmacists in the patient care pathway [Section 6.1] it is essential that pharmacists are engaged as a critical stakeholder in public consultations pertaining to risk:benefit assessment – and more broadly (and substantially) in the translation of healthcare innovations.

7.5 Limitations

The assessment protocol utilised was successful in the sense statistically significant results with real world practicability were generated. However, a number of limitations were identified.

Country selection was dictated by the countries in which the software provider had best coverage and access to potential respondents. However, these jurisdictions are not necessarily those with the greatest interest in and/or public consultation efforts into risk:benefit analysis. Both countries provided submissions, including supported by regional pharmacy associations, to the EMA risk:benefit analysis consultation (Mt-Isa et al., 2014). Additionally, there is no reason to assume that professional attitudes towards risk:benefit analysis and/or the technical knowledge of respondents should differ between the regions surveyed, or others in Europe.

The relatively low response rate is a source of frustration and limits the overall statistical validity of the results obtained. Future work to improve response rates – including appropriately incentivising pharmacists in a manner which does not introduce behavioural response biases – would be valuable.

Finally, it would be helpful to stratify responses by respondent characteristics. For example, respondent experience levels, general demographics and the type of pharmacy (community, hospital, dispensing clinician) (van Grootheest and de Jong-van den Berg, 2005). Experimental therapeutics, and thus those most likely to implement future recommendations to risk:benefit appraisal in RCTs, are most likely to be dispensed by hospital pharmacies (Schulz and Grimes, 2002).

7.6 Conclusion

Based upon the data generated in both the pilot and full studies it is evident that the pharmacists surveyed believe they have an important role in the assessment of risk:benefit

appraisal and the communication of this to patients. And that this stakeholder group should be deeply engaged in any future public consultations and/or practical assessments into risk:benefit appraisal – in particular, the implementation of adherence strategies pertaining to the EU FMD.

Chapter 8

Regenerative Medicine System Level Implications of Risk:Benefit Appraisal

8.1 Introduction

A sustained narrative thread throughout this body of research is the impact of systems and technology risks on the progress of healthcare translation. Critically, these two classes of risk are not mutually exclusive as they pertain to healthcare.

Scientific innovations drive the creation and mitigation of technology risk factors, with technological uncertainty a constant 'ebb and flow' in response. Concurrently, systems risks – that is to say the rules governing the technology innovation and risk environment – are equally responsive. Depending on individual technologies and individual stakeholder viewpoints, systems risks may be regarded as catalytic, innocuous or obstructive.

Irrespective of idiosyncratic viewpoints, it is broadly acknowledged that emerging combinational treatment approaches [Figure 8.0] fundamentally redistribute (although do not uniformly reduce) healthcare risks – in innovation and adoption – and contribute to the leverage of technology and systems risks. Herein, this feature of contemporary healthcare translation will be evaluated in the context of two *en vogue* emerging technologies: combinational diagnostics and regenerative medicines.

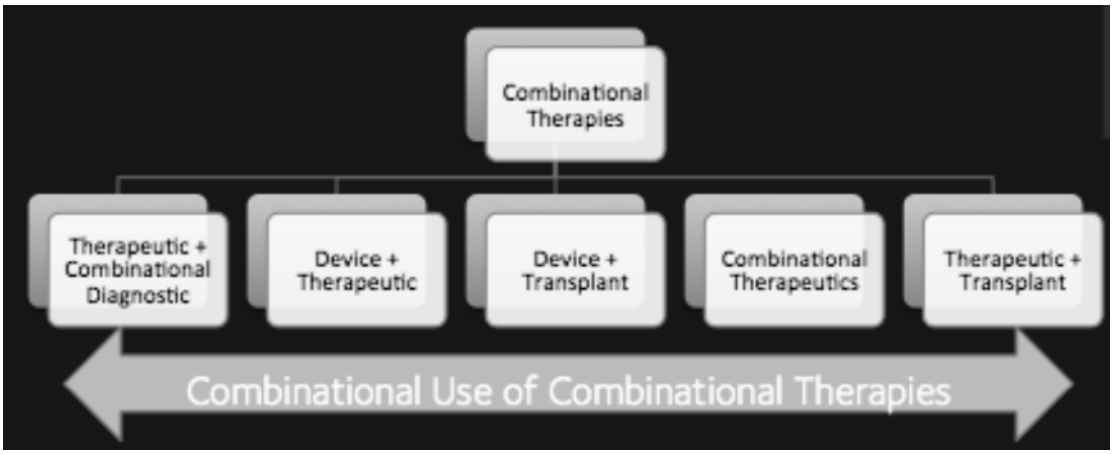


Figure 8.0: Hierarchy of Combinational Therapies and their Potential Combinatorial Application

8.2 Investigation Structure

This investigation will chronologically follow the healthcare translation cycle [Figure 8.1] (Mason and Manzotti, 2010) commencing with analysis of the role of risk sharing strategic partnerships in regenerative medicine; continuing thereafter to determine changing opportunities and challenges relating to intellectual property, biomanufacturing and clinical trials and adoption. A synthesis of the research conducted will be provided in Section 8.2 with full publications appended [Appendix 4.].

The details of DB contributions to all publications is provided within individual publications and in Tables 8.0-8.3.

The principal purpose of this analysis is to demonstrate the application of risk:benefit appraisal skills obtained in Sections 1.0-7.0. and apply them to emerging stakeholders and emerging technologies – which are subject to the greatest risks, benefits and uncertainties. Thereby meeting the initial aim of the body of research to conduct an academically rigorous study with clear 'real world' practicability, combining research depth and breadth [Figures 1.0 and 1.1].

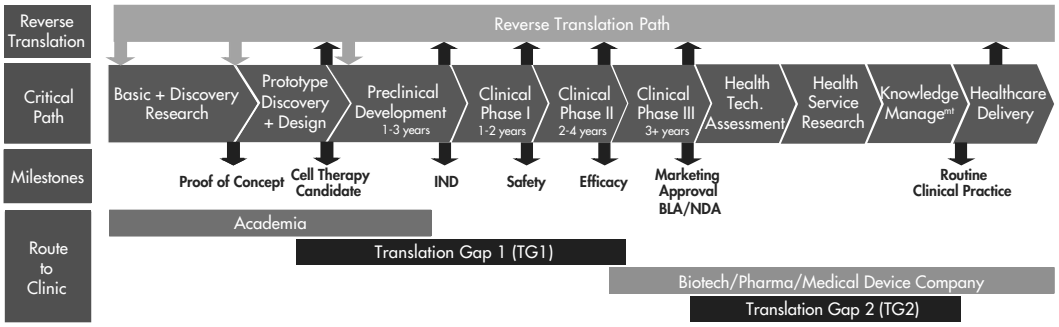


Figure 8.1: Healthcare Translation Cycle (Adapted from Cooksey, 2006 and Mason and Manzotti, 2010)

8.3 Research Synthesis

8.3.1 Strategic Partnerships and Risk Sharing Models

Publication Number	Reference	DB Authorship	DB Contribution
1	**Stem Cells and Development (2013) 22: 63-72** *The Implementation of Novel Collaborative Structures for the Identification and Resolution of Barriers to Pluripotent Stem Cell Translation*; Brindley, D.A., French, A., Suh, J., Roberts, M., Davies, B., Pinedo-Villanueva, R., Wartolowska, K., Rooke, K., Kramm, A., Judge, A., Morrey, M., Chandra, A., Hurley, H., Grover, L., Bingham, I., Siegel, B., Rattley, M.S., Buckler, R, McKeon, D., Krumholz, K., Hook, L., May, M., Rikabi, S., Pigott, R., Morys, M., Sabokbar, A., Titus, E., Laabi, Y., Lemaitre, G., Zahkia, R., Sipp, D., Horne, R., Bravery, C., Williams, D., Wall, I., Snyder, E.Y., Karp, J.M., Barker, R.W., Bure, K., Carr, A.J. and Reeve, B.	First Author	- Study design - Study execution - Manuscript preparation

1	**Trends in Biotechnology (2014), 32:9:436-440** *Global Strategic Partnerships in Regenerative Medicine;* French, A., Suh, J.Y., Suh, C.Y., Rubin, L., Barker, R.W., Bure, K., Reeve, B. & Brindley, D.A.	Senior Author	- Study design - Study execution - Manuscript preparation

Table 8.0: Bibliography and DAB Contribution Part A

Publication one (French et al., 2014b, Brindley et al., 2013b) evaluates unique systems risks in regenerative medicine relating to biomanufacturing, regulation, intellectual property and clinical adoption. The piece focuses on similarities and differences between such challenges faced for other technologies, including monoclonal antibodies (mAbs), and those faced by the developers of regenerative therapeutics. This culminates in an assessment of "challenges in the risk:benefit appraisal of cell-based healthcare innovations (Brindley et al., 2013b); for example, ethical and practical challenges pertaining to the use of placebo arms in cell based therapy clinical trials.

Subsequently, publication two (French et al., 2014b) presents and evaluates a comprehensive landscape of strategic partnerships in regenerative medicine. This analysis includes co-development partnership agreements in regenerative medicine by leading pharmaceutical companies, the majority of which have limited familiarity with regenerative medicines (French et al., 2014b). A key trend observed is the augmented role of non-profit companies (French et al., 2014b), disease specific foundations and academic institutions in regenerative medicine translation compared to previous technologies, attributable in part due to unique technological risks in regenerative medicine, and also differences in systems risks – including the contemporary balance of industrial internal versus external research and development (R&D), and intellectual property structures.

8.3.2 Changing Intellectual Property Models

Publication Number	Reference	DB Authorship	DB Contribution
3	**Nature Biotechnology (2014) 32: 742–748** *The Global Intellectual Property Landscape of Induced Pluripotent Stem Cell Technology;* Roberts, R.M., Wall, I.B., Bingham, I., Icely, D., Reeve, B., Bure, K., French, A. & Brindley, D.A.	Senior Author	- Study design - Study execution - Manuscript preparation - Data analysis

Table 8.1: Bibliography and DAB Contribution Part B

Adding substantial depth to initial analysis of the regenerative medicine (induced pluripotent stem cell, iPSC) intellectual property landscape in publication one (Brindley et al., 2013b), publication three (Roberts et al., 2014) addresses a major deficiency in academic and industrial literature, and seeks to assess the hypothesis: “the distribution of critical intellectual property in iPSCs is fundamentally different to previous therapeutics.”

Historically, critical intellectual property for therapeutics has focused on formulation(s) and/or structure(s) of pharmaco-active molecules. However, this is challenging to replicate in regenerative medicine as the pharmaco-active molecule is a living cell itself. Thus the living cell is utilised as a therapeutic entity as opposed to an expression system as in the case of mAbs and mammalian cell and bacterial culture strategies.

They key finding of the analysis is that critical intellectual property in regenerative medicine is focused in five key areas: cell culture surfaces and devices; cell separation; culture media; gene vectors; and sequencing technologies (Roberts et al., 2014). Consequently, this has substantial implications for the distribution of technology and systems risks in regenerative medicine translation.

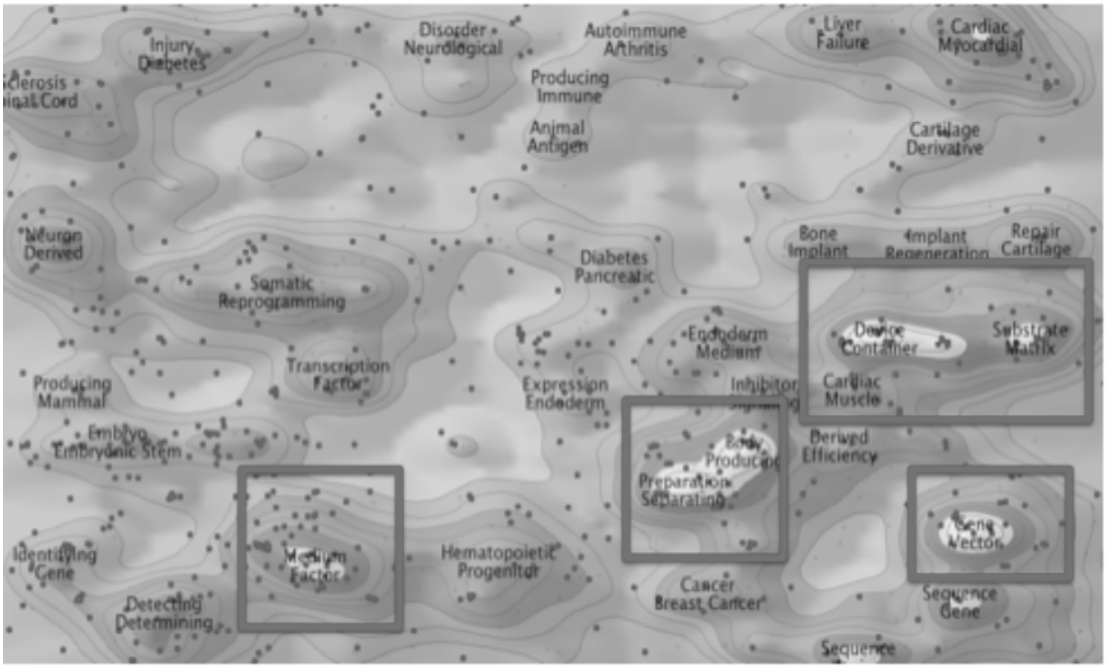


Figure 8.2: Intellectual Property Topographical Landscape for Induced Pluripotent Stem Cells (iPSCs)

8.3.3 Standards and Biomanufacturing

Publication Number	Reference	DB Authorship	DB Contribution
4	**Cell Stem Cell** *The Global Intellectual Property Landscape of Induced Pluripotent Stem Cell Technology;* Roberts, R.M., Wall, I.B., Bingham, I., Icely, D., Reeve, B., Bure, K., French, A. & Brindley, D.A.	Joint Senior Author	- Study design - Study execution - Manuscript preparation
5	**Stem Cells Translational Medicine** *The Global Intellectual Property Landscape of Induced Pluripotent Stem Cell Technology;* Roberts, R.M., Wall, I.B., Bingham, I., Icely, D., Reeve, B., Bure, K., French, A. & Brindley, D.A.	Senior Author	- Study design - Study execution - Manuscript preparation -

6	**Bioprocess International (2013) 11:3: 18–25** *Automation of Cell Therapy Biomanufacturing: Minimizing Regulatory Risks and Maximising Return on Investment;* Brindley, D.A, Wall, I.B. & Bure, K.	First Author	- Study design - Study execution - Manuscript preparation - Data analysis
7	**Bioprocess International (2014) 12:3: 14–21** *Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence: A Concise Review*; Brindley, D.A., French, A.L., Baptista, R., Timmins, N., Adams, T., Wall, I. and Bure, K	First Author	- Study design - Study execution - Manuscript preparation - Data analysis
8	**StemBook (August 2014 Edition)** *Cell Therapy Biomanufacturing Risk Management*; Rehki, R., Wall, I., French, A., Bure, K., Carr, A.J. and Brindley, D.A (2014) featured in "Cell Therapy Translation" edited by Williams, D. and Scadden, D.	Senior Author	- Study design - Study execution - Manuscript preparation
9	**"The Commercial Translation of Cell Based Therapies"** Cell Therapy Manufacturing: Identifying and Meeting Demand Springer Brindley, D.A., Smith, D., Davie, N.L. and Carmen, J. (2013) "Cell Therapy Manufacturing: Identifying and Meeting Demand" featured in "The Commercial Translation of Cell Based Therapies" Springer, edited by Vertes, A.	Contributing Author	- Study design - Study execution - Manuscript preparation

Table 8.2: Bibliography and DAB Contribution Part C

A substantial volume of research was conducted into biomanufacturing strategies, due to the interdependency of biomanufacturing strategies on cellular critical quality attributes (CQAs) for cell based therapeutic products, thus the convergence of system and technology risks.

Publication four (Silva, 2015) undertakes a comprehensive assessment of iPSC generation methods – integrative and non-integrative (Silva, 2015) – and extrapolates their impact on biomanufacturing strategies for cell for human transplantation. This builds on the findings of the intellectual property landscape presented in publication three (Roberts et al., 2014) and provides the basis for the physical versus reference standards assessment presented in publication five (French et al, 2015).

Publications six (Brindley, 2013) and seven (Brindley et al., 2014) implement investigations into material and reference standards, and assess the amenability of existing and future bioprocessing technologies to standards adherence and/or development. Additionally, the use of bioprocess automation as a risk management tool is proposed and supported by process data (Brindley, 2013); and contrasted versus existing manual and/or open bioprocessing strategies evaluated in publications eight (Rehki, R. et al, 2014) and nine (Carmen et al, 2014).

8.3.4 Clinical Trials and Adoption

Publication Number	Reference	DB Authorship	DB Contribution
10	**The Pharmacogenomics Journal (2014) 34:1-7** *An Evaluation of Regulatory and Commercial Barriers to Stratified Medicine Development and Adoption;* Meadows, N., Morrison, A., Brindley, D.A., Schuh, A. & Barker, R.W.	Contributing Author	- Study design - Study execution - Manuscript preparation - Data analysis
11	**Nature Medicine (2013) 19:5:530** *Good Genomic Practice (GGP):*	Joint First Author	- Study design - Study execution

	Essential for the Effective Use of Genomic Technologies to Support Improved Clinical Decision-Making; Barker, R.W., Brindley, D.A.* & Schuh, A.		- Manuscript preparation - Data analysis
12	**Nature (2013) 502:38** *Better drug access for terminal patients;* Brindley, D.A., Barker, R.W. and Lachmann, P.J. (2013)	First Author	- Manuscript preparation
13	**Journal of Tissue Engineering (2014) 5:1-8** *A Quantitative Assessment of Barriers to the Clinical Adoption of Cellular Therapies;* Davies, B., Rikabi, S., French, A., Pinedo-Villanueva, R., Morrey, M.E.,Wartolowska, K., Judge, A., MacLaren, R.E., Mathur, A., Williams, D.J., Wall, I.B., Birchall, M., Reeve, B., Atala, A., Barker, R.W., Cui, Z., Furniss, D., Bure, K., Snyder, E.Y., Karp, J.M., Price, A., Carr, A.J.* & Brindley, D.A.*	Joint Senior Author	- Study design - Study execution - Manuscript preparation - Data analysis
14	**British Medical Journal (2014) 348:3253** *Use of placebo control in the evaluation of surgery: a systematic review;* Wartolowska, K., Judge, A., Hopewell, S., Collins, G.S., Dean, B.J.F., Rombach, Brindley, D.A., Savulescu,J., Beard, D.J. and Carr, A.J.	Contributing Author	- Risk:benefit appraisal discussion - Manuscript preparation
15	**RAPS Principles of Global Regulatory Affairs** Borderline Regulation of Stem Cell Technologies: Therapies, Devices and	Senior Author	- Study design - Study execution - Manuscript preparation

	Combinational Products; Smith, J., Carr, A.J. and Brindley, D.A.		- Regulatory landscaping
16	**Rejuvenation Research (2014) 17:1:84-8** *An Assessment of the Key Barriers to the Commercialization and Clinical Adoption of Pluripotent Stem Cell Therapies;* French, A., Bure, K. & Brindley, D.A.	Senior Author	- Study design - Study execution - Manuscript preparation - Data analysis
17	**Rejuvenation Research (2013) 16:2:164-70** *Commercialization of Regenerative Medicine: Learning from Spin-Outs;* French, A., Buckler, R.L. & Brindley, D.A. .	Senior Author	- Study design - Study execution - Manuscript preparation - Data analysis
18	**Healthcare Insights (2014), 8:9:9-11** 'Bench to Bicycle:' A Clinical Perspective on Personalized Medicine: Genomics, Wearable Medical Devices and Regenerative Medicine; Brindley, D.A.	Sole Author	- Study design - Study execution - Manuscript preparation

Table 8.3: Bibliography and DAB Contribution Part D

The rate-limiting critical step in healthcare translation is final clinical adoption and its on-going regulatory oversight. This is particularly challenging in the emerging era of stratified medicine – utilising therapeutics and combinational diagnostics - where existing regulatory assessment and clinical implementation systems are not structured to effectively accommodate these technological advancements.

Consequently, a comprehensive evaluation to the barriers to commercialisation and clinical adoption of stratified medicines, including a number of cases studies, is presented in publication 10 (Meadows et al., 2014). And building upon principles applied in

biomanufacturing standards [Section 8.2.2] a robust framework to implement “Good Genomic Practice (GGP)” is presented in publication 11 (Barker et al., 2013).

A very personal illustration of the challenges – and potentially personal loss – perpetuated by the inadequate management of healthcare technology and systems risks is presented in publication 12 (Brindley et al., 2013a). The short letter remembers the eminent statistician, and latterly campaigner for expanded access to medicines, and his ultimately unsuccessful endeavours to obtain access to experimental therapeutics due to inadequate existing standards of care to treat motor neurone disease (MND aka amyotrophic lateral sclerosis, ALS).

The portfolio of publications concludes with an evaluation of important limitations – and in some cases perversities – is the commercialisation and clinical adoption of novel therapeutics. Publication 13 (Davies et al, 2014) assesses clinical attitudes to *en vogue* cell based therapies, and identifies the trinity of cost-effectiveness, efficacy and reimbursement as the most significant barriers to the broad clinical adoption of cell based therapies, across the clinical indications (Davies et al, 2014; Figure 3). This is complemented by publication 14 evaluating the use of placebo controls in the evaluation of surgery, which identifies a number of cell based therapy trials that employ placebo controls in clinical trials (Wartolowska et al., 2014). Curiously, however, in one particular study, despite the placebo surgery study arm being equivocal and/or superior to the active cell based therapy treatment, patients (Parkinson’s disease) still opted for the active treatment (Gross et al., 2011). Thus, while efforts to improve the rigour and transparency of clinical studies are welcome, patient beliefs about medicines – including their necessity concerns – are unavoidable (Horne and Weinman, 1999).

Publication 15 (Smith, J., et al) outlines a number of regulatory challenges posed by the regulation of borderline [combinational use of therapeutics and devices] healthcare innovations – such as those outlined above – and demonstrates the complexity of an

inherently heterogeneous regulatory environment [system risks] and its limited amenability to increasingly complex therapeutics [technology risks]. This tenet is echoed in publications 16 (French et al., 2013) and 17 (French et al., 2014a) that quantitatively evaluate a number of barriers to the effective and sustainable translation of regenerative medicines.

Finally, and potentially self-indulgently, publication 18 (Brindley, 2015) is a personal perspective on surviving an earthquake, cycling around corrugated roads the 'morning after [the earthquake]' – and how this relates to the future role of wearable medical devices in patient adherence. Now that's healthcare risk management.

8.4 Limitations

The principal limitation of this application of risk:benefit appraisal to emerging technologies, principally, regenerative medicines – encompassing cell, gene and immunotherapy – and combinational diagnostics, is the potential poor transferability and reproducibility of results when applied to other types of therapeutic technology. However, these technologies are broadly applicable; for example, to emerging synthetic biology and next generation sequencing – including CRISPR – approaches (Sander and Joung, 2014). And as such should be robust and of benefit to those engaged in healthcare translation.

Regulatory and intellectual property assessments are subject to a jurisdictional bias. For example, while the results presented are representative of patents filed in the EU and US, patent utilisation may differ across markets, due to economic incentives such as 'Patent Box(es)' and/or limitations on patentability, including business methods in the US that are not permissible in the EU (Dolgin, 2010).

Standards, reference and material, are valuable tools to generate and leverage consensus; however, they can also act to stymie innovation. For example, guidelines such as Good Manufacturing Practice (GMP) reagents represent adherence to a quality management system process, not necessarily the use of specialised reagents. Therefore, in the case of cell therapy biomanufacturing, where due to the nascence of the industry GMP reagents and

technologies are not uniformly available, this represent a barrier to technology development. This is perhaps embodied the quotation, “even a coffee cup can be GMP” (Pers Comm, Bure, K., Smith, J. 2014).

Ultimately, it is critical that all stakeholders remain cognisant of mutual idealities, limitations and practicalities so that in an effort to minimise system and technology risks, they are not simply redistributed – or increased.

8.5 Conclusions

The conflation and leveraged impact of systems and technology risks is tangible and substantial for both regenerative medicine and combinational diagnostics. However, multiple strategies are available for mitigate these risks through advances in strategic partnerships; biomanufacturing; intellectual property; and clinical adopt

Chapter 9

Healthcare Risk Management: Future Academic Research Strategy and Industrial Impact

9.1 Introduction

This investigation into the risk:benefit appraisal of healthcare innovations has always sought to be multi-dimensional to maximise the originality and impact of the findings presented. The first of these dimensions is the balance between research depth and breadth [Figures 1.0 and 1.1]. Secondly, the critical interaction between system and technology risks in healthcare translation [Section 1.0]. And finally, presented herein, the equipoise of short term and long term research objectives.

Despite the multi-year nature of the research programme, in the context of the long product development and life cycle horizons in biomedicine, the investigation presented in sections 1.0 – 9.0 represent relatively short investigations. Therefore, to maximise their impact as a foundation for future long-term research, a proposed future academic research strategy and examples of its potential industrial impact is presented herein.

9.2 Healthcare Risk Management: Defining an Appropriate Scope

To date, 'healthcare risk management' has been applied as a nebulous descriptor, encompassing actuarial, financial and clinical trial assessments of approved and pre-licensure healthcare innovations. Consequently, monitoring and implementing the literature in this nascent field is challenging – and its impact may be constrained.

Herein the following definition of healthcare risk management is applied:

"The analysis and optimisation of system and technology risks pertaining to the development and adoption of healthcare innovations."

9.3 Healthcare Risk Management: Academic Research Strategy

While remaining cognisant of the major confounders of the need to respond to changing academic and industrial needs, and the availability of research funding, the following vignettes describe potential future research projects that fall within the scope of healthcare risk management [Section 9.2]. And provide an opportunity for academically rigorous research with clear commercial practicability.

9.3.1 Risk:Benefit Appraisal of Healthcare Innovations

Hypothesis: The inadequate reporting of negative and equivocal clinical trial results prohibits the effective implementation of standardised and transparent risk:benefit appraisal methodologies.

Evidence: Implementation of risk:benefit appraisal balanced scorecard in multiple pools of blinded data for exemplar pre-licensure healthcare innovations – some groups with access to negative results and others without. Thereafter, the data yielded will be critically analysed and compared.

Academic Impact: Quantitative assessment of the criticality of negative results in the evaluation of novel healthcare innovations.

Industrial Impact: Provision of an academically robust basis to inform decisions to report or not report negative clinical results.

9.3.2 Risk Management Implications of Novel Regulatory Pathways

Hypothesis: Novel regulatory models decrease, as opposed to, increase or simply re-distribute system risk(s) in the development of healthcare innovations.

Evidence:

a) Systematic review of worldwide accelerated regulatory pathways
b) Development of multi-variable scenario analysis tools for therapeutic and device clinical trials
c) Construction of case studies on existing combinational therapeutics – successes and failures
d) Development of multi-variable scenario analysis tool for exemplar expedited regulatory pathways
e) Deployment of multi-variable scenario analysis tool for case study combinational therapeutics seeking expedited regulatory pathways

Academic Impact: Development of a multi-variable scenario analysis tool for exemplar expedited regulatory pathways that can be made available open access to be evaluated and developed by researchers worldwide.

Industrial Impact: Provision of a robust basis to inform decision making regarding optimal regulatory pathways for pre-licensure healthcare innovations and contribute to submissions to worldwide regulators during public consultations.

9.3.3 Changing Concentration of Risk and Value in Life Science Intellectual Property

Hypothesis: Open innovation models, including the delayed filing of formal intellectual property, reduce system risks and maximise value creation in the development of healthcare innovations.

Evidence: The rate of technological development will be studied using patents, publications, citations, clinical trial applications and progression as proxies – of innovations promulgated by open innovation versus conventional approaches.

Academic Impact: Validation of existing academic open innovation initiatives and academically validated assessment of best practices.

Industrial Impact: Assist industrialists in the selection and management of optimum partnership and technology development models.

9.4 Execution Risks

The two greatest execution risks to this research programme are the availability of appropriate data and of the human capital required to perform the research. For example, commercially available tools utilised in intellectual property and clinical trial landscaping is not typically available or utilised in academia. Therefore, a strategic relationship with a data vendor will be required to ensure the requisite access. Such commercial partners may also provide a helpful source of human capital, given limited access to 'translational' non-wet lab researchers.

Ensuring the international validity of all findings, while achieving sufficient academic depth into a single jurisdiction in the case of regulatory and/or intellectual property pathways is also a major execution risk. And is perhaps best embodied in the need to ensure industrial impact, while providing sufficiently rigorous academic insights to achieve publication in 'top tier' journals and contribute to a sustainable long-term research agenda.

Finally, in order to successfully devise and execute an impactful and sustainable research strategy it will be necessary to effectively create and manage inter and intra institution collaborations – including those across multiple academic disciplines. Therefore, strict time management will be required to ensure that the optimal balance between collaboration development and tangible research outcomes is struck.

9.5 Conclusion

Healthcare risk management is presently a disparate discipline, and as such its academic and industrial impact is constrained. The long term aim of this detailed investigation into the risk:benefit appraisal of healthcare innovations is to apply the tools developed and academic insights obtained to provide academically rigorous and commercially practicable answers to research questions, such as those outlined above [Section 9.4]. And, critically, to provide unique opportunities to translational researchers – to develop into the academic and industrial leaders of tomorrow.

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Optimising the Quality and Effectiveness of Risk:Benefit Appraisal Methodologies Utilised in Randomised Control Trials



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Submitted in partial fulfilment of the requirements

for the degree of Doctor of Philosophy

Supervisors

Prof. Andrew J. Carr

Prof. Sir John I. Bell

Hilary Term 2015

Volume II

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11. Appendices

11.1 Pilot Expert Elicitation Study Presentation

Risk Benefit Analysis

Expert Elicitation

David Brindley

August 2013

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Background

- This work forms part of an ongoing investigation by the University of Oxford (NDORMS) and the Centre for the Advancement of Sustainable Medical Innovation (CASMI)
- The purpose of the investigation is to assess the *quality* and *effectiveness* of existing risk: benefit appraisal methodologies
- Expert elicitation is being utilized as part of the assessment of key drivers of *effectiveness*
- All types of *healthcare innovation* are bring considered, including but not restricted to, therapeutics, medical devices and surgical interventions

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Value of Your Contribution

- Your experience as a XXXX makes you an expert whose opinion we value
- However, you are not expected to know specific answers to all questions
- Some questions may elicit straightforward responses, while others will require greater consideration
- This is not an examination. There are not any 'right' or 'wrong' answers
- This work is being conducted because, to our knowledge, expert elicitation has not been utilized previously to systematically devise 'utility weightings' for use in risk: benefit appraisal
- If at any point you have any queries, you are free to pause the process and pose any questions that you may have

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Your Contribution

The following slides will discuss the following:

- Background to Risk: Benefit Analysis
- The Importance and Context of Your Contribution
- Principles of Expert Elicitation

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Background to Risk: Benefit Analysis (1)

- Foundations of the existing regulatory process (for therapeutics)

1. *Safety*
2. *Identity*
3. *Efficacy/ Potency*
4. *Purity*

- The design of this regulatory process was informed significantly by high-profile product failures; notably, Thalidomide
- Few adaptions have been made to this process to accommodate technological advances, including monoclonal antibodies and (stem) cell based therapeutics

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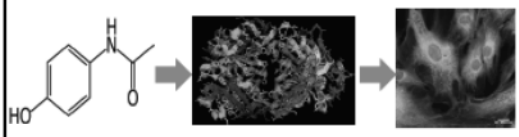
Background to Risk: Benefit Analysis (2)

- However, this existing methodology is proving to be inappropriate for novel healthcare innovations



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Background to Risk: Benefit Analysis (3)

- Therefore, risk: benefit analysis aims to provide a regulatory decision support tool.
- A major aim of this expert elicitation process is to determine, from *your* stakeholder viewpoint, which are the most essential and least essential factors determining the perceived quality of any risk: benefit appraisal technique(s)

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The Importance and Context of Your Contribution

- Two major limitations of existing risk: benefit appraisal techniques:
  - *Failure to accommodate multi-stakeholder viewpoints (utility weightings)*
  - *Failure to assess uncertainty*
- You have been identified as a key member of one of the following groups: clinicians, fundamental scientists, regulatory experts, statistician/epidemiologist or industrial leader

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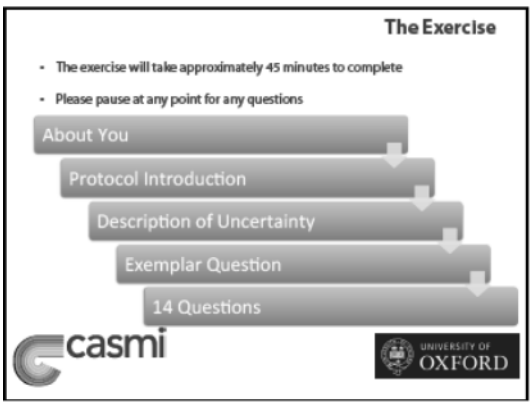
The Exercise
The exercise will take approximately 45 minutes to complete
Please pause at any point for any questions
About You
Protocol Introduction
Description of Uncertainty
Exemplar Question
14 Questions
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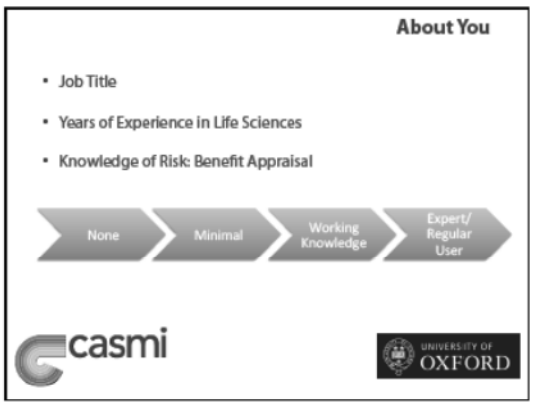
About You
Job Title
Years of Experience in Life Sciences
Knowledge of Risk: Benefit Appraisal
None
Minimal
Working Knowledge
Expert/ Regular User
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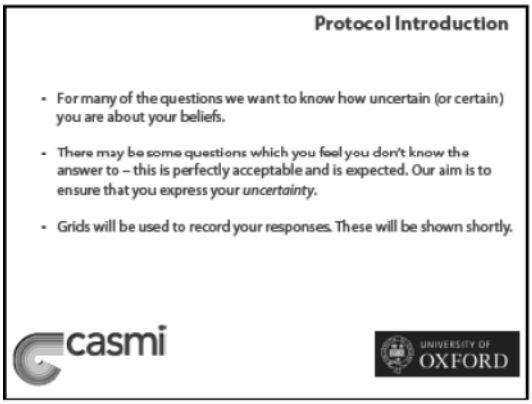
Protocol Introduction
For many of the questions we want to know how uncertain (or certain) you are about your beliefs.
There may be some questions which you feel you don't know the answer to – this is perfectly acceptable and is expected. Our aim is to ensure that you express your *uncertainty*.
Grids will be used to record your responses. These will be shown shortly.
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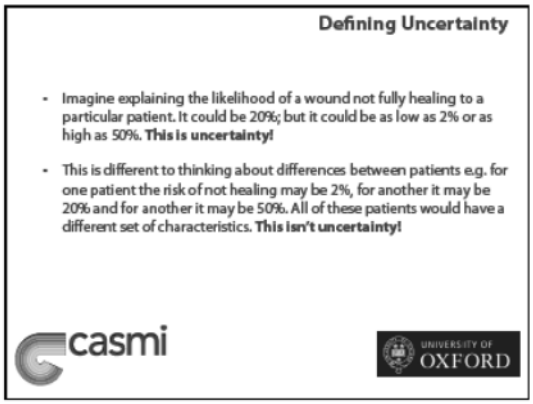
Defining Uncertainty
Imagine explaining the likelihood of a wound not fully healing to a particular patient. It could be 20%; but it could be as low as 2% or as high as 50%. **This is uncertainty!**
This is different to thinking about differences between patients e.g. for one patient the risk of not healing may be 2%, for another it may be 20% and for another it may be 50%. All of these patients would have a different set of characteristics. **This isn't uncertainty!**
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Equipment: Grids (1)

- We will present you with one sheet of paper with a grid for each question.
- Possible values are given along the bottom of the grid, ranging from 0 (entirely unnecessary) to 100 (entirely essential)
- All answers will be required in this format
- You will be provided with 21 counters which you are to place on the grid representing your belief and uncertainty about the question

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Equipment: Grids (2)

- Please begin by placing two of the counters at the bottom of the grid. One must represent the lowest value you believe is likely, the other the highest
- Place the remaining 19 counters between these two extremes. The more likely you believe a response is, the more chips you should place in that column
- You can place all 21 counters in one column if you feel that there is no uncertainty around the answer
- These possible scenarios will now be explained pictorially

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Worked Example

Question:

What proportion of pregnant women do you think are 50 years or older?

Please be mindful of the degree of certainty in your response and how this is reflected by the distribution of counters on the grid

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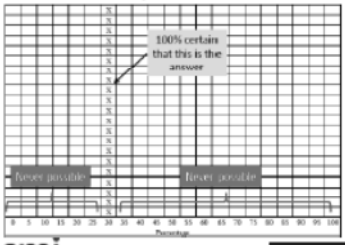
Example: Absolute Certainty

What proportion of pregnant women do you think are 50 years or older?



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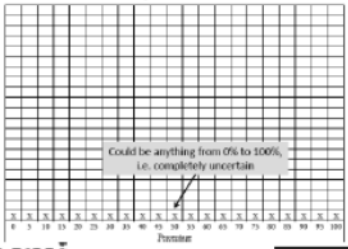
Example: Absolute Uncertainty

What proportion of pregnant women do you think are 50 years or older?



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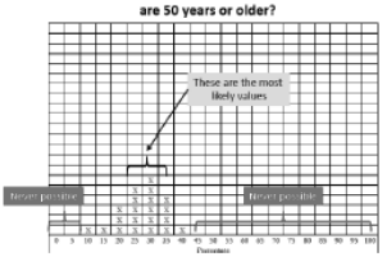
Example: Typical Distribution

What proportion of pregnant women do you think are 50 years or older?



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Practice is Over!

- Your INDIVIDUAL responses that are of interest – not what you believe to be the 'census' amongst your professional peers
- Your responses will be recorded anonymously and pooled along with other respondents to inform the assignment of 'utility weightings'
- Please feel free to amend responses throughout the process
- Use a 'fresh' grid for each question
- Questions are welcomed!
- And (even though it's not an examination) good luck!

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Familiarization

- The terminology below will appear in the following questions
- Prior understanding of the terminology is not required



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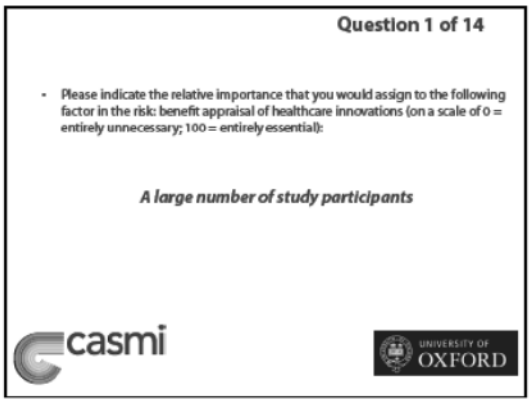
Question 1 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
A large number of study participants
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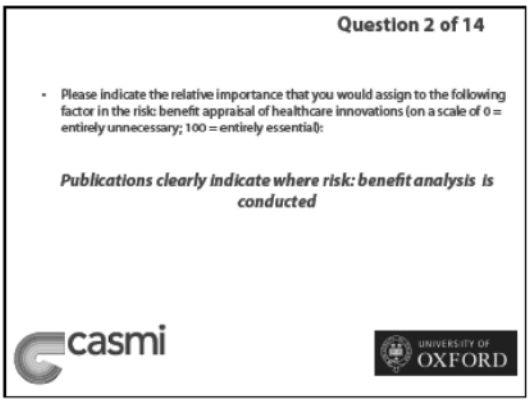
Question 2 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
Publications clearly indicate where risk: benefit analysis is conducted
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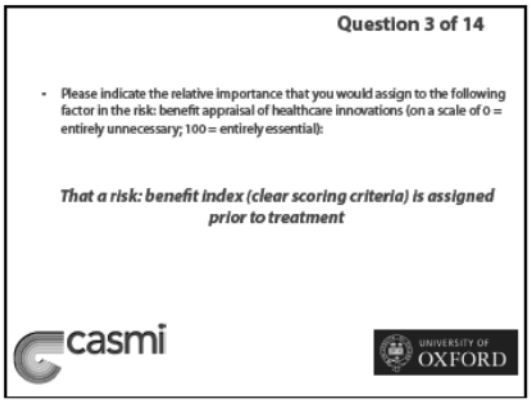
Question 3 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That a risk: benefit index (clear scoring criteria) is assigned prior to treatment
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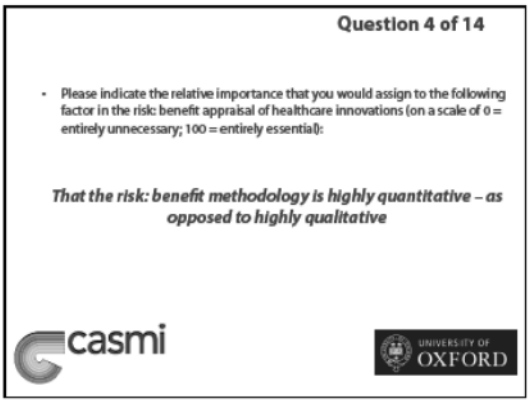
Question 4 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That the risk: benefit methodology is highly quantitative – as opposed to highly qualitative
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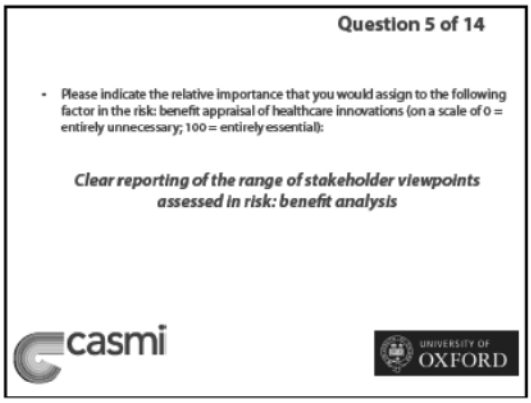
Question 5 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
Clear reporting of the range of stakeholder viewpoints assessed in risk: benefit analysis
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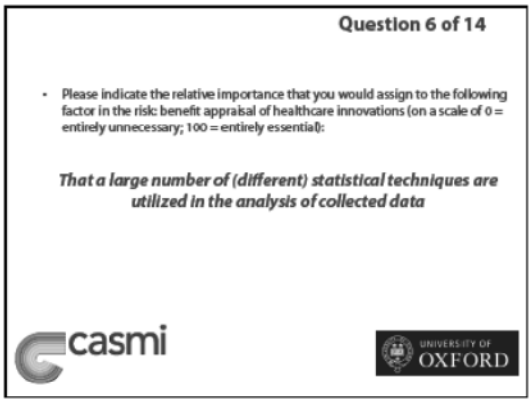
Question 6 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That a large number of (different) statistical techniques are utilized in the analysis of collected data
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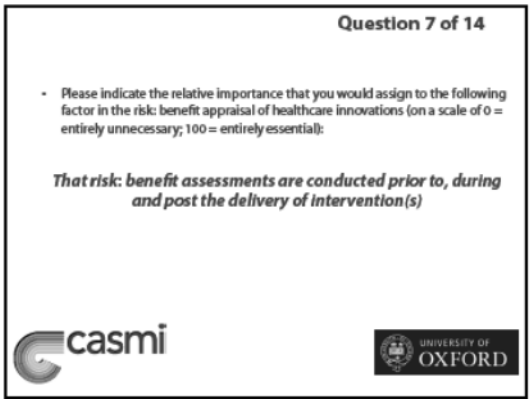
Question 7 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That risk: benefit assessments are conducted prior to, during and post the delivery of intervention(s)
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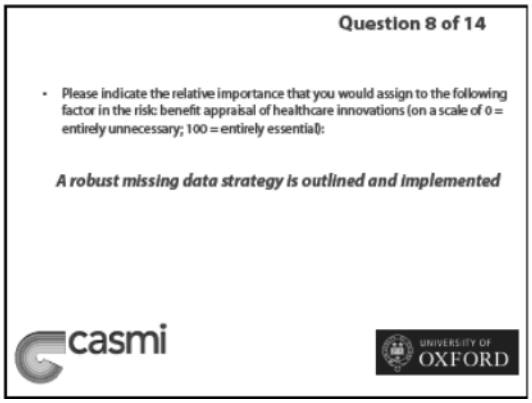
Question 8 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
A robust missing data strategy is outlined and implemented
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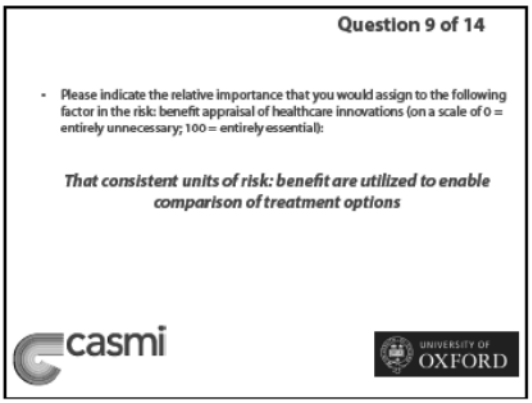
Question 9 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That consistent units of risk: benefit are utilized to enable comparison of treatment options
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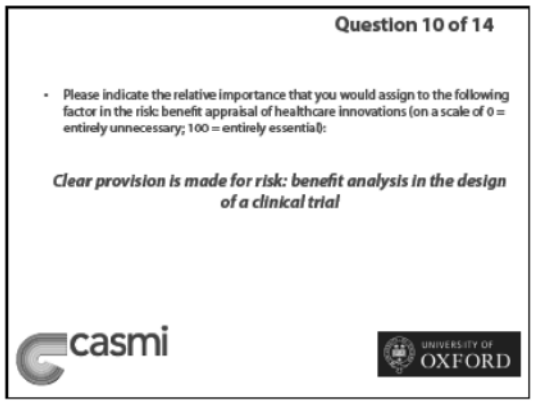
Question 10 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
Clear provision is made for risk: benefit analysis in the design of a clinical trial
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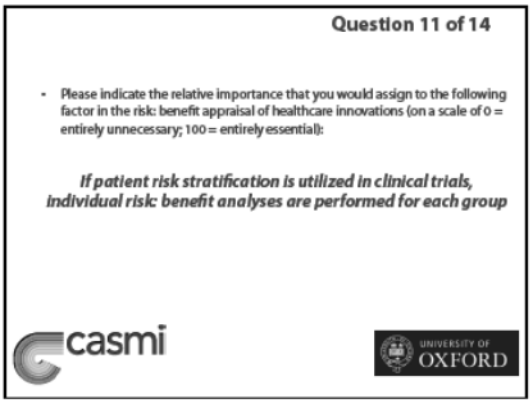
Question 11 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
If patient risk stratification is utilized in clinical trials, individual risk: benefit analyses are performed for each group
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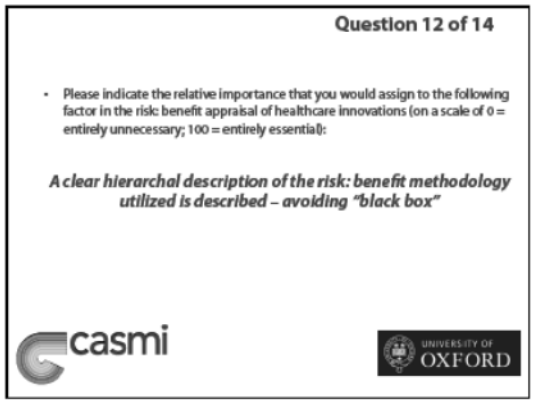
Question 12 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
A clear hierarchal description of the risk: benefit methodology utilized is described – avoiding "black box"
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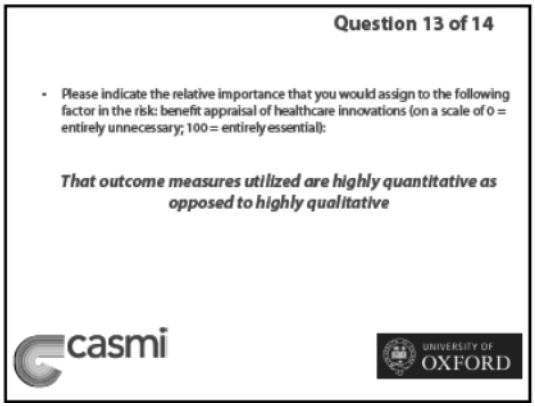
Question 13 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That outcome measures utilized are highly quantitative as opposed to highly qualitative
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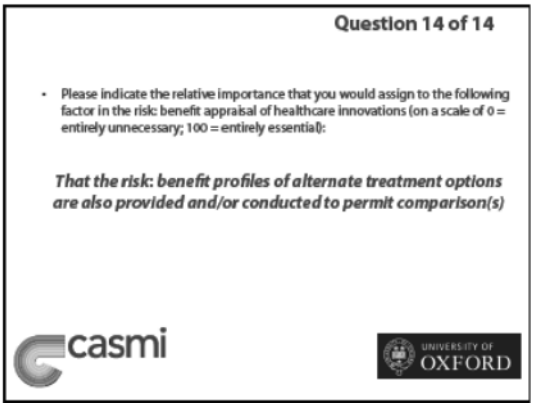
Question 14 of 14
Please indicate the relative importance that you would assign to the following factor in the risk: benefit appraisal of healthcare innovations (on a scale of 0 = entirely unnecessary; 100 = entirely essential):
That the risk: benefit profiles of alternate treatment options are also provided and/or conducted to permit comparison(s)
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11.2 Expert Elicitation Evaluation Questionnaire



In order to maximize the long-term value of your recent expert elicitation exercise, we would appreciate your continued participation by completing the following questionnaire. The purpose of this survey is to assess the relative strengths and weaknesses of the protocol utilised, in order to optimise future work.

Section A

For each of the following factors, prospective please **rank the relative success** of the following features of the expert elicitation protocol utilized, from your perspective, on a scale of 1 to 5, where 1 represents a *minimally successful* factor and 5 represents a *highly successful* factor. Please provide ***all*** responses in this manner unless otherwise indicated.

(1) *Clarity of Technique(s):* Please rank the relative success, on a scale of 1-5, the clarity of the expert elicitation protocol utilised in conveying how to express your responses during the assessment.

(2) *Clarity of Questions:* Please rank the relative success, on a scale of 1-5, of the clarity questions.

(3) *Relevance of Questions:* Please rank the relative success, on a scale of 1-5, of the questions utilised in terms of their relevance to evaluating the quality and effectiveness of existing risk: benefit appraisal methodologies.

(4) *Context:* Please rank the relative success, on a scale of 1-5, of the protocol utilised in providing adequate background to risk: benefit appraisal methodologies to inform your responses.

(5) *Timing:* Please rank the relative success, on a scale of 1-5, of the protocol utilised in terms of the duration of the exercises conducted.

Section B

Please provide simple 'yes' or 'no' answers to the following questions:

(6) Has the exercise increased the likelihood that you may conduct further individual research into risk: benefit analysis?

(7) Has the exercise increased the likelihood that you may seek to integrate risk: benefit analysis techniques into your own research?

(8) Would you appreciate further training in risk: benefit analysis?



Section C

Where appropriate, please provide answers in written prose to the following questions:

(9) Do you believe that any key factors relevant to the risk: benefit analyses of healthcare innovations were omitted from the survey? If so, please detail these below.

(10)Currently, the study assesses the views of clinicians, fundamental scientists, regulatory professionals, industry leaders and epidemiologists/ statisticians. Do you believe that the opinions of other key stakeholders should be assessed? If so, please detail these below.

Thank you for your participation



11.3 Initial Systematic Review Records

Cochrane

Reference Number	*Citation*
1	COENEN, S., VAN ROYEN, P., MICHIELS, B. & DENEKENS, J. 2004. Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. The Journal of antimicrobial chemotherapy, 54, 661-72.
2	MORROW, D. A., ANTMAN, E. M., MURPHY, S. A., QIN, J., RUDA, M., GUNERI, S., JACOB, A. J., BUDAJ, A. & BRAUNWALD, E. 2007. Effect of enoxaparin versus unfractionated heparin in diabetic patients with ST-elevation myocardial infarction in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction study 25 (ExTRACT-TIMI 25) trial. American Heart Journal, 154, 1078-84, 1084 e1.
3	O'DONOGHUE, M., MORROW, D. A., CANNON, C. P., GUO, W., MURPHY, S. A., GIBSON, C. M. & SABATINE, M. S. 2008. Association between baseline neutrophil count, clopidogrel therapy, and clinical and angiographic outcomes in patients with ST-elevation myocardial infarction receiving fibrinolytic therapy. European Heart Journal, 29, 984-991.
4	SCIRICA, B. M., CANNON, C. P., SABATINE, M. S., JAROLIM, P., SLOANE, S., RIFAI, N., BRAUNWALD, E. & MORROW, D. A. 2009. Concentrations of C-reactive protein and B-type natriuretic peptide 30 days after acute coronary syndromes independently predict hospitalization for heart failure and cardiovascular death. Clinical chemistry, 55, 265-73.

EMBASE

Reference Number	*Citation*
1	2011. Substance use in pregnancy: No. 256, April 2011. International Journal of Gynecology and Obstetrics, 114, 190-202.
2	ABRAMS, P., BLAIVAS, J. G., FOWLER, C. J., FOURCROY, J. L., MACDIARMID, S. A., SIEGEL, S. W. & VAN KERREBROECK, P. 2003. The role of neuromodulation in the management of urinary urge incontinence. BJU International, 91, 355-359.
3	AL-INANY, H., YOUSSEF, M., ABOULGHAR, M., BROEKMANS, F., STERRENBURG, M., SMIT, J. & ABOUSETTA, A. 2011. GnRH antagonists are safer than agonists: Risk/Benefit ratio has changed. Human Reproduction, 26, i334.
4	ALLEN, D. B. & CARREL, A. L. 2004. Growth hormone therapy for Prader-Willi syndrome: A critical appraisal. Journal of Pediatric Endocrinology and Metabolism, 17, 1297-1306.
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46 HALASKA, M., RALPH, G., WIEDEMANN, A., PRIMUS, G., BALLERING-BRUHL, B., HOFNER, K. & JONAS, U. 2003. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World Journal of Urology, 20, 392-9.

11.4 Eligible Systematic Review Records

Overview							Research Profile	
Reference Number	Citation	Database Source	Number of Participants	Indication	Field	Funding	Journal impact factor.	Number of citations to date.
1	1991. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. American Journal of Medicine, 90, 450-9.	Medline	817	Severe Hypoglycemia	Endocrinology	Public	5.43	49
2	1992. A multicentre, randomized trial on the benefit/risk profile of amiodarone, flecainide and propafenone in patients with cardiac disease and complex ventricular arrhythmias. Antiarrhythmic Drug Evaluation Group (A.D.E.G.). European Heart Journal, 13, 1251-8.	Medline	141	Complex ventricular arrythmia and cardiovascular disease	Cardiology	Not disclosed	10.478	Unknown
3	ADAMS, H. P., JR., EFFRON, M. B., TORNER, J., DAVALOS, A., FRAYNE, J., TEAL, P., LECLERC, J., OEMAR, B., PADGETT, L., BARNATHAN, E. S., HACKE, W. & AB, E.-I. I. I. 2008. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke, 39, 87-99.	Medline	808	Acute Ichemic Stroke	Cardiology	Private - delivered by an academic institution.	5.756	21
9	BAI, W., HENNEICKE-VON ZEPELIN, H.-H., WANG, S., ZHENG, S., LIU, J., ZHANG, Z., GENG, L., HU, L., JIAO, C. & LISKE, E. 2007. Efficacy and tolerability of a medicinal product containing an isopropanolic black cohosh extract in Chinese women with menopausal symptoms: a randomized, double blind, parallel-controlled study versus tibolone. Maturitas, 58, 31-41.	Medline	244	Menopausal symptoms	Gynecology	Not disclosed	2.32	3
10	BEISCHER, W., DEMBSKI, J. C., GRUSS, J. D., HOFGARTNER, F., HORSCH, A., HORSCH, S., KUHLMANN, H. W., LOOSE, D. A., MIETASCHK, A., SCHWILDEN, E. D., SPENGEL, F., SPITZER, W., STABEN, P., STALLKAMP, B., STURZEBECHER, C. S., TOKHI, M. & VON BILDERLING, P. 1998. Low-dose iloprost infusions compared to the standard dose in patients with peripheral arterial occlusive disease Fontaine stage IV. DAWID Study Group. Vasa, 27, 15-9.	Medline	302	Peripheral arterial occlusive disease Fontaine stage IV	Cardiology	Not disclosed	1.308	Unknown
20	BUTTGEREIT, F., DOERING, G., SCHAEFFLER, A., WITTE, S., SIERAKOWSKI, S., GROMNICA-IHLE, E., JEKA, S., KRUEGER, K., SZECHINSKI, J. & ALTEN, R. 2008. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet, 371, 205-14.	Medline	288	Rhuematoid Arthritis	Musculoskeltal	Private - delivered by an academic institution.	38.28	161
30	COLWELL, J. A. 1996. The feasibility of intensive insulin management in non-insulin-dependent diabetes mellitus. Implications of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM. Annals of Internal Medicine, 124, 131-3.	Medline	153	Non-Insulin Dependent Diabetes Mellitus	Endocrine	Public/ Charitable	16.7	2
35	DHAINAUT, J.-F., LATERRE, P.-F., JANES, J. M., BERNARD, G. R., ARTIGAS, A., BAKKER, J., RIESS, H., BASSON, B. R., CHARPENTIER, J., UTTERBACK, B. G., VINCENT, J.-L. & RECOMBINANT HUMAN ACTIVATED PROTEIN, C. W. E. I. S. S. G. 2003. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Medicine, 29, 894-903.	Medline	1271	Multiple Organ Dysfunction	General Medicine	Private	5.399	134
37	DORSCHNER, W., STOLZENBURG, J. U., GRIEBENOW, R., HALASKA, M., SCHUBERT, G., MURTZ, G., FRANK, M. & WIENERS, F. 2000. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. European Urology, 37, 702-8.	Medline	98	Urinary incontinence	Urology	Private - delivered by an academic institution.	8.493	60
42	GAJDOS, V., SOUBEYRAND, B., VIDOR, E., RICHARD, P., BOYER, J., SADORGE, C. & FIQUET, A. 2011. Immunogenicity and safety of combined adsorbed low-dose diphtheria, tetanus and inactivated poliovirus vaccine (REVAXIS ()) versus combined diphtheria, tetanus and inactivated poliovirus vaccine (DT Polio ()) given as a booster dose at 6 years of age. Human Vaccines, 7, 349-56.	Medline	760	Polio Vaccination	Infectious diseases	Private - delivered by an academic institution.	3.58	1
46	HALASKA, M., RALPH, G., WIEDEMANN, A., PRIMUS, G., BALLERING-BRUHL, B., HOFNER, K. & JONAS, U. 2003. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World Journal of Urology, 20, 392-9.	Medline	358	Detrusor Instability	Urology	Not disclosed.	2.411	159
50	HEID, F., SCHMIDT-GLINTZER, A., PIEPHO, T. & JAGE, J. 2007. Epidural ropivacaine -- where are the benefits? A prospective, randomized, double-blind trial in patients with retropubic prostatectomy. Acta Anaesthesiologica Scandinavica, 51, 294-8.	Medline	40	Anesthetic agents	Anesthesia	Undisclosed	2.188	Unknown
51	HELBLING, B., JOCHUM, W., STAMENIC, I., KNOPFLI, M., CERNY, A., BOROVICKA, J., GONVERS, J.-J., WILHELMI, M., DINGES, S., MULLHAUPT, B., ESTEBAN, A., MEYER-WYSS, B., RENNER, E. L. & SWISS ASSOCIATION FOR THE STUDY OF THE, L. 2006. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. Journal of Viral Hepatitis, 13, 762-9.	Medline	124	Fibrosis/ Cirrhosis	Musculoskeletal	Undisclosed	4.088	59
55	HOFFMANN, K., AUER, T., STUCKER, M., HOFFMANN, A. & ALTMEYER, P. 1998. Comparison of skin atrophy and vasoconstriction due to mometasone furoate, methylprednisolone and hydrocortisone. Journal of the European Academy of Dermatology & Venereology, 10, 137-42.	Medline	10	Skin atrophy and vasoconstriction.	Dermatology	Undisclosed	2.98	Unknown
57	INVESTIGATORS, E.-P., BULLER, H. R., PRINS, M. H., LENSIN, A. W. A., DECOUSUS, H., JACOBSON, B. F., MINAR, E., CHLUMSKY, J., VERHAMME, P., WELLS, P., AGNELLI, G., COHEN, A., BERKOWITZ, S. D., BOUNAMEAUX, H., DAVIDSON, B. L., MISSELWITZ, F., GALLUS, A. S., RASKOB, G. E., SCHELLONG, S. & SEGERS, A. 2012. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. New England Journal of Medicine, 366, 1287-97.	Medline	4832	Pulmonary Embolism	Cariology	Private	53.298	79

59	KAUFMANN, R. M., KRAFT, B., FREY, R., WINKLER, D., WEISZENBICHLER, S., BACKER, C., KASPER, S. & KRESS, H. G. 2010. Acute psychotropic effects of oral cannabis extract with a defined content of Delta9-tetrahydrocannabinol (THC) in healthy volunteers. Pharmacopsychiatry, 43, 24-32.	Medline	16	Drug induced psychotropic effects	Psychiatry	Public/ charitable	2.071	1
60	KIRCH, W., BURGER, K. J., WEIDINGER, G. & WELZEL, D. 1990. Efficacy and tolerability of the new calcium antagonist isradipine in essential hypertension. Journal of Cardiovascular Pharmacology, 15 Suppl 1, S55-9.	Medline	86	Hypertension	Cardiology	Undisclosed	2.287	13
61	KIRCHNER, M. & MARSHALL, D. 2006. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthritis & Cartilage, 14, 154-62.	Medline	314	Osteoarthritis	Musculoskeletal	Undisclosed	4.365	52
63	KLEIN, G., KULLICH, W., SCHNITKER, J. & SCHWANN, H. 2006. Efficacy and tolerance of an oral enzyme combination in painful osteoarthritis of the hip. A double-blind, randomised study comparing oral enzymes with non-steroidal anti-inflammatory drugs. Clinical & Experimental Rheumatology, 24, 25-30.	Medline	90	Osteoarthritis	Musculoskeletal	Undisclosed	2.148	37
65	KORTING, H. C., SCHOLLMANN, C., WILLERS, C. & WIGGER-ALBERTI, W. 2012. Bioavailability, antipsoriatic efficacy and tolerability of a new light cream with mometasone furoate 0.1%. Skin Pharmacology & Physiology, 25, 133-41.	Medline	31	Inflammatory skin disorders	Dermatology	Public/ Private	2.92	3
66	KRUG, N., HOHLFELD, J. M., GELDMACHER, H., LARBIG, M., HEERMANN, R., LAVALLEE, N., NGUYEN, D. T., PETZOLD, U. & HERMANN, R. 2005. Effect of loteprednol etabonate nasal spray suspension on seasonal allergic rhinitis assessed by allergen challenge in an environmental exposure unit. Allergy, 60, 354-9.	Medline	165	Seasonal allergic rhinitis.	ENT	Public/ Private	6.271	17
68	LASSEN, M. R., DAVIDSON, B. L., GALLUS, A., PINEO, G., ANSELL, J. & DEITCHMAN, D. 2007. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. Journal of Thrombosis & Haemostasis, 5, 2368-75.	Medline	1238	Thromboprophylaxis	Haematology	Undisclosed	5.731	218
72	LEYNADIER, F., MEES, K., ARENDT, C. & PINELLI, M. E. 2001. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. Acta Oto-Rhino-Laryngologica Belgica, 55, 305-12.	Medline	470	Seasonal allergic rhinitis.	ENT	Undisclosed	1.861	Unknown
73	LLORCA, P.-M., LANCON, C., DISDIER, B., FARISSE, J., SAPIN, C. & AUQUIER, P. 2002. Effectiveness of clozapine in neuroleptic-resistant schizophrenia: clinical response and plasma concentrations. Journal of Psychiatry & Neuroscience, 27, 30-7.	Medline	37	Schizophrenia	Psychiatry	Undisclosed	5.34	32
75	LUPORINI, G., BARNI, S., MARCHI, E. & DAFFONCHIO, L. 1998. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. European Respiratory Journal, 12, 97-101.	Medline	140	Metastatic lung cancer	Oncology	Undisclosed	5.895	45
77	MACPHEE, G. J., MCPHAIL, E. M., BUTLER, E. & BRODIE, M. J. 1986. Controlled evaluation of a supplementary dose of carbamazepine on psychomotor function in epileptic patients. European Journal of Clinical Pharmacology, 31, 195-9.	Medline	8	Epilepsy	Neurological	Undisclosed	2.845	33
88	OBERMAYR, R. P., MAYERHOFER, L., KNECHTELSDORFER, M., MERSICH, N., HUBER, E. R., GEYER, G. & TRAGL, K.-H. 2005. The age-related down-regulation of the growth hormone/insulin-like growth factor-1 axis in the elderly male is reversed considerably by donepezil, a drug for Alzheimer's disease. Experimental Gerontology, 40, 157-63.	Medline	24	Growth hormone secretion.	Endocrinology	Undisclosed	3.644	33
93	REINALTER, S. C., GRONE, H. J., KONRAD, M., SEYBERTH, H. W. & KLAUS, G. 2001. Evaluation of long-term treatment with indomethacin in hereditary hypokalemic salt-losing tubulopathies. Journal of Pediatrics, 139, 398-406.	Medline	12	Tubulopathies	Hepatology	Undisclosed	4.115	24
104	THRAILKILL, K. M., QUATTRIN, T., BAKER, L., KUNTZE, J. E., COMPTON, P. G. & MARTHA, P. M., JR. 1999. Cotherapy with recombinant human insulin-like growth factor I and insulin improves glycemic control in type 1 diabetes. RhIGF-I in IDDM Study Group. Diabetes Care, 22, 585-92.	Medline	223	Diabetes	Endocrinology	Undisclosed	7.141	84
112	WANG, T. Y., WHITE, J. A., TRICOCI, P., GIUGLIANO, R. P., ZEYMER, U., HARRINGTON, R. A., MONTALESCOT, G., JAMES, S. K., VAN DE WERF, F., ARMSTRONG, P. W., BRAUNWALD, E., CALIFF, R. M. & NEWBY, L. K. 2011. Upstream clopidogrel use and the efficacy and safety of early eptifibatide treatment in patients with acute coronary syndrome: an analysis from the Early Glycoprotein IIb/IIIa Inhibition in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) trial. Circulation, 123, 722-30.	Medline	9166	Acute coronary syndrome	Cardiology	Private/ public.	14.816	15
115	WOHLRAB, J., BECK, G. M., NEUBERT, R. H. H., SISCHKA, U. & KREFT, B. 2010. Hydrocortisone aceponate activity and benefit/risk ratio in relation to reference topical glucocorticoids. Skin Pharmacology & Physiology, 23, 177-82.	Medline	31	Use of topical steroids in general dermatological indications.	Dermatology	Undisclosed	2.92	2
EMBASE								
40	CHAWLA, S. P., GRUNBERG, S. M., GRALLA, R. J., HESKETH, P. J., RITTENBERG, C., ELMER, M. E., SCHMIDT, C., TAYLOR, A., CARIDES, A. D., EVANS, J. K. & HORGAN, K. J. 2003. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer, 97, 2290-2300.	Embase	257	Chemotherapy induced nausea and vomiting.	Oncology	Undisclosed	4.771	152

72	GALLI, E., BASSI, M. S., MORA, E., MARTELLI, M., GIANNI, S., AURICCHIO, G., ARABITO, E. & ROSSI, P. 2006. A double-blind randomized placebo-controlled trial with short-term beta-glucuronidase therapy in children with chronic rhinoconjunctivitis and/or asthma due to dust mite allergy. Journal of Investigational Allergology and Clinical Immunology, 16, 345-350.	Embase	125	Chronic rhinoconjunctivitis	Opthalmology	Undisclosed	2.269	2
95	KAVANAUGH, A., FLEISCHMANN, R. M., EMERY, P., KUPPER, H., REDDEN, L., GUERETTE, B., SANTRA, S. & SMOLEN, J. S. 2013. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-Week results from the randomised, controlled OPTIMA study. Annals of the Rheumatic Diseases, 72, 64-71.	Embase	1032	Rhuematoid Arthritis	Musculoskeletal	Private-public	8.727	18
103	LEHERT, P., POIRIER-LITTRE, M. F., PRINGUEY, D. & GALINOWSKI, A. 1998. New statistical proposals to evaluate the benefit/risk ratio of long-term treatment of depression. Application to a one-year double-blind study comparing medifoxamine with fluoxetine. Clinical Drug Investigation, 15, 285-295.	Embase	313	Clinical depression	Psychiatry	Private-public	1.822	Unknown
144	SINGH, R., ALPERN, L., JAFFE, G. J., LEHMANN, R. P., LIM, J., REISER, H. J., SALL, K., WALTERS, T. & SAGER, D. 2012. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clinical Ophthalmology, 6, 1259-1269.	Embase	263	Diabetic retinopathy	Opthalmology	Undisclosed	2.083	1

11.5 Pharmacist Questionnaires

Note: Inconsistencies herein, including font and questionnaire structure intentional, and reflect the exact questionnaires distributed to international respondents following independent translation. However, the logos of the University of Oxford and Aegate Ltd are omitted.

11.5.1 English: Pharmacist Questionnaire

***

Oxford Pilot Risk Benefit Questions

Aegate is currently working with the University of Oxford to develop and deploy its authentication services. An important part of this initiative is better understanding the attitudes of service stakeholders, including pharmacists, to on-going regulatory initiatives.

The study aims to evaluate the impact of healthcare risk management initiatives on pharmacists; for example, the EU Falsified Medicines Directive (FMD) and European Medicines Agency (EMA) risk:benefit appraisal consultation.

Therefore, we would greatly appreciate your time in completing four short multiple-choice questions as part of this study. The questions should not take more than three minutes to complete.

The results will be recorded anonymously and used to inform Aegate's service development and Oxford University's research in healthcare risk management. Ultimately, better representing the views of pharmacists at all levels: government, manufacturers, payers and regulators.

All data collected will be distributed to respondents at the end of the study.

We thank you for your participation.

Question 1

Do you believe that pharmacists have an important role in helping patients understand the relative risks and benefits of medicines?

Strongly Agree
Agree
Disagree
Strongly Disagree

Question 2

Please indicate the importance of the following characteristics of data provided by medicine manufacturers to pharmacists – either in Patient Information Leaflets (PILs) or direct to pharmacist communications – when attempting to evaluate the risks and benefits of medicines, with a view to informing the advice you are able to offer to patients:

a) Large number of statistical techniques used to analyse and express collected clinical trial data

Critical
Preferable
Neutral
Unimportant

b) Clear hierarchal description – for example, a flow chart outlining the methodology utilised – of the methodologies utilised by manufacturers to evaluate the risks and benefits of a given medicine

Critical
Preferable
Neutral
Unimportant

c) Consistent units used to express risks and benefits of medicines

Critical
Preferable
Neutral
Unimportant

d) Evaluation of risks and benefits of alternative medicines to permit comparison

Critical
Preferable
Neutral
Unimportant

Question 3

Should a formal risk-benefit analysis be conducted within all clinical trials?

Strongly Agree
Agree
Disagree
Strongly Disagree

Question 4

If a formal risk benefit analysis is conducted in a clinical trial, should its results be included in the Patient Information Leaflet (PIL) for the medicine?

Strongly Agree
Agree
Disagree
Strongly Disagree

***

11.5.2 Dutch: Pharmacist Questionnaire

***

Oxford University Pilot Study

A Risk Benefit Survey

Aegate werkt samen met de Universiteit van Oxford aan de verdere ontwikkeling van zijn authenticatie dienst. Een belangrijk onderdeel van dit initiatief is een klare kijk krijgen op de standpunten die apothekers en andere belanghebbenden aannemen ten opzichte van nieuwe wettelijke verplichtingen.

Deze studie heeft tot doel de impact van risicomanagement initiatieven bij apothekers te evalueren. Het gaat hier bijvoorbeeld over de Europese richtlijnen rond namaak geneesmiddelen (FMD) en de nieuwe maatregelen van het Europees Geneesmiddelen Agentschap (EMA) om via overleg tot betere risicobaten analyses te komen.

Mogen wij u vragen een paar minuten van uw tijd te besteden aan het beantwoorden van vier korte, multiple-choise, vragen.

De resultaten zullen anoniem worden geregistreerd om het Oxford onderzoeksteam te informeren over het risicobeheer in de gezondheidszorg.

Het uiteindelijk doel is het standpunt van de apothekers in deze materie beter kenbaar te maken op alle niveaus: overheid, industrie, betalers en regelgevers.

De resultaten van deze enquête worden aan de deelnemers verteld op het einde van de studie.

Wij danken u voor uw deelname.

Vraag 1

Denkt u dat de apothekers een hoofdrol spelen bij het informeren van patienten over de risico's en baten van geneesmiddelen?

Helemaal mee eens
Akkoord
Niet akkoord
Zeker niet mee eens

Vraag 2

Gelieve de graad van belangrijkheid aan te geven bij de volgende kenmerken over de gegevens aangeleverd door de fabrikant van de geesmiddelen – hetzij via de bijsluiter of via rechtstreekse communicatie naar de apotheker - in een poging om de risico's en baten van geneesmiddelen te evalueren, met als bedoeling u meer informatie te geven over het advies dat u aan uw patienten kan bieden:

e) Een groot aantal statistische technieken gebruiken voor het analyseren en samenvatten van gegevens uit klinische proeven

Doorslaggevend
Te verkiezen
Geen mening
Onbelangrijk

f) Duidelijke hiërarchische beschrijving van de methodologie gebruikt door fabrikanten om de risico's en baten van een bepaald geneesmiddel te evalueren (bijvoorbeeld, een stroomdiagram om de gebruikte methodologie te omschrijven)

Doorslaggevend
Te verkiezen
Geen mening
Onbelangrijk

g) Consequente eenheden gebruiken om risico's en baten van geneesmiddelen uit te drukken

Doorslaggevend
Te verkiezen
Geen mening
Onbelangrijk

h) Evaluatie van risico's en baten van alternatieve geneesmiddelen om een vergelijking mogelijk te maken

Doorslaggevend
Te verkiezen
Geen mening
Onbelangrijk

Vraag 3

Moet er een formele risicobaten analyse worden gevoerd voor alle klinische studies?

Helemaal mee eens
Akkoord
Niet akkoord
Zeker niet mee eens

Vraag 4

Als er een risicobaten analyse wordt uitgevoerd in een klinische studie, moeten deze resultaten dan worden opgenomen in de bijsluiter van het geneesmiddelen?

Helemaal mee eens
Akkoord
Niet akkoord
Zeker niet mee eens

***

11.5.3 Italian: Pharmacist Questionnaire

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Oxford, Studio Pilota: rischio-beneficio.

Domande

Aegate collabora con l'Università di Oxford per sviluppare e realizzare servizi di autenticazione del farmaco. Una parte fondamentale di questa lavoro è quella di comprendere al meglio gli atteggiamenti da parte di tutti gli attori coinvolti, tra cui i farmacisti, nei riguardi delle iniziative in corso.

Lo studio si propone di valutare l'impatto della gestione del rischio sanitario per il farmacista; per esempio, copertura dei rischi da parte della Direttiva Europea sui Medicinali Falsificati (FMD) e l'Agenzia Europea del Farmaco (EMA): valutazione dei benefici.

Pertanto, come parte integrante di questo studio, sarebbe importante se poteste dedicare un po' del vostro tempo per rispondere alle domande a risposta multipla qui di seguito.

Rispondere non dovrebbero impegnarla per più di 3 minuti.

Le risposte saranno trattate in forma completamente anonima e utilizzate per lo sviluppo dei servizi di Aegate e dai ricercatori dell'Università di Oxford per studi sulla gestione del rischio in sanita'. In ultimo saranno usate per rappresentare il punto di vista dei farmacisti a tutti i livelli: istituzioni, produttori di farmaci, autorità amministartive e regolatorie.

I risultati del sondaggio saranno condivisi e distribuiti a tutti i partecipanti al termine dello studio

Vi ringraziamo per la vostra partecipazione.

Domanda 1

Ritieni che il farmacista ricopra un ruolo importante nell'aiutare i pazienti a comprendere i rischi-benefici dell'assunzione dei farmaci?

Pienamente d'accordo
Concordo
Disssento
Completamente in disaccordo

Domanda 2

Si prega di caratterizzare per importanza le informazioni fornite dai produttori di medicinali ai farmacisti - sia nei i foglietti illustrativi interni ai farmaci, sia nelle comunicazioni dirette al farmacista – sulla valutazione del rapporto rischio-beneficio nell'assunzione dei farmaci, finalizzato all'informativa che il farmacista può offrire ai pazienti:

a) Ampi studi statistici mirati ad analizzare e comunicare i dati raccolti negli studi clinici.

Critico
Preferibile
Neutro
Non importante

b) Descrizione chiara e gerarchica - ad esempio, un diagramma di flusso che illustri la metodologia utilizzata – o le metodologie utilizzate dalle aziende farmaceutiche per la valutazione dei rischi-benefici di un farmaco

Critico
Preferibile
Neutro
Non importante

c) Unità di misura coerenti per esprimere i rischi-benefici dei medicinali

Critico
Preferibile
Neutro
Non importante

d) Valutazione del rischio-beneficio di medicine alternative per consentirne il confronto

Critico

Preferibile
Neutro
Non importante

Domanda 3

Si dovrebbe condurre un'analisi formale del rischio-beneficio in tutti gli studi clinici?

Pienamente d'accordo
Concordo
Disssento
Completamente in disaccordo

Domanda 4

Se un'analisi formale del rischio-beneficio è condotta nello studio clinico, i risultati dovrebbero essere inclusi nell'opuscolo informativo del farmaco per il paziente?

Pienamente d'accordo
Concordo
Disssento
Completamente in disaccordo

***

11.6 Appended Publications

The following publications arose from the investigation presented in Sections 1.0-9.0.

Unless otherwise stated all supplementary materials are included.

Full details of D.A.B. contributions to all publications can be found in Section 9.0.

CellPress

Special Issue: Next Generation Therapeutics

Global strategic partnerships in regenerative medicine

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The approach to research and development in biomedical science is changing. Increasingly, academia and industry seek to collaborate, and share resources and expertise, by establishing partnerships. Here, we explore the co-development partnership landscape in the field of regenerative medicine, focusing on agreements involving one or more private entities. A majority of the largest biopharmaceutical companies have announced strategic partnerships with a specific regenerative medicine focus, signifying the growth and widening appeal of this emerging sector.

Regenerative medicine: a unique challenge and opportunity

Regenerative medicine offers novel opportunities to address unmet medical needs, and incorporates a range of scientific disciplines. While acknowledging the potential of endogenous repair and tissue engineering, we restricted our analysis to approaches that seek to replace or regenerate human cells or tissues, as well as cell-based approaches for drug screening and toxicology applications. This focus was identified due to the novelty and unique challenges of living cellular products. Several cellular therapies have achieved market approval, with many more entering clinical trials, marking the emergence of a sustainable industry [1,2].

Despite significant scientific advances and high expectations of therapeutic potential, numerous barriers persist, many of which are unique to this novel class of therapies. Cell therapy faces issues of scale and automation in biomanufacturing, challenges in securing intellectual property (IP) protection, and a range of regulatory and reimbursement uncertainties. Additionally, investment has been limited due to the early developmental stage of the field, perceived risks, as well as scientific, clinical, regulatory, and market uncertainties [3,4]. Drug discovery and toxicology applications have been more widely investigated and, in some cases, adopted, but still face challenges of scale and standardization, as well as uncertainty regarding correlation with clinical relevance. Research and development (R&D) has predominantly occurred in an academic setting, where clinician-led efforts, mostly under the auspice of the 'art of medicine', have resulted in numerous clinical trials. However, in comparison to company-sponsored trials, translation of academic efforts has been primarily limited to autologous 'procedural' approaches [5]. By contrast, the small number of cell therapies that have achieved market approval have all occurred via company-led routes [1].

The limited experience of the major pharmaceutical companies with therapeutic regenerative medicine approaches, combined with the industry-wide trend of decreasing in-house R&D, has fostered the growth of creative innovation models; public–private, private–private and multi-institutional partnerships have all been established [6–9]. Such collaborative approaches may be even more integral for innovative break-through technologies, such as in the field of regenerative medicine [7]. Here, we focus on co-development partnerships that include one or more private organizations.

The landscape of co-development partnerships in regenerative medicine

An opinion frequently held is that the commercialization expertise and financial resources of the pharmaceutical industry will be required for the regenerative medicine field to mature effectively as a major therapeutic class. Over the past decade, the pharmaceutical industry has aligned itself with academic groups as well as with small and medium-sized enterprises (SMEs) to co-develop potential therapies (Table 1). In comparison to therapeutic classes, such as monoclonal antibodies, partnership activity remains

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Keywords: strategic partnerships; cell therapies; regenerative medicine; stem cells; translation.
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0167-7799/
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Table 1. Co-development partnership agreements in regenerative medicine involving the top 22 pharmaceutical companies (ranked by 2012 revenue), (2004–2014)

No.	Company	Partnership
1	Johnson & Johnson (New Brunswick, NJ)	2005: invests in Tengion (Winston-Salem, NC) during Series A financing that resulted in US$39 million (Tengion, 2005)
		2012: partners with HSCI and Evotec (Hamburg) as part of the 'BetaCure' program to develop small molecule therapy for endogenous beta-cell generation for type 1 diabetes (HSCI, 2012)
		2014: partners with Capricor (Beverly Hills, CA), a deal that included a US$12.5 million initial payment for the development of allogeneic cardiac-derived cells for myocardial infarction (Capricor-Therapeutics, 2014)
NY	Pfizer (New York City, NY)	2009: Pfizer and UCL form collaboration to advance stem-cell based therapies for age-related macular degeneration (UCL, 2009)
		2009: forms an alliance with Athersys (Cleveland, OH) to co-develop MultiStem(R) (Pfizer, 2009)
		2012: Pfizer among other pharma companies invest a total of US$72.7 million for the creation of StemBANCC (Pfizer, 2012)
		2012: Pfizer Canada invests CA$500,000 in Centre for Commercialization of Regenerative Medicine (CCRM) to establish Pfizer-CCRM Innovation Fund that would accelerate regenerative medicine technologies for drug screening and therapeutic applications (CCRM, 2012)
3	Novartis (Basel)	2009: collaborates with HSCI on multi-year project to understand group of neuromuscular disorders (HSCI, 2009)
		2012: forms partnership with the University of Pennsylvania, including a US$20 million investment, to develop CAR-T cells for the treatment of leukemia (UPenn, 2012)
		2013: partners with Regenerex LLC (Louiseville, KT) to co-develop their Facilitating Cell Therapy Platform (FCRx) to promote immune tolerance (Novartis, 2013)
4	Sanofi (Paris)	2009: Sanofi-Aventis forms stem cell partnership with Salk Institute for 5 years (Salk, 2009)
		2012: Roche Pfizer, Sanofi establishes US$72.7 million Stem-cell bank through StemBANCC (Roche, 2012b)
5	Merck & Co (White house station, NJ)	N/A
6	GlaxoSmithKline (Brentford)	2008: enters into 5-year, US$25 million alliance with the Harvard Stem Cell Institute in stem cell science (GSK, 2008)
		2013: announces collaborative agreement with the UK Cell Therapy Catapult (Catapult, 2013)
7	Abbott (Abbott Park, IL)	2012: joins consortium of pharma companies for the creation of StemBANCC (Roche, 2012b)
8	Roche (Basel)	2008: partners with Stem Cells 4 Safer Medicines to generate stem cell repository for toxicology testing in high-throughput platforms
		2009: signs US$10.36 million 2-year collaboration with I-STEM (Institute for Stem Cell Therapy and Exploration of Monogenic Diseases) (I-Stem, 2009)
		2011: forms agreement with UCLA Stem Cell and Cancer Researchers to provide researchers with Roche's leading-edge technologies (UCLA, 2011)
		2012: Roche partners with HSCI to develop stem cell assays for autism spectrum disorders (Roche, 2012a)
		2012: spearheads StemBANCC initiative with IMI to generate 1500 iPS stem cell lines. US$72.7 million funded (Roche, 2012b)
9	Bayer (Leverkusen)	N/A
10	AstraZeneca (London)	2006: forms agreement with Cellartis (Paris) to develop improved safety screening systems based on human embryonic stem cell-derived liver and heart muscle cells, extended in 2009 (AstraZeneca, 2009)
		2010: forms research collaboration with Joslin Diabetes Center to understand the causes of type 2 diabetes by using stem cells (Joslin, 2010)
		2010: enters into a 3-year collaboration with UCL to develop regenerative medicines for diabetic retinopathy (UCL, 2010)
		2013: reaches agreement with Cellular Dynamics International, Inc. (Madison, WI) to develop new iPSC-derived cell types and screening applications (CDI, 2013b)
		2013: partners with the Wyss Institute, Harvard University to develop 'organ-on-a-chip' technologies (Wyss, 2013)
		2014: forms licensing and research collaboration with Immunocore (Abingdon) to codevelop 'Immune Mobilising Monoclonal T-Cell receptor against Cancer (AstraZeneca, 2014)
11	Eli Lilly (Indianapolis, IN)	2011: partners with Juvenile Diabetes Research Foundation to fund early-stage research that could enable patients with type 1 diabetes to regenerate insulin-producing cells (Lilly, 2011)
12	Teva (Petach Tikva)	2010: Mesoblast forms a strategic alliance with Cephalon Inc. (now owned by Teva) to develop and commercialize novel adult stem cell therapeutics (Teva, 2010)
13	Boehringer Ingelheim (Ingelheim am Rhein)	2012: invests in the US$72.7 million StemBANCC initiative along with Roche, Pfizer, and Sanofi (Roche, 2012b)
14	Bristol-Myers Squibb (New York City, NY)	2013: Bristol-Myers Squibb supports research conducted at the University of Edinburgh in which scientists generated liver cells using stem cell technology (Bristol-Myers, 2013)
15	Amgen (Thousand Oaks, CA)	N/A

Table 1 (*Continued*)

No.	Company	Partnership
16	Takeda (Osaka)	2011: makes strategic investment in Fate Therapeutics (San Diego, CA) to develop foundation in regenerative medicines (Takeda, 2011)
		2012: becomes strategic investor in Juventas Therapeutics (Cleveland, OH) in series B round of funding (Takeda, 2012)
		2014: partners with UCL to develop iPS cell technologies to treat muscular dystrophy (UCL, 2014)
17	Merck KgaA (Darmstadt)	2011: IntelliCell BioSciences (New York City, NY) validates technology used to generate fat, or adipose stem cells (IntelliCell, 2011)
		2012: collaborates with VeriStem Technologies Inc. (Singapore) to develop optimized technologies for removal of undifferentiated stem cells from pluripotent stem cell cultures (EMD-Millipore, 2012)
		2012: collaborates with Mittelhessen University of Applied Sciences to develop optimized cell culture and harvesting process for bioreactor-based stem cell cultures (Merck, 2012
		2013: teams up with PharmaCell (Maastricht) to develop optimized large-scale expansion and harvesting of HepaRG cells using bioreactor technology (EMD-Millipore, 2013)
18	Baxter (Deerfield, IL)	N/A
19	Astellas (Tokyo)	2013: in collaboration with Kyoto University's Center for iPS Cell Research and Application, discovers methods to promote kidney regeneration in human embyronic stem and induced pluripotent stem cells (Astellas, 2013)
20	Daiichi Sankyo (Tokyo)	N/A
21	Gilead Sciences (Foster City, CA)	N/A
22	Novo Nordisk (Bagsvaerd)	2008: invests EUR 100 million in cooperative project with Cellartis (Paris) and the Swedish Lund University Stem Cell Center to develop a cell therapy for treatment of insulin-dependent diabetes (Novo-Nordisk, 2008)
		2012: partners with Juvenile Diabetes Research and the European Foundation for the study of diabetes (JDRF, 2012)

modest yet increasing. Out of the top 22 pharmaceutical companies (ranked by 2012 revenues), 16 have formed co-development partnerships with a primary focus on regenerative medicine technologies. Pfizer (New York City, NY), Roche (Basel), and AstraZeneca (London) have been most active when measured by the number of deals announced (Table 1). Outside of the largest pharmaceutical companies, several private companies have formed alliances with academic institutions, in addition to numerous private–private co-development partnerships, which may prove to be vital for the future of the industry (Table 2).

Of the academic institutions that have formed alliances with the pharmaceutical industry or other private companies, Harvard University in the USA and University College London (UCL) in the UK are predominant (Table S1 in the supplementary material online). This trend mirrors that of the biomedical science field more broadly, with these two institutions demonstrating the highest number of academic–industry partnerships across the breadth of biomedical sciences [8]. Diabetes, neurological, and cardiovascular disorders were the therapeutic areas most frequently identified as the focus of strategic alliances in the sector (Figure S1 in the supplementary material online).

Combining strengths and eliminating deficiencies through co-development partnerships

Co-development partnerships in the field can be grouped around access to three key components: (i) production technology and/or technological expertise; (ii) commercialization, regulatory and/or clinical trial expertise; and (iii) financing.

The production process closely defines cell therapy products. The process is complex, with a limitless number of variations in source, reagents, and temporal considerations, which can all impact on the physiochemical and functional characteristics of the product. Thus, the production process creates a barrier for industry attempts to replicate published protocols. Therefore, co-development, as opposed to internal replication of published academic findings, is advantageous. Additionally, multiple technologies are frequently required to produce a cell therapy product, which may also involve the use of a scaffold or other biomaterial typically more familiar to medical device organizations. Thus, partnering can bundle technologies, increasing the likelihood of success and enable production of the clinical product. Servicing product pipelines through partnership, as opposed to inhouse R&D efforts, also provides private companies with the opportunity to view a wider range of research (born out of publicly visible findings and a broadly collaborative approach).

Although technological knowledge in the field is largely concentrated in academia, expertise in commercialization, regulation, and clinical trials is typically lacking in academia. Input from the pharmaceutical industry in these vital areas is required to better navigate the complex route from bench to bedside. This is a core motivation in partnership announcements, such as in the Pfizer–UCL agreement to develop embryonic stem cell-based technologies for the treatment of retinal diseases (Table S1 in the supplementary material online). The pharmaceutical industry does bring significant experience in these areas, but it should be acknowledged that the regulatory environment for cell therapies will differ from that of conventional products. Moreover, combinational products currently require an additional regulatory pathway, in which the pharmaceutical industry has limited experience. Furthermore, autologous cell therapies do not align with current pharmaceutical

Table 2. Co-development partnerships in regenerative medicine involving private companies, nonprofit companies, and academic institutions (2004–2014)[a]

Organization	Organization	Year	Press release
Advanced Cell Technology (Marlborough, MA)	Roslin Cells (Edinburgh)	2011	(ACT, 2011)
BD (Becton, Dickinson and Company) (Franklin Lakes, NJ)	Fate Therapeutics (San Diego, CA)	2010	(Fate-Therapeutics, 2010)
California Stem Cell, Inc. (Irvine, CA)	University of California, Irvine	2014	(Cell, 2014)
Cell Medica (London)	Baylor College of Medicine	2010	(Cell-Medica, 2010)
Cellectis (Paris)	Stemgent (Cambridge, MA)	2013	(Cellectis, 2013)
Cellular Dynamics International (Madison, WI)	Coriell Institute	2013	(CDI, 2013a)
Cellular Dynamics International (Madison, WI)	Life Technologies (Carlsbad, CA)	2012	(Life-Technologies, 2012)
Evotec (Hamburg)	Harvard Stem Cell Institute	2012	(Evotec, 2012, Evotec, 2013)
GE Healthcare (Pittsburgh, PA)	BGI (Beijing)	2012	(GEHealthcare, 2012a)
GE Healthcare (Pittsburgh, PA)	Karolinska University Hospital	2012	(GEHealthcare, 2012b)
Genzyme Corp. (now a Sanofi Company)	Osiris Therapeutics, Inc. (Columbia, MD)	2008	(Therapeutics, 2008)
Intrexon Incorporation (San Diego, CA)	Sanford-Burnham Medical Research Institute	2013	(Sanford-Burham, 2013)
iZumi Bio (now iPerian) (San Francisco, CA)	Kyoto University	2009	(University, 2009)
Kiadis Pharma (Amsterdam)	Technische Universitat Munchen	2014	(Pharma, 2014)
Life Technologies (Carlsbad, CA)	HSCI	2013	(Life-Technologies, 2013)
Lonza (Basel)	Roslin Cells (Edinburgh)	2010	(Roslin-Cells, 2010)
Mesoblast (Melbourne)	Cephalon (now a subsidiary of Teva)	2010	(Cephalon, 2010)
Neostem, Inc (New York, NY)	University of California	2013	(Neostem, 2013a)
Novocell Inc. (San Diego, CA)	Kyoto University	2008	(University, 2008)
New York Stem Cell Foundation (NYSCF)	Harvard Stem Cell Institute	2011	(NYSCF, 2011)
Paragon (Baltimore, MD)	University of Maryland Baltimore	2011	(UMB, 2011)
Pluristem Therapeutics Inc. (Haifa)	CHA Bio&Diostech (Seoul)	2013	(Pluristem, 2013)
Progenitor Cell Therapy (Allendale, NJ)	ATMI Inc (Danbury, CO)	2013	(Neostem, 2013b)
Q Therapeutics (Salt Lake City, UT)	Buck Institute	2008	(Institute, 2008)
Stem Cells Inc.	ALS Therapy Development Institute	2008	(CSC, 2008)
TAP Biosystems (Hertfordshire)	Loughborough University	2010	
TAP Biosystems (Hertfordshire)	International Stem Cell Corporation	2010	(TAP-Biosystems, 2010)
Tengion	Celgene Corporation	2013	(Tengion, 2013)
Viacyte (San Diego, CA)	Juvenile Diabetes Research Foundation (JDRF)	2011	(JDRF, 2011)

[a]Blue shading, private company; red shading, academic institution; gray shading, nonprofit.

business models and will require a new approach to commercialization. Such unique requirements have also led to the creation of several 'translation centers', such as the Canadian Centre for Regenerative Medicine (CCRM) and the UK Cell Therapy Catapult (see the press releases listed in the supplementary material online).

Financing is a clear motivation behind co-development partnerships, both for academia to benefit from the financial resources of the pharmaceutical industry, and for the industry to access alternative funding streams, such as government grants and support from disease foundations. Indeed, public–private–patient partnerships are becoming an increasingly prevalent and impactful component of this ecosystem. The California Institute of Regenerative Medicine (CIRM) has been a uniting force behind several collaborative agreements and provides financial backing to facilitate co-development projects. An additional motivation for public–private partnerships can be seen in the Pfizer-Athersys (Cleveland, OH) agreement, which extends the reach of MultiStem® into new indications, thus requiring additional capital for development and costly clinical trials (Table S1 in the supplementary material online). In the risk-adverse climate following the recent economic recession, co-development partnerships allow cash-poor organizations access to vital capital while reducing the investment risk of the pharmaceutical industry. This can be done through use of staged milestone payments, often linked to key clinical inflection points. Additional motivations for private companies to pursue partnerships result from challenges around licensing and access to primary human tissue samples [6,10]. Moreover, academic medical centers typically benefit from existing relations with key patient populations.

Impact of the evolving partnership model

The trend towards an increasing number of partnerships between the pharmaceutical industry, academia and SMEs (as well as amongst SMEs) will continue as technologies mature, as the regulatory environment becomes more established, and as the first wave of 'big wins' in the sector materializes. Expectations are high for: the curative potential of CAR-T cell technologies in a range of cancers; the phase II trial of Capricor (Beverly Hills, CA) for myocardial infarction; and the Advanced Cell Technologies (Marlborough, MA) trial with human embryonic stem cell-derived retinal pigment epithelial (RPE) cells for retinal disorders. Any increased activity in utilizing stem cell technologies for drug discovery will ultimately depend on the ability to standardize screening platforms as well as predictive potential. Tissue constructs on plug-and-play chips, including those that seek to link multiple different organ systems through fluid flow, are on the horizon and may further increase the ability to predict clinical outcomes. Indeed, partnerships in this arena have already developed, with AstraZeneca teaming with the Wyss Institute at Harvard University around their 'organs-on-a-chip' technology.

Closer academic-industry links foster a new breed of commercially minded research scientists, with a greater understanding of translation and the ability to communicate more effectively with industry. On the academic side, partnerships can bring a new approach to decision making in research, introducing criteria that industry have developed through an intimate familiarity with the translation pathway. On the industry side, interactions can promote alternative ways of explorative thinking and generate fresh ideas in research.

However, there are various potential pitfalls in academic–industry partnerships that may prevent a positive synergistic outcome. The demanding quarter-to-quarter productivity expectations of industry can be onerous when applied in an academic setting, and may also inhibit the exploratory nature of academic research. Potentially contentious areas in academic–industry partnerships include ownership and IP, publishing and confidentiality, and differences in 'culture' and incentives.

Pharmaceutical companies have increasingly begun to engage in co-development partnerships with both academic institutions and SMEs in the field of regenerative medicine, illustrative of a maturing industry and the development of technologies with the potential to deliver both commercial and clinical benefits. Such alliances allow the strategic building of complementary capacities and capability, uniting financial capital, expertise in process development, and commercialization pathways with novel therapeutic products.

Acknowledgments

We wish to express our sincere thanks to the following organizations that have contributed to the consortium as funding and events partners, without whom the consortium and the benefits it will bring to stem cell translation would be constrained: CCRM, Celgene Cellular Therapeutics, Cell Therapy Catapult, CIRM, Eisai, GE Healthcare, Lonza, SENS Research Foundation, TAP Biosystems (now Sartorius Stedim), MEDIPOST Co., Ltd., MEDIPOST America Inc., New York Stem Cell Foundation and the NIH Centre for Regenerative Medicine. Additionally, CASMI is a past recipient of funding from the Technology Strategy Board to support an investigation into cell therapy regulation. We also wish to extend our sincere thanks to Yibing Qyang (Yale) for his support in the preparation of this manuscript, to Andy Carr (Oxford), Ivan Wall (UCL), Ben Davies (Oxford), and Jeff Karp (MIT/Harvard) for their invaluable support and insights.

Disclaimer statement

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B. gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury), a company that among other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. D.A.B. is subject to the Codes, Standards, and Guidelines of the CFA Institute, and, as such, stresses that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. Additionally, at time of publication, D.A.B. and the organizations with which he is affiliated, may or may not have agreed and/or pending funding commitments from the organizations named herein. D.A.B. has also conducted paid consultancy for Lonza Group within the past 7 years with a cumulative value of greater than US$10 000; travel support from Athersys Inc with a cumulative value of less than US$10 000 and entertainment from TAP Biosystems/Sartorius Stedim with a cumulative value of less than US$10 000. All other authors do not declare any additional conflicts of interest, as defined by the journal. However, we are happy to respond to direct requests for confirmation, and stress that affiliations stated may or may not constitute a disclosure of employment and/or ownership of financial instruments in the named entity.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tibtech.2014.05.007.

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STEM CELLS TRANSLATIONAL MEDICINE®

PERSPECTIVES

Enabling Consistency in Pluripotent Stem Cell-Derived Products for Research and Development and Clinical Applications Through Material Standards

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SUMMARY

There is a need for physical standards (reference materials) to ensure both reproducibility and consistency in the production of somatic cell types from human pluripotent stem cell (hPSC) sources. We have outlined the need for reference materials (RMs) in relation to the unique properties and concerns surrounding hPSC-derived products and suggest in-house approaches to RM generation relevant to basic research, drug screening, and therapeutic applications. hPSCs have an unparalleled potential as a source of somatic cells for drug screening, disease modeling, and therapeutic application. Undefined variation and product variability after differentiation to the lineage or cell type of interest impede efficient translation and can obscure the evaluation of clinical safety and efficacy. Moreover, in the absence of a consistent population, data generated from in vitro studies could be unreliable and irreproducible. Efforts to devise approaches and tools that facilitate improved consistency of hPSC-derived products, both as development tools and therapeutic products, will aid translation. Standards exist in both written and physical form; however, because many unknown factors persist in the field, premature written standards could inhibit rather than promote innovation and translation. We focused on the derivation of physical standard RMs. We outline the need for RMs and assess the approaches to in-house RM generation for hPSC-derived products, a critical tool for the analysis and control of product variation that can be applied by researchers and developers. We then explore potential routes for the generation of RMs, including both cellular and noncellular materials and novel methods that might provide valuable tools to measure and account for variation. Multiparametric techniques to identify "signatures" for therapeutically relevant cell types, such as neurons and cardiomyocytes that can be derived from hPSCs, would be of significant utility, although physical RMs will be required for clinical purposes. STEM CELLS TRANSLATIONAL MEDICINE *2015;4:1–8*

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INTRODUCTION

Human pluripotent stem cell (hPSC) technologies have a unique potential to address the increasing burden of unmet clinical need for many intractable diseases. However, a grasp of the fundamental biology, which is necessary to ensure invariant and reproducible, safe and effective cellular products from batch-to-batch and patient-to-patient, has eluded our reach. The field generally lacks standards that will enable scalable, automated manufacturing to build regulatory confidence and meet clinical needs.

Written standards exist in a vast range of industries, enabling dialogue between stakeholders via a common set of "rules" or "guidelines." Typically developed through consensus that emerges through an incremental process of discussion and revision among experts, standards can establish specifications, set minimum requirements, and provide a route by which valid comparisons can be made. Standards can also serve to protect the integrity of manufacturers, stimulate consumer confidence, and facilitate the uptake of new technologies into the market [1–3]. Importantly, physical standards or reference materials used for specific comparative purposes are needed to validate and provide a benchmark for assessments of product or analytical tools.

Outlining the need for routes to generating both developer-specific and, where appropriate, consensus physical (material) standards for stem cell translation has value for two primary reasons. First, physical standards will support and enable improved reproducibility and product consistency in research. Currently, the field, and biomedical research in general, suffers from issues of irreproducibility [4, 5], which impede progress and effective collaboration and could damage the public perception of stem cell research. Second, commercial and translational benefits will result from incorporating standardization principles early in research and development by building a base for quality assessment to prevent undue delays throughout clinical trials because of deficiencies in the necessary tools and data to meet regulatory requirements. Therefore, approaches for the derivation of standards and, especially, physical (material) standards could benefit early-stage researchers conducting preclinical phase investigation, as well as those engaged further along the translation pathway. However, it is vital to strike the proper balance to ensure that the benefits of standardization are not achieved at the expense of hindering innovation. In the present report, we are not trying to identify the preferred PSC line to generate clinical products nor a specification for the optimal cell type. Instead, we have focused on the need and possible mechanisms by which physical standards, reference materials (RMs), can be produced to analyze and thereby facilitate the consistent and reproducible generation of products from hPSCs. Because consensus (international) RMs might have limited application and would be more challenging to achieve, we have focused on in-house developer-specific RMs that can be generated by research laboratories and companies alike that are engaged in preclinical research and that can be applied in clinical trials and beyond to meet regulatory expectations. These principles and approaches also have application in drug screening and toxicology studies that use PSC-derived somatic cells with underlying expectations for reproducibility and consistency.

CLINICAL POTENTIAL OF PSC-DERIVED PRODUCTS

The utility of hPSCs in disease modeling is beginning to be demonstrated, and some of these models are now finding application as drug screening tools (reviewed in [6–8]). However, it is the application of PSCs as a cell source for therapeutic intervention that still garners the greatest enthusiasm within a healthcare context. To date, embryonic stem cell (ESC)-derived products have entered a limited number of clinical trials, pioneered by Geron Corporation (Menlo Park, CA, http://www.geron.com; assets now owned by Asterias Biotherapeutics) and more recently Advanced Cell Technology, Inc. (Santa Monica, CA, http://www.advancedcell.com), with a Pfizer/University College London trial that began in 2014 [9, 10]. Although Geron did not complete its trial of ESC-derived oligodendrocyte precursors for acute spinal cord injury owing to internal competing fund allocations, it pioneered a regulatory path and demonstrated the data requirement for testing PSC-derived products in humans [10]. This exercise proved educational, not only for the private sector, but also for the regulators themselves, who, until that time, had had no experience evaluating the safety of hPSC-derived products in actual patients.

Standards for hPSCs in their undifferentiated state are important for cell banking, both to demonstrate comparability and to show that cell lines are stable over time [11, 12]. A number of engaging perspectives on standards for hPSCs have been reported [11, 13–15]. However, because hPSCs in their undifferentiated state will not be the final product delivered to research subjects or patients, the standards should extend to validating early-stage translational research and the manufacture and scale-up process by which large numbers of somatic cells are derived from hPSCs. Just as with any cell therapy, owing to the unique nature of each product, written standards will have limited utility for hPSC-derived products. Instead, material standards, generated on a case-by-case basis, will be required to validate the process, method, and product consistency. Although such material standards will be the responsibility of the developer and will vary in accordance with the particular developer's technology, product, and target indication, a clearer understanding of the needs, requirements, and potential approaches by which these materials standards could be produced will benefit academic researchers and industry alike.

CHALLENGES OF HPSC TRANSLATION

The application of hPSC-derived products in a clinical setting has been challenged by the numerous inherent and unique barriers to translation, including scalability and manufacturability, and a variety of regulatory challenges:

Phenotypic and genetic instability

- Capacity to generate adult phenotypes
- Cost of cell culture processes
- Clarity of protection for intellectual property
- Differentiation efficiencies and time scales
- Tumorigenicity risks
- Immunological considerations
- Paucity regulatory and sponsor familiarity
- Limited positive cell therapy outcomes to date
- Each product must be considered by regulatory authorities on a case-by-case basis

hPSCs are highly reactive to their external environment. They can undergo significant changes in response to different culture conditions, to extended time in culture, and after cryopreservation

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[16–18]. Stability is also a key issue, both genetic stability and the physiological stability of hPSC-derived products. Compared with cells harvested from adult donors, hPSC-derived populations might have an increased propensity for continued proliferation, differentiation, and/or maturation. This was exemplified by the increased frequency of cyst formation from the ESC-derived oligodendrocyte precursor cell population in Geron's preclinical animal studies, which resulted in the Food and Drug Administration (FDA) placing the trial on hold. This issue was ultimately resolved by an additional level of cell selection [19]. Furthermore, hPSCs and their differentiated progeny have been demonstrated to be highly heterogeneous at the population level, with differentiation protocols asynchronously generating a variety of cell types [20]. Researchers are focusing on the generation of homogeneous-differentiated populations from hPSCs that would be amenable to clinical demands. However, it has been argued that mixed populations might be preferable to a single cell type in some cases, if the survival or efficacy of administered cells will be enhanced by the presence of interacting cell types. It will be more challenging to characterize and control the consistency and quality of mixed populations, acknowledging that the level of heterogeneity in cell products will always exceed that of traditional small molecules. These inherent characteristics and current methodologies all create significant challenges for the development of RMs for hPSC-derived products.

The challenges to the translation of hPSC-derived products are as follows:

Standards and Reference Materials

Standards fall into two main categories, written and physical (material), which must be clearly distinguished (Fig. 1). Written standards include codes of practice, standard operating procedures, agreed terminology, guidelines, and pharmacopoeia methods. Pharmacopoeia, particularly relevant to this discussion, are a series of monographs and general chapters documentation for active substances that outline the minimum requirements, describing the identity and permissible levels of impurities, in addition to appropriate methods to define purity and potency, with accompanying expected ranges (USP, 2011). Pharmacopoeia can require the use of consensus physical (material) standards, which currently only exist for small molecules and a limited number of biologics. The single example of a cell therapy monograph is currently being developed by the USP Convention for sipuleucel-T (Provenge; Dendreon, Seattle, WA, http://www.dendreon.com), a T-cell therapy for advanced prostate cancer that has been authorized by the FDA, although approval of the monograph could encounter challenges and application might be limited (USP, 2013). A variety of local and regional organizations are concerned with the publication of pharmacopoeia and/or the production of physical reference standards (Table 1). In addition, organizations such as the World Health Organization and the Joint Committee for Traceability in Laboratory Medicine—the latter in the context of laboratory medicine and in vitro diagnostics, can lead and coordinate in the establishment of higher order international RM [21].

RMs are highly characterized physical materials used with analytical methods for a specific comparison purpose and are a global regulatory expectation [22–25]. Physical (material) standards can be subsegmented into certified (consensus) and in-house (developer-specific) materials (Fig. 1). Although certified RMs are available for many biological substances, they have not yet been produced for cell therapies. The National Institute for Biological Standards and Control (NIBSC) has produced a RM of untouched (enrichment using negative selection techniques to prevent activation) $CD4^+$ cell-certified RM, intended for use in clinical diagnostics. This standard comprises fixed peripheral blood mononucleated cells prelabeled with a CD4 antibody conjugated to fluorescein isothiocyanate (NIBSC, SS-222); this approach could have some relevance for cell therapies, as discussed below [26]. Certified (consensus) RMs might have application when applied to specific characterization methodologies but are highly unlikely to have a broad application, especially considering the need for case-by-case development of cell therapies such as hPSC-derived products. Therefore, we have focused exclusively on in-house (developer-specific) RMs. There are two main categories of in-house, developer-specific RMs, "product" and "method" (Fig. 1).

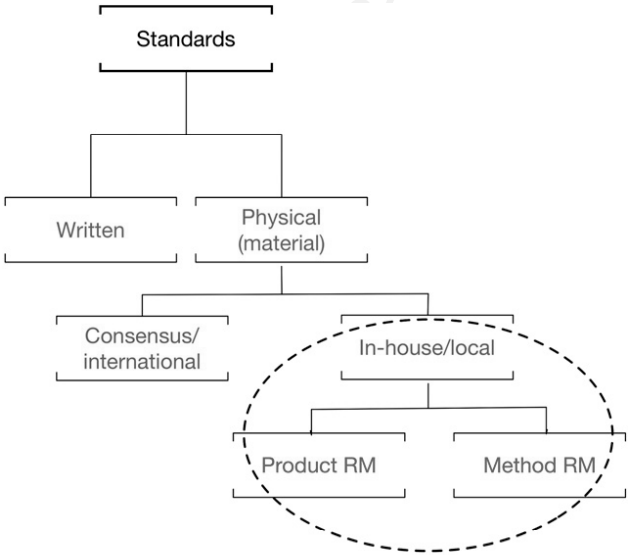

Figure 1. Overview of standards. Standards are a set of guidelines, rules, or requirements, typically set by a regulatory body or product manufacturer. They ensure that either during manufacture of a product or in the final product, some aspect, such as safety, performance, or quality, is consistent. Standards are either written, in the form of guidance, standard operating procedures, and pharmacopoeia, or they are physical (material). Physical standards are characterized materials used as a benchmark against which to compare attributes of a product and ensure consistency. They can be agreed on across organizations and countries (consensus) or can be developer-specific and local (in-house) (i.e., the standards are only adopted within the organization in question). These in-house material standards, called RMs, are the focus of our review and can be further divided into a product RM, which is a representative batch of the product, or a method (measurement) RM, which provides a reference for analytical measurements. Abbreviation: RM, reference material.

Potential Approaches to Developing Reference Materials for hPSC-Derived Products

The aim of the present discussion is to support the development of approaches and assays that will facilitate consistency and comparability in the production of differentiated cell types, such as cardiomyocytes, neurons, and T cells from hPSCs, or "hPSC-derived products." Batch-to-batch variation, if not assessed and controlled, will affect the quality of clinical hPSC-derived products. Moreover,

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Table 1. Organizations concerned with the generation and/or oversight of reference materials, including a list of major organizations that play a role in the production, guidance, and/or directives concerning reference materials for small molecule drugs and biologics

Organization	Region	Description	Web address
National Institute for Biological Standards and Control	United Kingdom	The leading WHO International Laboratory for Standards is responsible for >90% of global WHO standards	http://www.nibsc.org
USP Convention	US	The official organization that sets standards and generates reference materials implemented by the FDA as law in the United States, used globally in >140 countries	http://www.usp.org/about-usp
World Health Organization	International	Publishes the International Pharmacopoeia, which aims to harmonize global pharmaceutical standards and administers the establishment of international reference materials	http://www.who.int/medicines/publications/pharmacopoeia/overview/en/
European Directorate for the Quality of Medicines & Healthcare	Europe	Responsible for the European Pharmacopoeia commission, the evaluation of manufacturer's quality dossiers for certification, and market surveillance program	http://www.edqm.eu/en/edqm-homepage-628.html
Pharmaceutical and Medical Device Regulatory Science Society of Japan	Japan	Produces and distributes Japanese Pharmacopoeia Reference Standards as prescribed in the Japanese Pharmacopoeia (published by Pharmaceuticals and Medical Devices Agency)	http://www.pmrj.jp/hyojun/html/frm031.php?lang=e

Abbreviations: FDA, U.S. Food and Drug Administration; WHO, World Health Organization

approaches that enable the consistent production of differentiated cells will also be of significant benefit to drug and toxicity screening. The potential causes of variation in the production of somatic cells from hPSCs are numerous. "Products," such as cardiomyocytes, are generated from hPSCs by a highly dynamic differentiation process that might use a variety of methods [27], typically occurring via a number of stages. Even when considering the production of one specific product, from one hPSC line, using a single method, it is inevitable that the final product will demonstrate variability among the individual batches. This variability will arise in the form of variable levels of heterogeneity and "purity" of cell types and in inconsistencies in the differentiation and/or maturation stage of the product. Additionally, both genomic and phenotypic stability could demonstrate variation. We have detailed approaches to RM generation that might mitigate the current inconsistency and irreproducibility concerns.

An overview of the possible approaches to establish RMs for hPSC-derived products identified two main categories: those that use living, cellular RMs, either as product or method RMs, and those involving nonliving, noncellular materials, such as beads or DNA or RNA samples, as method RMs (Table 2).

Product Reference Material Approaches

"Product" RMs should be representative of the product and are used to validate comparability assessments throughout the product's lifecycle, including process change and optimization, and to detect process drift (Fig. 2A). Individual RMs will be designed to assist in the assessment of the product identity or its biological potency, and the respective purpose for the RMs must be clear at the outset.

The typical approach, which is common practice in the pharmaceutical industry, is to generate primary and secondary RMs that are samples of the product batch generated for preclinical and then pivotal studies. Secondary RMs are the working" samples used as a comparator in the relevant tests. Once the samples have been depleted, the secondary RM is generated from another batch and, through rigorous characterization, determined to be sufficiently comparable to the primary RM via a direct comparison. Ideally, the quantity of primary RM would be sufficient to last for the lifecycle of the product (in some cases, more than 20 years). However, and as discussed below, limitations could be present that would preclude this period of coverage.

A second potential method to product RM generation involves a "pooling" approach, in which cells from a number of different batches are pooled. If RMs are generated using a pooling approach, the differences due to heterogeneity within the product will be averaged out, providing a broad-ranging background against which measurements can be assessed. This could be beneficial in a number of circumstances.

In a limited number of cases, biologically equivalent cellular populations might be suitable product RMs. For example, if $CD4^+$ T lymphocytes are derived from hPSC lines, $CD4^+$ T lymphocytes harvested from healthy donors might be suitable as a product RM or, potentially, as a method RM for a limited number of assays. This approach might only be appropriate for a limited number of cell types that can be obtained from healthy donors without causing a detrimental effect. Although this approach might have potential utility, it must be acknowledged that the heterogeneity in the "biologically equivalent" RMs would need to be analyzed and accounted for.

The considerations of whether these approaches would be suitable, in addition to the critical criteria of relevance to the product, include stability, feasibility, and cost. Stability will need to be monitored over time and stability profiles determined so that new RM can be prepared before expiry. Because the batch sizes for hPSC-derived products are expected to be smaller than typically seen with small molecules and even biologics, the amount of product that can be stored as RM will also be limited. The practicalities of RM quantity requirements will vary and should be mapped out and planned for by developers. An additional challenge for

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Table 2. Potential approaches to generating reference materials for PSC-derived products

RM category	RM description	Type	Explanation
Product	Primary/ secondary	Cellular	Generated as per product. Primary and secondary RMs. Secondary RM is used as the working material that, when depleted, is replaced with product from a new batch and qualified against the primary RM.
Product	Pooled	Cellular	Generated as per product. RMs are produced from a pooled bank of cells. A potential benefit is that variability is averaged across the population.
Product/ method	Biological equivalent	Cellular	For a limited number of cell types that can be harvested from donors noninvasively (e.g., from blood), biological equivalent cell populations can be used as a RM (e.g., expression of CD4 levels on peripheral blood T cells and on PSC-derived T cells).
Method	Cell lines	Cellular	Cells lines could have application in a number of characterization assays.
Method	Noncellular	Noncellular	Samples such as fixed cells for cell surface marker staining, DNA samples for sequencing or genotyping, and RNA for expression profiling.
Not a physical RM	"Virtual"	Noncellular	Use of transcriptome, proteome, phosphoproteome, or epigenetic mapping to generate a complex data set that, when computational algorithms are applied, identifies a product "signature" (e.g., concept from PluriTest, PSC scorecard) (data from Müller et al. [34], 2011; Bock et al. [35], 2011).

In-house RM for hPSC-derived products will enable the analysis and qualification of consistency and promote reproducibility. Product RMs are used to ensure that a product batch is representative of an intended product and to identify process drift. Method RMs are used to validate data derived from specific assays, define assay acceptance criteria, and as a tool to detect method drift.
Abbreviations: PSC, pluripotent stem cell; RM, reference material.

approaches that rely on cellular RM is that the cell banks of differentiated products will need to be cryopreserved, which will affect not only viability, but also, potentially, functional parameters. This will become an issue if the product is to be used "fresh" but is less of a concern if the product will be cryopreserved as a part of the production process.

Method Reference Material Approaches

"Method" RMs are used to qualify, validate, and define the acceptance criteria for specific assays, to calibrate methods and equipment, and to identify method drift over time (Fig. 2B).

Cell lines could be valuable method RMs in some settings. An example of such an approach is the use of embryonal carcinoma line 2102Ep, which has a good stability profile in culture. This cell line has demonstrated utility in flow cytometry assays for the characterization of a range of hESCs by the International Stem Cell Initiative [28], despite a number of reported biological differences between hESCs and the embryonal carcinoma line [15, 29]. This approach might also be relevant for a number of differentiated cell types, if an appropriate cell line is available or can be produced. Immortalization of primary cells to generate stable cell lines will affect signaling pathways and some phenotypic characteristics; therefore, the suitability of cell lines as method RMs will depend on the application. It should also be acknowledged that the standardization, characterization, and qualification of cell lines as method RMs would require a considerable amount of workup and validation.

Noncellular (nonviable) method RMs could include fixed cells, beads, DNA/RNA samples, and reference cytokines. Fixed cells, most suitably from a product sample, can be used as a RM for assays that compare cell surface marker expression, such as the clinical application of the NIBSC $CD4^+$ T cell sample for HIV testing, and applications to assess heterogeneity/composition criteria [26]. However, the process of fixation changes the properties of the cell, which could negate its use as a method RM compared with the nonfixed product in some flow cytometry-based assays. Bead-based approaches have routinely been used for flow cytometry purposes, to both calibrate and establish baseline readings for cytometers and to apply compensation settings. However, bead-based approaches also have stability issues and would most likely need to be used in conjunction with a cellular method RM.

RM for molecular biology assays should be more readily achievable, because DNA and RNA samples, in the appropriate conditions, have demonstrated good stability profiles, are easily stored, and can be generated in large quantities relative to the amount of material required for any given assay. In most cases, method RMs for molecular biology assays would be produced from a sample of the product batch. One issue to be considered is the selection of suitable positive controls in assays such as reverse transcription polymerase chain reaction (RT-PCR). Semiquantitative measurements of gene expression are typically made in relation to the expression of "housekeeping genes." However, a number of studies have identified changes in the expression levels of these presumably stable genes in concordance with the differentiation status of hPSCs and other stem cell types; therefore, these would be an unsuitable baseline for these assays [30, 31]. Similarly, although microarray-based assays detect the relative levels of all transcripts in the genome, they do not identify alternatively spliced transcripts that might be critical for cellular function. RNA sequencing (RNAseq) is increasing in popularity and has the potential to identify splice variants and absolute amounts of transcripts. A challenge for an RNAseq approach, however, is the large variation in the results from different sequencing laboratories, a problem that must be solved by a normalization method before sequencing-based

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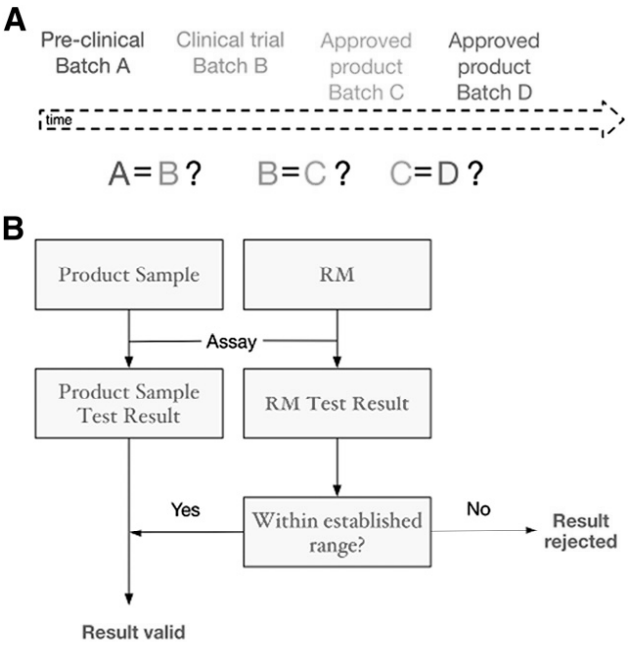

Figure 2. Reference materials are required to demonstrate product comparability over time (product RM) and to validate assay results (method RM). Product RMs are representative of some aspect of quality of a final product, and method RMs are used within assays to confirm the accuracy of the analysis of the product. They have multiple applications, two of which are depicted. **(A)**: Product RMs are required to demonstrate that product drift does not occur. Product drift is the gradual change in a "product," potentially caused by a gradual change in a manufacturing process that can occur through iterations over time. Product RMs are a representative batch against which other batches can be compared to demonstrate consistency in characteristics such as identity and purity. For example, RMs generated with batch B, such as a sample of the iPSC batch, will be retained to use as a comparator with batch D to ensure that characteristics of batch D are within the expected range according to batch B. **(B)**: Method RMs are needed to validate assay results alongside the product sample. For example, specific embryonic carcinoma (EC) lines, whose cell-surface antigens are well characterized, can be used as a quality control for flow cytometry assays in which human embryonal stem cells (hESCs) are also tested. If the score for the EC line is less than a certain predetermined threshold, the results of the accompanying assay of hESCs would not be included in additional analysis. Thus, the results will be representative of the actual hESCs and not of any problem in the assay, because the assay has been validated against a method RM with known characteristics. Abbreviation: RM, reference material.

assays can be reliable—another example of the need for physical reference materials to enable comparability testing. Written standards that identify a consensus minimum requirement for quantitative RT-PCR and microarray assays have been described [32, 33].

Reference cytokines, such as those used to calibrate enzyme-linked immunosorbent assays (ELISAs), are available in some instances in the form of certified (international) RMs. However, although a reference cytokine can serve to define standard curves and therefore a link to a known concentration of that cytokine for an assay such as an ELISA, the reference cytokine is not a RM for the biological assay that results in cytokine release.

Although not a material standard, approaches that create product "signatures" from complex data sets and applied algorithms might have application in demonstrating comparability. Examples of such an approach that has been developed to assess (undifferentiated) iPSC populations by gene expression analysis include the hPSC Scorecard and PluriTest, either by genome-wide microarray (PluriTest [34]) or PCR analysis of a set of selected genes (Scorecard [35]), establishing a typical gene expression profile. Users analyze their samples via the same method (array or PCR) and compare their samples to the established standard generated, in this case, from previous product batches. Such a comparison informs users regarding how similar their sample profile is to the expected profile. This approach might be suitable for the assessment of hPSC-derived products, in which a developer would perform a gene array (or other) analysis using multiple samples from different product batches. Then, using a similar approach to that of the PluriTest, an expression signature for the product would be generated with the identification of "acceptable" levels of variation. This data set could then be used as a "virtual" method RM when assessing the comparability of future product batches using the same method, in the context of a specific product (Fig. 3). This approach would facilitate a move away from the inaccurate use of a limited set of cell surface markers, which are typically used to characterize and identify cell populations. Clearly, this approach would require validation and the application of a suitable RM. Q:7

The method RMs we have described will typically display greater stability profiles than product RMs owing to the inherent plasticity of living cells and their responsiveness to the environment. Feasibility factors, including the ability to generate sufficient batch sizes, will also be more amenable to method RM approaches, which should, in general, also carry lower costs. A rational mix of method RMs for different assays within the overall characterization process and robust product RMs will be required.

A final consideration is how the data will be made available and managed once the method and/or product RMs have been established. Given that discussion has focused on development of in-house RMs, external publication and management of data might not be required. However, rapid dissemination of open access and peer-reviewed publications for community wide access would be beneficial as a "formal" record and to catalyze multistakeholder dialogue. Eventually, it might be possible to develop online data repositories managed by experts in both research and regulation that would act as a centralized resource.

The approaches we have outlined are by no means exhaustive. Innovative thinking is required to envisage novel routes to RMs that would be appropriate to the unique characteristics of hPSC-derived products and cell-based therapies. It is clear that the different approaches will have varying levels of application, depending on the specific product and clinical application.

CONCLUSION

Uncontrolled variability and irreproducibility are key considerations for the translation of PSC-derived therapeutics and for the cell therapy field more broadly. We have outlined the need for RMs, discussed the potential challenges faced by hPSC-derived products, and identified possible approaches to alleviate consistency and reproducibility concerns in the production of hPSC-derived products. A range of cellular and noncellular approaches to product and method RM generation can be envisioned and have been described here, including relevant considerations. The ambition behind our report is for the research community and tool providers to engage around these requirements and existing industry and regulatory models and terminology, such that potential approaches will be

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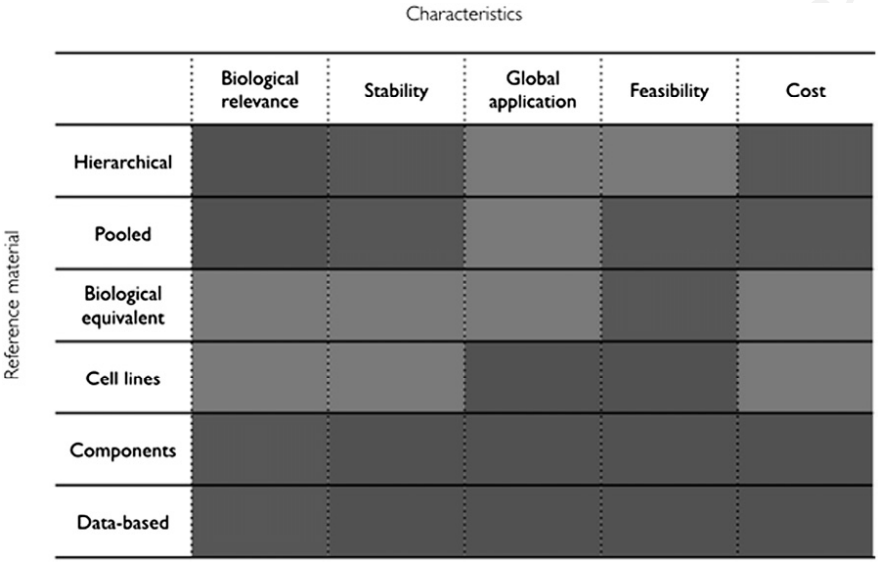

Figure 3. Assessing the suitability of alternative reference material (RM) approaches. Alternative routes to generating product and method RMs include cellular (pluripotent stem cell [PSC]-derived; primary/secondary and pooling, non-PSC-derived; cell lines and biological equivalent cells) and noncellular approaches. A third approach, although not a physical RM, is to use large data sets (e.g., gene array) generated for a specific product that can then be stored as a "virtual" signature to facilitate comparability. When alternative RMs are assessed for characteristics of suitable reference materials, it is clear that biological relevance correlates inversely with many desirable criteria such as stability, cost, feasibility, and the potential for global comparisons. Blue indicates desirable or positive features (e.g., high biological relevance, low cost); gray, neutral feature (e.g., limited biological relevance, midrange cost); and red, undesirable or negative features (e.g., low biological relevance, high cost).

assessed and incorporated into practice, as appropriate, and that novel thinking will lead to approaches that more satisfactorily ulfill the needs outlined.

Acknowledgments

Q:8 We express our sincere thanks to the following organizations that have contributed to the consortium as funding and events partners—without whom the consortium and the benefits it will bring to stem cell translation would be constrained: GE Healthcare, CCRM, TAP Biosystems (now Sartorius Stedim), Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, NIH Center for Regenerative Medicine, New York Stem Cell Foundation, ThermoFisher Scientific, Eisai, Medipost (US), Medipost (Korea), Celgene, Roche, and Oxford Biomedica. Additionally, the Oxford–UCL Centre for the Advancement of Sustainable Medical Innovation is a past recipient of funding from the Technology Strategy Board to support an investigation into cell therapy regulation. We also Q:9 extend our sincere thanks to Prof. Peter Andrews (Sheffield University) for contributing to this research.

Author contributions

A.F., C.B., I.W., K.B., J.M.K., E.Y.S., and D.A.B.: conception and design, administrative support, provision of study material or patients, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; A.C., P.A., J.D.G., N.A., H.K., R.W.B., A.M., J.C.W., D.W., G.G.-G., D.S., S.O., J.F.L., J.A.S., M.S.R., B.R., and A.J.C.: provision of study material or patients, data analysis and interpretation, manuscript writing, final approval of manuscript; G.S.: conception and design, administrative support, manuscript writing, final approval of manuscript

Disclosure of Potential Conflicts of Interest

R.W.B. is a compensated board member and has compensated shares and options in Celgene Corporation. B.R. is a compensated consultant for Boehringer-Ingelheim Pharmaceuticals and has compensated stock options in Pathfinder Cell Therapy. J.C.W. is an uncompensated cofounder of Stem Cell Theranostics; is an uncompensated consultant for Merck; has uncompensated research funding from the NIH, the California Institute for Regenerative Medicine, and Sanofi; and has uncompensated stock options in Stem Cell Theranostics. S.O. has compensated employment and uncompensated intellectual property rights with A*Star. D.A.B. is a stockholder in Translation Ventures Ltd. The other authors indicated no potential conflicts of interest.

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The Implementation of Novel Collaborative Structures for the Identification and Resolution of Barriers to Pluripotent Stem Cell Translation

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AU2▶ ## ABSTRACT

> Productive collaborations, often spanning academia and industry, are vital in driving technological development in stem cell science.

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AU3▶ ## INTRODUCTION

Stem cell technologies can stake a reasonable claim as the leading biomedical advancement of the new millennium. Previous decades were dominated by the elucidation of the structure of DNA, paving the way for progress in genomics and proteomics. Simultaneously, the socioeconomic context for scientific translation has evolved.

Reduced in-house research and development (R&D) productivity combined with increasing shareholder pressure in a challenging fiscal climate has catalyzed increased engagement between academia and industry. This has occurred via the provision of public–private partnerships, cross-licensing agreements, and other collaborative models. Concurrently, the roles of patient advocacy groups and disease-specific foundations have undergone extraordinary development, as observed in the recent approvals of Kalydeco (Ivacaftor; Vertex Pharmaceuticals, Cambridge, MA) and Glybera (Alipogene Tiparvovec; uniQure, Amsterdam, The Netherlands).

The demands of life science translation have changed; consequently, life science research is increasingly multidisciplinary and multi-institutional. However, the stem cell community has arguably been slow to respond to such changes in the ecosystems in which it operates, perhaps in part because of historic global and regional disharmonies in the funding landscape for stem cell technologies. The field has been particularly slow to innovate the way in which it identifies research opportunities and structures the collaborative relationships to enable the delivery of ambitious translational agendas.

The Centre for the Advancement of Sustainable Medical Innovation (CASMI) Translational Stem Cell Consortium (CTSCC) was formed to redress this unacceptable status quo and act as a global nexus for stem cell translation.

Inspired by thought leaders in open innovation, the CTSCC aims to approach its research in two novel ways. First, it attempts to disaggregate the formulation of research problems from their delivery. In the past, research questions have been posed *and* answered by academia. Conversely, the research questions tackled by the CTSCC are formulated by a range of stakeholders in the stem cell translational pathway. This has been achieved by outlining their most pressing issues and assembling the very best teams to deliver academically rigorous and commercially practicable answers [1,2]. Second, the CTSCC attempts to utilize a requirements-based approach whereby the hurdles of potential technology adopters, including end users such as clinicians, are first assessed. Then, based upon these specifications, the highest possible impact contributions from all stakeholders are identified, including those from fundamental scientists (Fig. 1).

Accordingly, the principal translational needs identified by CTSCC partners are categorized into five focus areas: Standards, Biomanufacturing, Regulation and Intellectual Property, Strategic Partnerships, and Clinical Adoption. Additionally, the Consortium's technological focus was defined around pluripotent stem cells (PSCs), particularly induced pluripotent stem cells (iPSC) and embryonic stem cells, and their use in drug screening, as therapeutics themselves or as potential targets. However, because of the limited commercial development of PSC technologies to date [1–3], obtaining data from relevant nonpluripotent products is necessary to extrapolate likely future trends.

This unique and holistic approach to the effective and sustainable translation of stem cell technologies, generously supported by our funding and delivery partners, formally commenced in the elegant surroundings of the Saint James Club in Paris, France, on the July 30, 2013. Herein, we will provide an overview of the issues raised, which we hope will stimulate input from the global stem community.

Event structure

The event format was based upon that of the Harvard Stem Cell Institute, Harvard Business School and Multiple Myeloma Foundation, 2nd Conference on Advancing the Role of Non-Profit Organizations in Drug Development, held on May 17, 2013 (Boston, MA).

The event was divided into five sections, reflecting the focus areas outlined above. Each section was framed by two short provocative presentations from academic and industry leaders, followed by roundtable discussions of precirculated questions (Table 1). Importantly, seating arrangements were made such that an expert from each focus area was seated at each table, in order to encourage interdisciplinary discussions. Primary discussion points were then summarized and debated by an expert panel. The points raised were collated and have been incorporated into a questionnaire that has been

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Table 1. Roundtable and Panel Discussion Questions

Focus area	*Roundtable and panel discussion questions*
Standards	What are the key deficiencies in existing iPSC and ESC standardization efforts, and how can we best act to harmonize these efforts?
Biomanufacturing	What are the key outstanding challenges as we seek to remove the "art" and cost from the manufacture of iPSC therapies?
Strategic partnerships	Which models for strategic partnerships are accelerating stem cell translation most effectively? And for those that are not, why not?
Regulatory and intellectual property	Building on community experience with ASCs, what regulatory uncertainties remain with respect to ESCs and what additional uncertainties are perceived for iPSCs?
Clinical adoption	Failure to demonstrate sufficient efficacy represents a major barrier to the adoption of existing cellular therapeutics. What steps (and data) are required to confer stakeholder confidence and successful adoption?

ASCs, adipose-derived stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

distributed to all delegates who have been asked to prioritize, refine, and define the future work of the CTSCC.

Overview of roundtable and panel discussions

Standards

Defining standards for PSC technologies is inherently complex because of the heterogeneity and plasticity of both the cells themselves and their therapeutically relevant differentiated products [4,5]. Indeed, it is differences between these cells that will make one product a success and another product a failure in relation to a particular indication. Therefore, for PSC-derived cell products, the provision of a generalized standardization specification would be challenging. Similar challenges have been encountered in the clinical implementation of genomics in stratified medicines and their delivery through the use of companion diagnostics [6,7].

Rapid technological progress within the field, such as the generation of iPSC lines using small molecules alone, will likely continue with vigor [8] further stimulating efforts to standardize iPSC lines suitable for clinical and industrial use [9]. Reference standards for methodologies and instrumentation would bring a wide range of benefits, facilitating comparability and reproducibility, which are fundamental challenges for the sector. Reference standards are also a decisive requirement for the development of manufacturing instrumentation and reagents, as well as for the manufacturing process itself [10]. Furthermore, reference standards would enable productive communication with the regulatory authorities and provide a positive step toward global harmonization [11]. Pertinent questions relate to the type of in-process measurements that should be recorded and their acceptable ranges, including the identification of permissible and potentially efficacious ranges for PSC products.

Progress has been made with regard to the minimum requirements for PSC banking, as well as efforts to coordinate approaches and concepts in the academic R&D space [12–14]. Characterization of cell therapies more broadly requires an assessment of cellular critical quality attributes associated with identity, purity, potency, and safety (Table 2). Approaches taken to assess PSC identity include transcriptomics, analysis of the phosphoproteome, expression of pluripotency markers, telomere length, and epigenetic signatures [15–19]. ◀TABLE2

Pluripotency potential, in relation to the ability to differentiate into all three germ layers, has been commonly assessed by embryoid body differentiation, teratoma formation, and directed differentiation methodologies. Therapeutic potency assays for differentiated cell types, however, will vary on a cell type-to-cell type and indication basis. With PSC products, it may become increasingly necessary to model the in vivo environment in vitro, to predict cell identity and potency in a physiologically relevant context. Moreover, for the scalable and reproducible generation of PSC products, nondestructive methods to continuously monitor and characterize cells in real time are required. Biomaterials may play a pivotal role in controlling the environment of implanted cells, in addition to biodistribution and engraftment profiles [20,21]. Here, the triad of cell therapy, host, and biomaterial interaction must be predicted. In summary, standardization efforts in the PSC sector should focus on defining methods, and instrumentation to accelerate effective translation.



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Table 2. FDA Definitions of Critical Quality Attributes as Per CFR 21 600.3 and Part 610

Safety	"...the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered taking into consideration the character of a product in relation to the condition of the recipient at the time."
Purity	"...relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances."
Potency	"...is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."

Biomanufacturing

Firmly positioned at the interface of the focus areas selected for investigation, biomanufacturing is in some respects responsive, and others informative. For example, technical specifications for biomanufacturing equipment respond to the needs defined by clinicians, operators, validation teams, and regulators. However, bioprocessing parameters can also inform the work of fundamental scientists and development groups, particularly around standardization of industrial-scale processes. These are then subject to current Good Manufacturing Practice (cGMP) requirements, which seek to remove the "art" from inherently manual (and hence variable) laboratory processes [22].

Encouragingly, there is evidence that the expertise required to conform to cGMP standards, often limited in academia, is being provided by public and/or privately funded translation centers. Additionally, contract manufacturing organizations are engaging at progressively earlier stages of development with academia and/or small–medium enterprise. There are considerable benefits in expanding communication between academia and early-stage providers so that initial processes are amenable to industrial scale-up.

Throughout the day, a number of lessons were highlighted that can be learnt from the evolution of cell-based high-throughput screening technologies and early monoclonal antibody manufacturing strategies. Critically, the provision of in-process analytical technologies and process automation advances [23] will facilitate improvements in the consistency of cellular bioprocesses and the comparability of products manufactured—an essential step toward broad stakeholder adoption [24].

Additionally, strong market prospects exist to innovate better cGMP-level processing tools that are cognizant of the final product sterilization limitations to develop microcarriers or aggregate processes for bioreactor production and to adapt existing process and media development technologies for cost of goods reductions [25,26]. Media development and in-process technologies to monitor expansion and differentiation of stem cell-derived products in real time represent a major unmet market need [27]. Also, novel release criteria offer opportunities for bioprocess engineers to develop non-invasive monitoring and testing platforms to enable thorough product characterization, a necessity for biologically active products [28].

Strategic partnerships

Successful translation of scientific discoveries from the lab to the clinic requires the coordination of multiple stakeholders in the healthcare industry who are each crucial to the translational process. This interdisciplinary network, its utility and its effectiveness, plays an important role in stem cell science. Therefore, the emergence of strategic partnerships in the stem cell space has demonstrated that productive collaborations, often spanning academia and industry, are vital in driving technological developments [29]. As such, it is critical to understand the various partnerships that have been forged to date and identify which models for strategic partnerships are accelerating stem cell translation most effectively. It is hoped that these findings may also elucidate new opportunities for collaborations that could address translational gaps.

First, when academia, foundations, service providers, and/or pharmaceutical companies enter into collaborations, it is imperative that all partners have clearly aligned interests and a shared vision. Increasingly, it is essential that university technology transfer offices are engaged in this process, to ensure that underlying intellectual property (IP) licensing agreements support, as opposed to constrain, multistakeholder collaborations.

In order for the partnership to add value, groups should communicate how each partner can combine their capabilities, expertise, and resources in the most effective and additive manner. Some categories

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AUI0▶ **Table 3. Evaluation of Biomanufacturing Automation**

Advantages of biomanufacturing automation	*Disadvantages of biomanufacturing automation*
Improved reproducibility	Initial capital expenditure
Reduced contamination risks	Potentially limited flexibility
Potential for improved product quality	Physical footprint
Enhanced productivity	Staff training requirements
Electronic process monitoring and record retention	Operational costs, including servicing
Reduced labor costs	Reliability concerns

of strategic partnerships that have been formed within the stem cell landscape include academic and industry partnerships for commercializing early-stage stem cell research; academic and industry partnerships for advancing the clinical translation of stem cell therapeutics; public and private partnerships for launching specific stem cell initiatives; strategic partnerships for improved manufacturing of stem cell products; and strategic partnerships involving major publicly funded translational institutions.

While the growing number of strategic partnerships is an excellent catalyst for stem cell translation, it is crucial that patient benefit is not delayed because of the poor coordination of partner contributions. This is a critical role of the growing international network of stem cell translation centers. However, several significant questions remain, including, how exactly we define a translation center, what are their optimal funding sources and capabilities, and how should access to said resources be allocated among stakeholders? TABLE5▶ By comparing commonalities between different centers and understanding their strengths and weaknesses, we aim to suggest the criteria of effective models for future strategic partnerships—within and beyond the stem cell community.

Regulation and IP

Stem cell therapy has stimulated the emergence of a new area of interest in law, particularly concerning the optimal routes by which to capture value in the development and delivery of cell-based technologies. An example would be the as yet unproven value of (biomanufacturing) process patents. Consequently, some investor hesitance persists.

The stem cell IP landscape is vast and poorly understood, despite a number of efforts to perform broad IP landscaping exercises (Table 4). However, prior studies failed to effectively distinguish between different aspects of stem cell R&D. Patent data analytic software offers a powerful tool to mine and reveal decisive trends and information, since a number of factors can skew results, such as delays in the granting of applications in the face of different regulatory challenges.

Therefore, the value and best practices for freedom-to-operate licensing schemes, such as that offered by iPS Academia Japan, remains uncertain. Other proposed solutions include creating a stem cell research exemption to patent infringement and compulsory broad licensing for publicly funded discoveries. There may be a requirement for novel mechanisms that facilitate collaboration and expedite commercial translation through patent brokering or clearing houses, without undermining industrial proprietary value. However, it is reasonable to assert that the impact of such challenges will decline overtime as the number of clinical stage, and ultimately revenue-generating products, increases.

Regulation is a challenging topic in that few PSC technologies are near a clinical stage; therefore, regulatory recommendations must be based on similar technologies and assessed potential risks. Significant risks debated at the event were biodistribution, tracking, cell overgrowth, immunogenicity, inappropriate homing, teratoma formation, and allowable residual pluripotent cell level in final differentiated product. The impact of deficiencies in regulatory training for academics was also highlighted.

Historically, regulatory standards have commonly relied heavily on defining the basis of the mechanism of action for the treatment, which in many cases is not fully elucidated for cellular therapeutics. Appropriately, there remains a strong regulatory stimulus for the development of in vivo monitoring technologies to determine cell engraftment, distribution, and fate.

In order to produce affordable therapies, duplicate costs and delays to meet unnecessary regulatory standards must be ◀TABLE4 avoided. Presently, separate regulatory approvals are required for multiple components of combinational products (cells + biomaterials). Although there are strong regulatory arguments for this approach, there is also compelling evidence from a practical and commercial perspective against this approach—not least because of the unique financial risks associated with the development of combinational products [21]. Subsequently, bolstered stakeholder efforts are required to investigate robust risk:benefit appraisal methodologies for cell-based therapies (Table 5).

Clinical adoption

Stem cells of all varieties have held the promise of delivering a wide variety of healthcare treatments for a number of years; however, in most cases their broad clinical efficacy is yet to be satisfactorily established. The academic and professional literature is replete with short case



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Table 4. Notable Stem Cell Intellectual Property Landscape Reports

Title	*Publication date*	*Supported by*
Regenerative Medicine Report	July 2013	(UK) House of Lords Science and Technology Committee
Taking Stock of Regenerative Medicine in the United Kingdom	July 2011	(UK) Dept. of Health, Dept. for Business Innovation and Skills, Office of Life Sciences
Stem Cells: The UKSCN Patent Watch Landscape	June 2012	Intellectual Property Office, Patent Informatics Team
Regenerative Medicine: The Patent Landscape in 2011	June 2011	Intellectual Property Office, Patent Informatics Team
iPSCs Patent Landscape	On-going	Californian Institute for Regenerative Medicine (CIRM)
Intraoperability Problems: Inconsistent Stem Cell IP and Research Regimes Within Nations	May 2011	CJ Murdoch, Stanford J Law Sci Policy
Regenerating Intellectual Property: Europe after Warf	March 2012	*The Delivery of Regenerative Medicines and Their Impact on Healthcare*, edited by C Prescott, DJ Polak
Stem Cells: IP Landscape	January 2006	IP Technol Law J, by Ebersole, Edmund, and Schwartzman
Patents and Misplaced Angst: Lessons for Translational Stem Cell Research from Genomics	May 2013	By DJH Mathews, R Cook-Deegan, T Bubela Cell Stem Cell 12(5):508–512
Human Induced Pluripotent Stem Cells: A Review of the US Patent Landscape	July 2010	By BP Georgieva, JM Love; Regen Med 5(4):581–591
Statement on Data and Materials Sharing and Intellectual Property in Pluripotent Stem Cell Science in Japan and China	November 2012	Hinxton Group
The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development	April 2007	By K Bergman, GD Graff Nat Biotechnol 25:419–424

series and reports detailing their use in small numbers of patients, while only a small number of comparative trials have been conducted [30]. From a clinical perspective, the most significant question to consider with any new product is: *Does this provide a better outcome for the patient than currently available treatments?* The second consideration is: *At what cost does this improvement come?* Establishing answers to these questions are essential steps in the broad adoption of cell-based therapies and/or biomaterials, requiring appropriately designed and conducted clinical trials.

Clinical trials may be designed to enable the comparison of new technologies with the currently accepted gold standard [31]. In the treatment of cartilage defects in the knee, comparisons to microfracture, the best available option currently in use, are most appropriate and will provide the most relevant clinical data. The relatively high cost of cell-based treatments is solely justified, in this instance, if they provide long-term symptom relief. Autologous chondrocyte implantation and similar stem cell–based treatments are only legitimately cost effective from a healthcare system point of view if they lead to a significant delay in the necessity for end-stage treatments such as joint arthroplasty when compared with procedures such as microfracture [32].

Equally critical is the selection of appropriate endpoints and follow-up timeframes. Validated clinical outcome measures are vital to allow a reproducible assessment of interventions and to monitor long-term progress. Of equal importance is the assurance that follow-up periods are sufficiently long to determine whether treatment is worthwhile in the long-term and to monitor treatment reproducibility



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Table 5. Challenges in the Risk:Benefit Appraisal of Cell-Based Healthcare Innovations

1. Limited, but rapidly growing; development and implementation of risk:benefit appraisal methodologies for all types of healthcare innovation to date
2. Transient vs. permanent characteristics of cell-based therapies and impact on duration of exposure to risks and/or benefits
3. Limited clinical data for pluripotent cell types
4. Lack of defined mechanisms of action (MoAs)—in part due to limitations in cell characterization and standardization
5. Limited regulatory guidance specifically for the risk:benefit appraisal of cell-based therapies. However, a growing body of regulatory guidance exists for established technologies.
6. Conflation of product (allogeneic) and service (autologous) models
7. Difficulties in defining the scope of risk:benefit analysis for cell-based therapies. For example, may extend to the risks conferred by final formulation and fill procedures in hospital pharmacies
8. Requirement to assign appropriate "utility weightings" to alternate risk:benefit factors under analysis
9. Need for academia-initiated clinical studies to include (qualitative and quantitative) risk:benefit evaluations, which may be unfamiliar to academic investigators
10. Unique challenges of assessing the combined risk and benefits of combinational products (cells + biomaterial)
11. Requirement for patient stratification and effective integration into risk:benefit analyses
12. Challenges in defining appropriate patient follow-up periods

Table 6. Barriers to Clinical Adoption of Cell-Based Therapies

Issue	*Potential solution*
High cost of procedure	Demonstrate superior long-term outcomes compared with current potentially more affordable treatment options
Increased morbidity	Demonstrate short-term morbidity offset by long-term outcomes
Difficulty in treatment comparison	Ensure that robust outcome measures are used in all trials to allow comparison between them
Requirement for long-term benefit	Adequately designed clinical trials with appropriate follow-up periods
Lack of clinical engagement	Ensure that clinicians involved in initial design stages of interventions and trials

in the target patient population. It is also imperative that trials be conducted so that all results are reported in a manner that allows treatment comparison and does not neglect negative outcomes. This can then inform the optimal patient selection for the specific cell-based treatment and correctly assess the full impact upon the healthcare infrastructure.

> From a clinical perspective, the most significant question to consider with any new product is: *Does this provide a better outcome for the patient than currently available treatments?*

Finally, clinician engagement can be assured only upon demonstration that the new technologies are effective enough in both medium- and long-term to warrant the increased cost and potential heightened short-term morbidity for patients. Achieving these aims can be greatly assisted by establishing early clinician involvement in both initial product development and trial design.

CONCLUSION

The multistakeholder pursuit of sustainable and efficient stem cell translation is essential to the delivery of patient outcomes. However, as this event demonstrates, this remit will not be achieved unless rigorous and continuous assessments of the translational environment



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are conducted—not least the requirements of ultimate clinical adopters.

Therefore, while existing efforts of translatory and trade organizations in the stem cell space to convene multistakeholder meetings are welcomed, arguably their value has been limited by the quality of the interaction between the participants. As such, the most impactful discussions and collaborative relationships forged at this meeting are a result of disaggregating the formulation and delivery of research questions—a process supported by a (mildly) draconian seating arrangement forcing unconventional multidisciplinary interactions.

Hence, the stem cell community needs to innovate and translate more *effectively*, with a focus on clinical and commercial needs, and we firmly believe that the work of the CTSCC will continue to be an essential mechanism to facilitate this.

We extend our sincere thanks to all participants in the CTSCC's activities, including this meeting, and look forward to contributing academically rigorous and commercially practicable findings to the global stem cell technology industry.

ACKNOWLEDGMENTS

We wish to extend their thanks to the following individuals whose contributions have been critical to the development of the CTSCC: Stewart Abbot (Celgene), Houman Ashrafian (University of Oxford), Elona Baum (Californian Institute for Regenerative Medicine [CIRM]), Robert Beale (CFF),Chas Bountra (University of Oxford), James Bradner (Harvard), John Brown (UK Cell Therapy Catapult), Guillermo-Garcia Cardena (Harvard), Dan Cho (CFAR), Emanuela Costigliola (GE), George Church (Harvard), George Daley (Harvard), Barry Dornfeld (CFAR), Nick Edwards (CASMI), Simon Ellison (UK Cell Therapy Catapult), Paul Fairchild (University of Oxford), Thomas Fellner (Lonza), Kathy Giusti (MMRF), Joe Gold (Stanford University), Christopher Huge (CFAR), Johan Hyllner (UK Cell Therapy Catapult), Perry Karsen (Celgene), Karim Lakhani (HBS), Mark Lewis (Loughborough University), Neil Littmann (CIRM), Andrew Lo (MIT), Lorenz Mayr (AstraZeneca), Alison McEwen (UKTI/FCO), Stephen Minger (GE), David Newble (TAP Biosystems), Mahendra Rao (NIH Center for Regenerative Medicine), William Sahlman (HBS), John Sinden (ReNeuron), Sue Solomon (New York Stem Cell Foundation), Matthias Steger (Roche), Molly Stevens (Imperial College London), Thomson Reuters IP Team (London), Keith Thompson (UK Cell Therapy Catapult), Sam Ulin (ClearView Healthcare Partners), Nat Welch (CFAR), Michael West (BioTime), Joe Wu (Stanford University), and Jesus Zurdo (Lonza).

We wish to express our sincere thanks to the following organizations that have contributed to the consortium as funding and events partners—without whom the consortium and the benefits it will bring to stem cell translation would be unacceptably constrained: GE Healthcare, CCRM, TAP Biosystems, Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, and NIH Centre for Regenerative Medicine. Additionally, CASMI is a past recipient of funding from the Technology Strategy Board in order to support an investigation into cell therapy regulation.

Author Disclosure Statement

To request individually from all authors.

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The global intellectual property landscape of induced pluripotent stem cell technologies

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Will freedom to research and innovate be restricted as the induced pluripotent stem cell field advances toward the clinic, or are concerns premature within a rapidly changing ecosystem?

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Intellectual property (IP) rights lie at the core of the commercialization process, serving as a powerful incentive to harness the potential of technologies for therapeutic applications. However, when filed inappropriately—with broad or premature claims, for example—or when mismanaged, patents can obstruct vital precompetitive collaborations, dampen investor interest and threaten clinical translation and patient access[1–3]. Moreover, uncertainties, including those around the validity of claims or the priority of ownership rights, can depress progress[4].

Stem cell derivation and cellular reprogramming techniques are broadly enabling technologies for which ready access is essential to a sustainable cell therapy industry. Pluripotent stem cells (PSCs) have the potential to transform future healthcare. Clinical trials using embryonic stem cells (ESCs) have begun to show early promise[5]; however, concerns remain regarding limited supply and ethics. In 2007, scientists at Kyoto University and, independently, at the University of Wisconsin, reprogrammed adult human skin cells to generate induced pluripotent stem cells (iPSCs)[6,7]. In addition to long-term therapeutic potential, iPSC technologies are valuable tools for drug discovery, toxicology testing and disease modeling.

Although the total number of stem cell patent filings has declined since 2008, patents for iPSC technologies continue to increase[8]. Analysis of the blistering pace of scientific progress in this area indicates that the growth is unlikely to abate. Widespread concern has been voiced that the emerging ecosystem is becoming burdened by prohibitive and cumulative licensing fees that could restrict scientists' freedom to research and patients' equitable access to resulting medical benefits[2–4,8,9]. Although these concerns may be allayed through innovation and industry growth cycles, the upstream production and downstream differentiation of iPSCs into desired cell lineages for application requires numerous interrelated, complex technologies. This distinguishes cellular patents from the evolution of other highly patented industries such as small-molecule drugs and electronics. No single company currently controls the IP for all techniques, methods and reagents required for the production of iPSCs[10]. A global race is underway to establish the most suitable and efficient methods for each of these component technologies.

Although it may be beneficial for competing industry that no single entity dominates market access to all fundamental iPSC technologies, congestion of patents related to broadly enabling technologies, referred to as a 'patent thicket', has the potential to bottleneck innovation. If ownership of overlapping fundamental aspects is spread across several patent holders, research may become encumbered by the negotiation of complicated stacked licensing with prohibitive fees and royalty schemes that drain value from innovation. This is referred to in IP rights theory as 'anti-commons' innovation[11]. Funders may, consequently, be deterred by vulnerability to future challenges against IP ownership of a product after costly development.

Analysts estimate that total global revenues for companies that supply iPSC research products was $837 million in 2012 and that this will exceed $1 billion by 2015 (ref. 12). Additionally, 22% of stem cell researchers report having used iPSCs[12]. With first-in-man clinical research studies underway this year at RIKEN[4], now is a critical time in iPSC technology R&D to address the validity of any potential IP obstacles to the commercial translation of medical advancements.

Despite extensive literature, a current, global analysis that focuses exclusively on the burgeoning IP landscape for iPSC technologies has not been performed. To provide clarity, we consider the broad landscape and discuss the validity of mounting concerns over licensing practices for this nascent ecosystem, possible solutions and the emergence of other forms of IP that could erect barriers to open and collaborative science. Accordingly, we have employed commercial software to analyze patent

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Table 1 General iPSC technology category distribution of estimated patent filings: production (upstream technologies) versus differentiation (downstream technologies)

	iPSC main technology categories	
	Production	Differentiation
Estimated no. of patent families (patented inventions)	650	1,300–1,400

data, which identified a fragmented patent landscape with internationally dispersed ownership around complex, interrelated technologies.

Technology areas and trends

To identify the major trends, a raw data set was harvested to include a broad range of technologies related to iPSCs, comprising 4,651 documents with 1,388 Derwent World Patents Index (DWPI) families (patented inventions) using Thomson Innovation software. This initial collection was characterized and cleaned, both manually and using Thomson Data Analyzer software (see **Supplementary Note**). Patents filed and/or granted between 1 September 2006 and 31 December 2013 were searched using keywords in patent titles, abstracts and claim sections across a complete global data set of 50 patent authorities.

The challenge in isolating the iPSC patent landscape from the broader pluripotent landscape (**Supplementary Fig. 1**) is in the high degree of overlap in terminology, techniques and applications that relate to both ESCs and iPSCs. Another particular challenge is the significant overlap between cellular processes and materials claimed for reprogramming and differentiation.

To narrow the search within pluripotency, we selected more rigorous keyword searches (**Supplementary Table 1**) to yield data sets that were further manually refined through random sampling of more than 700 patents (**Supplementary Table 2**). The data set therefore represents an over-inclusive estimation rather than a precise figure.

The iPSC R&D pipeline is divided between upstream production and downstream differentiation techniques. Production refers to the reprogramming of somatic cells to a pluripotent state. Once reprogrammed, these cells are selected and replicated. Candidate pluripotent cell colonies are then characterized for confirmation of a pluripotent phenotype before further propagation. The resulting iPSCs can serve as important research tools for a range of downstream applications that differentiate iPSCs into specialized cells. The differentiated cells created from PSCs can then be used for drug screening, toxicity testing, disease modeling or therapeutic application.

Differentiation technologies are the largest group of iPSC patents. In this broad category of patents, referred to as the 'differentiation patents', iPSCs have a range of roles, from central to more ancillary. In the latter, pluripotent cells are cited merely as a possible starting material for the invention, among other listed cell types. Including differentiation patents within the iPSC landscape initially gives a broad overview with considerable overlap with the wider PSC (iPSC and ESC) landscape. A conservative estimate of the number of differentiation patents is 1,300–1,400 patent families (inventions) with 4,500–5,000 documents overall (**Table 1** and **Supplementary Table 3**). This figure would probably be higher if more differentiation patents for ancillary technologies that cite iPSCs in their claims were included.

The category of patents related to iPSC production, an estimated 650 filings, includes culture techniques, growth factors and technologies essential to the generation of iPSCs (**Table 1** and **Supplementary Table 3**). Estimates do not account for discontinued or denied applications. Excluding ancillary technologies such as culture techniques, we identified 299 patents for reprogramming methods.

A digital representation of the broad iPSC patent landscape provides a macroscopic glimpse of patenting trends and can help visualize technology clusters (**Fig. 1**). Automated software clusters similar terminology found in the patents' titles, claims and abstracts. Patents are represented by dots, and those with similar terminology are delineated by contour lines. The greater the similarity in the patents' terminology, the greater the elevation of the cluster contour. The white 'snow-capped' peaks represent areas of high patent activity for the labelled terms: multiple sclerosis, spinal injury and diabetes research; cancer research; reprogramming methodologies; gene therapy and tissue engineering; and cell culturing mediums and techniques, including assays to confirm pluripotency and cell population selection techniques (**Fig. 1**).

Although a number of the peaks involve cell-reprogramming techniques distributed among a range of technology areas

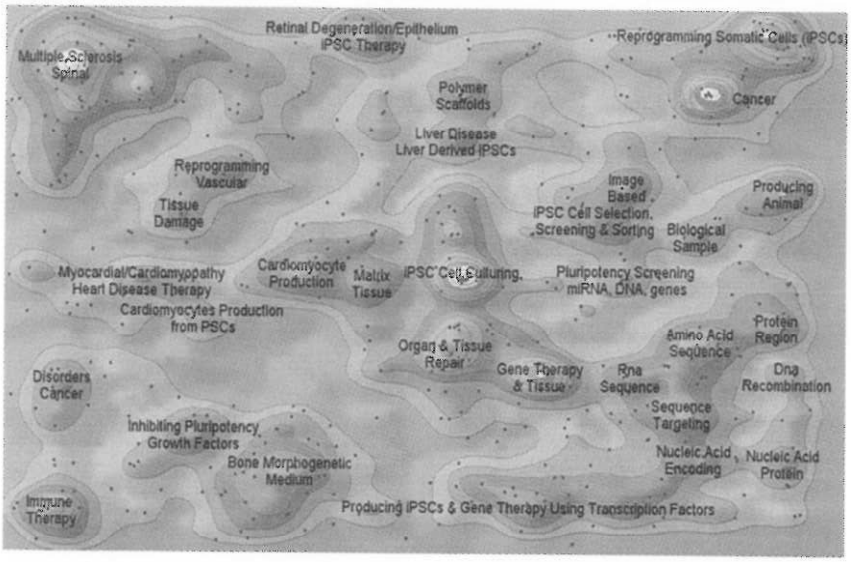

Figure 1 Broad iPSC technology patent landscape. The five white 'snow-capped' peaks indicate technology areas of high patent activity: cell culture (including cell selection and characterization techniques), spinal injury, cancer (involving cancer cells, inhibiting teratoma formation or research intended as a therapeutic indication toward cancer), reprogramming methodologies and patent documents that cite gene therapy or tissue engineering purposes. Each dot represents a patent. The stronger the correlation of automatically clustered terminology within a contour, the higher the elevation of related patents. The patent map, generated using Thomson Innovation software, provides a representative overview of the original raw patent collection before it was cleaned to remove patents that do not directly claim iPSCs as a central aspect of the patented invention. This initial raw data set of 1,388 patent families with 4,651 total documents comprises both granted and pending applications from 1 September 2006 to 31 December 2013. (Source: Thomson Reuters)

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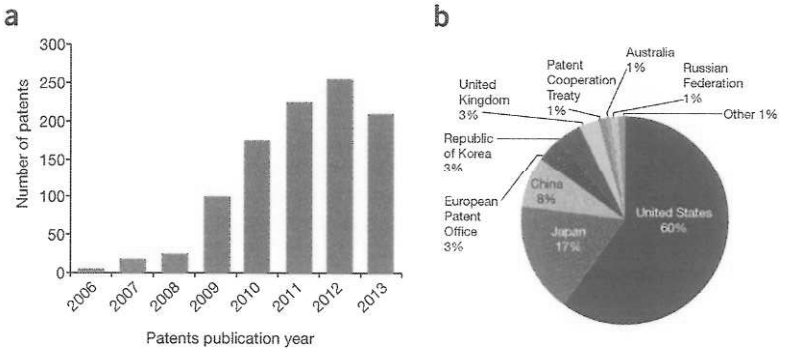

Figure 2 Trends in iPSC patent document filings. (**a**) The number of total patented inventions filed for iPSC technologies has increased each year since 2006, peaking in 2012. (**b**) National contributions to iPSC invention by earliest priority country. The United States dominates the fundamental technology platforms in the field, followed by Japan, as could be predicted on the basis of technology origin and subsequent national focus. China and the Republic of Korea significantly contribute in addition to the European Patent Office and the United Kingdom.

(**Supplementary Fig. 2**), the map flushes out a visual of the third-largest category of iPSC-related patents (generalized from the size of the snow-capped peaks in **Fig. 1**): cell-culturing techniques and growth factors. This category includes technologies for both the generation and differentiation processes.

Each of these broad categories represents a technology umbrella for a series of complex, multistep processes. Therefore, each step in the iPSC 'pipeline' further subdivides into specific areas of research and IP proliferation. Because accepted best-practice standards within the industry for each of these steps do not yet exist, they represent current and potentially profitable technology gaps but, equally, concerns for patent thicket formation.

Patent filing profile

Published patent applications filed on iPSC-related technologies nearly doubled from 2009 to 2010 (**Fig. 2**). In 2012, Shinya Yamanaka shared the Nobel Prize in Physiology or Medicine with John Gurdon for their contributions to reprogramming. In the same year, published patent applications relating to iPSCs reached an all-time high (**Fig. 2**). Despite a modest dip in 2013, a similar number (150) of new filings on discoveries broadly relevant to iPSCs can be expected in 2014. This trend is unlikely to decrease, provided a nonobvious, novel step change in reprogramming standards is not discovered.

Patent activity was analyzed by priority country to indicate geographical concentration of iPSC research. The United States and Japan clearly lead, with the greatest contributions to iPSC patented inventions, but research is active on a global stage (**Fig. 2**). In 2013, Japan passed legislation to expedite approval of candidate stem cell therapeutics without phase 3 clinical trials[13]. If this regulation results, as anticipated, in the acceleration of therapeutic products to market, the corresponding patents may also be expedited, as was the grant of Yamanaka's patent in 2008. However, this remains to be seen. Meanwhile, the United States has steered in a different direction. The federal appeals court ruled in February 2014 that more-than-minimally manipulated stem cell therapies must be regulated as a (biological) drug in accordance with US Food and Drug Administration regulations, rather than more leniently as a medical practice or medical device (cellular product)[14].

Still, the United States, with its significant margin for pending and issued patents, is unlikely to be surpassed by Japan. Additionally, the United States has a more diverse base of assignee expertise compared to Japan's concentration in a handful of institutions (**Table 2**). However, in an

Table 2 Leading 10 assignees and inventors (924 patent family cleaned subset of collection)

Rank	Organization	Top inventors
1	Kyoto University (Kyoto, Japan)	Yamanaka, S., Takahashi, K., Nakagawa, M.
2	University of California, Santa Cruz (Santa Cruz, California)	NA
2	General Hospital Corp. (Boston)	Hochedlinger, K., Maherali, N.
2	Harvard College (Boston)	Maherali, N., Hochedlinger, K.
4	National Institute of Advanced Industrial Science and Technology (Kyoto, Japan)	Yamanaka, S., Goshima, N., Mochizuki, H., Kawamura, Y., Maekawa, M.
4	Whitehead Institute of Biomedical Research (Cambridge, Massachusetts)	Jaenisch, R., Hochedlinger, K., Young, R.A.
4	Wisconsin Alumni Research Foundation (Madison, Wisconsin)	Thomson, J.A., Chen, G., Yu, J.
5	Cellular Dynamics International (Madison, Wisconsin)	Mack, A., Yu, J., Thomson, J.A.
5	Guangzhou Institutes of Biomedicine and Health (Guangzhou, China)	Pei, D.Q., Esteban, M., Quin, D.J., Chen, J.K., Yang, J.Y.
6	Agency for Science, Technology & Research (Singapore)	Ng, H.H.
6	Salk Institute for Biological Studies (La Jolla, California)	Belmonte, J.C.I., Gage, F.H., Raya, A.
6	Stanford University (Stanford, California)	NA
7	Advanced Cell Technology (Marlborough, Massachusetts)	Lanza, R., West, M.C., Lu, S.J.
7	Sangamo Biosciences (Richmond, California)	Holmes, M.C., Gregory, P.D., Urnov, F.
7	University of Tokyo (Tokyo)	Nakauchi, H., Takayama, N., Eto, K.
8	Johns Hopkins University (Baltimore, Maryland)	NA
9	Keio University (Tokyo)	Okano, H., Fukuda, K., Hattori, F.
10	Children's Medical Center (Boston)	Daley, G.Q., Agarwal, S., Park, I.H.
10	Primegen Biotech (Irvine, California)	Silva, F.J., Sayre, C.B.

Only inventors with three or more patents are named. NA, not applicable.

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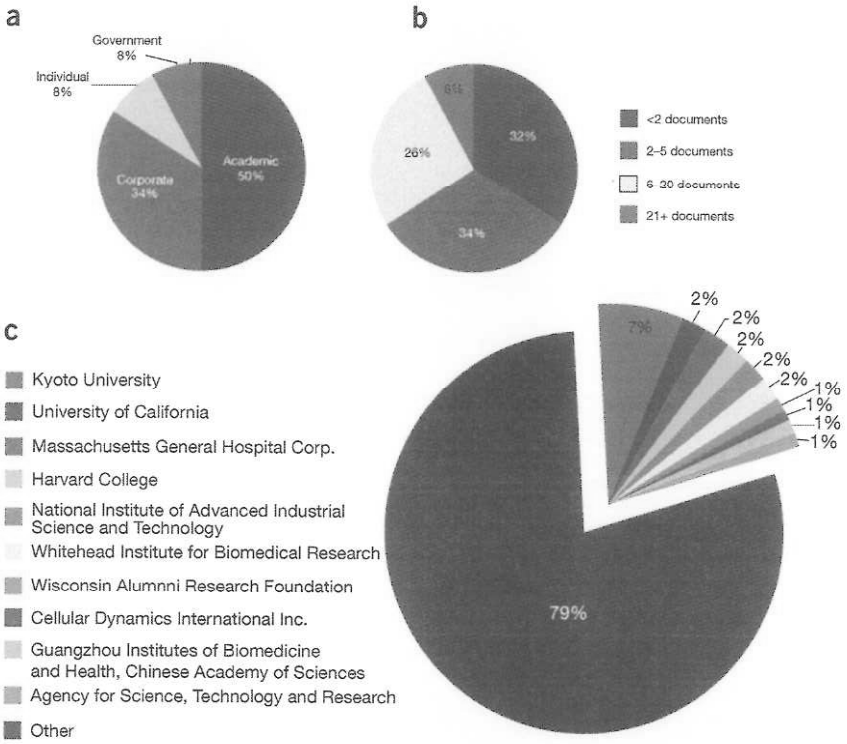

Figure 3 The distribution of ownership origination shows a fragmented landscape with public-sector dominance and a growing cottage biotech industry. (**a**) Breakdown of sector participation in iPSC R&D shows a significant number of iPSC patents in government, nonprofit and academic institutions (58%). The public sector dominance is unsurprising for emerging technologies. However, 34% corporate ownership indicates that this field has started to actively privatize at an early stage. (**b**) Distribution of patented inventions among patent holder organizations. The domination of lower-value patent portfolio holdings shows a large number of smaller players in the sector, indicating that the 34% corporate face of iPSC patent ownership is composed largely of small biotechnology companies. The thin distribution of patent ownership reveals a highly fragmented landscape. (**c**) The ten leading organizations, determined on the basis of overall patent-document numbers for iPSC inventions, shows Kyoto University as the top iPSC patent holder (both for overall applications and granted patents). Despite the overall dominance of the United States, Japan has two institutions, Kyoto University and the National Institute of Advanced Industrial Science and Technology, in the top ten organizations for iPSC inventions, in addition to the Guangzhou Institutes of Biomedicine and Health in China and the Agency for Science, Technology and Research in Singapore.

assessment of patents' value to the field through citation analysis compared with the location of the top assignees (patent holders), the geographical hubs for iPSC research are Japan, Massachusetts, California, Wisconsin and the United Kingdom (**Table 2**, **Table 3** and **Fig. 2**).

China and South Korea both have strong footing in the top five countries filing iPSC patents (**Table 2** and **Fig. 2**). Their positioning is stronger for iPSCs than for PSCs or general stem cell patents[15]. In terms of patent filing numbers, China appears to be the third strongest contributor to iPSC-related inventions exceeding the European Union (EU). The EU has a similar patent activity level to South Korea (**Fig. 2**). This distinguishes the iPSC patent landscape. By contrast, the EU is the third highest contributor with regard to patents filed for embryonic stem cells discovery and stem cell research more generally. Although these geographical comparisons include more ancillary iPSC technologies and do not account for validity of the patents filed, they clearly indicate greater global participation than other areas of stem cell research[15].

After the United Kingdom, Germany is the top patent-filing country in the EU for all stem cells[15]. For the iPSC patent landscape, the United Kingdom remains the strongest patenting EU member state. Germany is active in the PSC space but does not seem currently to have a leading presence in iPSC technology (**Fig. 2**). German institutions, however, are the second largest contributors, behind France, of regional EU patent applications. It is possible that a stronger presence has yet to emerge owing to the year-and-a-half time from filing to publication.

Even in the broader pluripotent cell landscape, Kyoto University is the established leader among patent applicants[15]. However, until as recently as 2012, the Wisconsin Alumni Research Foundation was the institution granted the most stem cell patents[15]. Unsurprisingly, in the iPSC space, Kyoto University leads for total filed and granted patent applications. Unlike the majority corporate ownership of stem cell technologies[15], iPSC technologies are emerging and, therefore, still dominated by public sector R&D, with only 34% of patents owned by corporate entities (**Fig. 3a**).

Patent distribution and patent thickets

Patent portfolios remain small and thinly distributed among many entities: 66% of applicants own fewer than five patent applications, and 32% have one patent application (**Fig. 3b**). IP dominance over iPSC technologies is established by relatively small holdings of six to more than 21 filings in a portfolio (**Fig. 3b**). The total number of patents owned may be higher than shown, because an assignee may hold several patents worldwide for any single invention. Here, we restricted analysis to the number of inventions to determine an entity's impact as well as portfolio diversity.

The ten leading assignees and inventors at leading institutions (**Fig. 3c**) reveal a significant overall international contribution to the field, indicating a global dispersion of basic iPSC technologies.

The growing disparity between granted and pending applications further clouds the certainty of what parties may validly claim (and license) which technologies. Regulatory and legal challenges have contributed to an increased delay in examination, particularly before the European Patent Office, although granted patents are still subject to challenge. Only 11% of patents are issued, and an overwhelming 89% of applications await examination (**Fig. 4**).

This distribution pattern is typical of an emerging technology. However, thin patent distribution among industry also warrants concern for patent-thicket formation. Strong competition by many actors in the field can fuel developments, but it also indicates that the task of coordinating access to interrelated enabling technologies might require an onerous and complex licensing scheme.

Despite the public sector's dominance, a substantial number of smaller biotech companies occupy the other end of the filing spectrum. Many of these have filed only one iPSC-related patent. The 34% contribution from the private sector therefore constitutes

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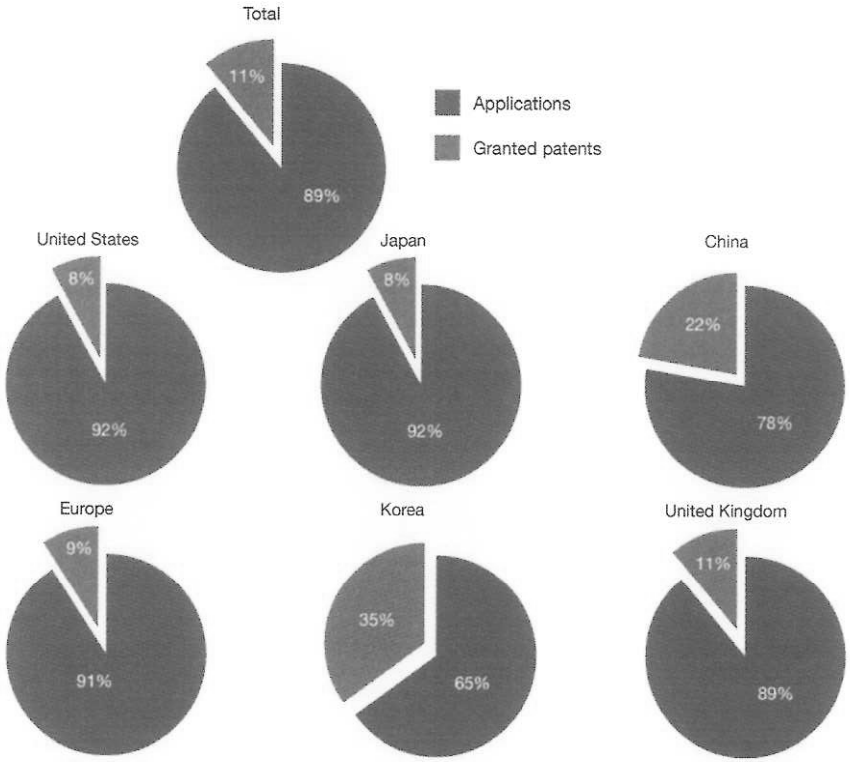

Figure 4 The percentage of patents granted globally is low and varies between countries. Only 11% of all filed iPSC-related patents have been granted, leaving 89% pending examination, adding to the uncertainty of who will hold rights in what technologies. The ratio of iPSC granted patents to pending applications for each of the leading five patenting nations and the EU (through its regional patent application process) by priority country is shown.

a large number of companies holding a low number of patents (**Fig. 3a**). Further in-depth analysis of company profiles and collaborations would probably prove to be of interest.

This analysis does not reflect the licensing of portfolios to 'exploitation companies' that privately manage the licensing arrangements for a range of patent holders. By way of example, iPS Academia Japan (iPS AJ) is a subsidiary of Kyoto University that is privately funded and has widely sublicensed iPSC patent portfolios from several universities and research institutions in Japan and beyond, including Axiogenesis AG of Cologne, Germany, and Auckland UniServices Ltd. of New Zealand. Its total licensed patent portfolio includes an estimated 74 families (an estimated 280 applications with 70 patents granted worldwide). iPS AJ manages IP for iPSC-related technologies, cellular products, drug discovery and cell therapy studies. All licenses are nonexclusive; those to universities are on a royalty free basis, and those to industry are royalty bearing. It also actively fosters international alliances and collaborative R&D for therapeutic benefit.

In this way, rather than relying on stretched technology transfer offices that may lack the expertise, private IP collectives could compete to attract portfolio management, consolidate portfolio holdings under one roof and improve licensing transparency. Another clear solution to negotiating a fragmented landscape is to 'bundle' related rights to platform technologies through cross-licensing schemes. These cross-licensed rights are then available for license as a 'package' by a single provider. The management and expertise required for such patent bundling may still best be handled by a company or clearing house, however.

The reasons for patenting an array of methods for the same general technology, such as upstream iPSC production, are multifactorial and do not always indicate a thicket. Inventive steps sometimes address different processes, stages or mechanisms of action that achieve the same function. Alternatively, many patents may seem to focus on the same specific technology in part because working with multiple cell types across different species presents unique challenges. The validity of independent claims to the same iPSC technologies is nonetheless becoming increasingly murky. A splintered approach to developing platform technologies is currently in progress and reflected by the rapidly increasing entanglement of IP among a web of assignees. Although the conditions for a patent thicket exist within the iPSC innovation ecosystem, there are a number of reasons why escalating numbers of dispersed patents may not signify the erection of an anti-commons obstacle.

Next-generation technology

The first methods of generating iPSCs involved retroviral delivery of reprogramming factors through random integration and were therefore deemed unsafe for therapeutic application. Recent patents claim substantially different methods of and materials for delivering reprogramming factors. For example, small-molecule reprogramming, as recently described in mouse cells[16], represents a breakthrough technology that may be unaffected by any patent thicket around reprogramming technologies[17]. Unless held to be an obvious progression from previous knowledge, the technology described in these later patents should be able to operate freely with respect to the same technology—production of iPSCs from somatic cells.

Table 3 Assignees with the most fundamental iPSC patents by forward-citation number

Assignee	Number of citations for most cited patent	Number of patents with >5 forward citations
Kyoto University	104	9
University of California	9	2
General Hospital Corp.	20	2
Harvard College	20	3
Whitehead Institute of Biomedical Research	18	5
Wisconsin Alumni Research Foundation	37	4
National Institute of Advanced Industrial Science and Technology	3	0
Cellular Dynamics International	12	3
Guangzhou Institutes of Biomedicine and Health	2	0
Advanced Cell Technology	15	5

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How the field will develop, and whether next-generation technologies must license extensive portfolios or will avoid infringement of prior patents, remains to be seen. As discussed, the patent diaspora may merge naturally through the cross-licensing of readily available commercially bundled technologies. As therapies or products near market, industry-led mergers and acquisitions or strategic partnerships may also develop a coherent IP infrastructure. Consolidation of the IP landscape, through market trends and industry growth, for better-resourced innovation has yet to take shape. The possibilities suggest that concerns are premature and the iPSC landscape may merely reflect a normal early growth cycle within a dynamic industry.

However, practices can be implemented to foster the incentives the patent system offers while protecting translation from patent mismanagement. Improved transparency through the creation of a centralized IP registry that would track current nonconfidential licensing practices would better inform any freedom-to-operate concerns[2].

The wider context of iPSC technologies

The validity and quality of individual claims asserted by patents is not assessed here. Even the most fundamental iPSC patents granted, first in 2008 by Yamanaka in Japan and then in 2010 to Kazuhiro Sakurada in the United Kingdom, have not escaped challenges to validity by patents held by Rudolf Jaenisch[18,19], which significantly predate them. Nonetheless, the patent landscape cannot be understood in isolation from its greater legal, scientific and regulatory context, in which unique challenges exist for the cell therapy industry as a whole. An appreciation of these issues is vital to the understanding of the complexity of claiming proprietary rights in living biomaterials from donors.

A number of recent judicial decisions in the United States and Europe potentially limit the scope of IP rights claimed for stem cells, but iPSC-related inventions remain actively patent eligible. Notably, however, the EU awaits express judicial confirmation this year that iPSCs do not fall within its broad interpretation of 'human embryo' by inducing germ and other cells into an embryonic-like state[20].

The US Supreme Court decision in *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.* invalidated patents on isolated DNA sequences, causing concern that patents claiming ownership of a donor's isolated stem cells may be refused on similar 'product of nature' grounds. A challenge to the broad ESC patents held by the Wisconsin Alumni Research Foundation was then reinvigorated in the United States[21]. iPSCs are less susceptible to these patentability concerns. Although more recent methods do not rely on genetic manipulation, complex steps chemically manipulate the cells so that they function in a manner that does not occur in nature. Thus, more akin to recombinant DNA, iPSCs are likely to be patentable as both process and composition-of-matter (cell) claims; unless the latter is deemed legally excluded subject matter. Likewise, because iPSCs are not sourced from human embryos, they present fewer ethical challenges. The controversy surrounding human ESCs has confused and cast aspersions on iPSC patentability. Greater legal clarity, beyond Europe[18], is required to overcome misperceptions.

IP barriers and solutions

IP support currently available is likely to be insufficient for the large number of small biotech companies, for which the main issue may be initial stacked licensing fees. Typically, these smaller companies with undeveloped IP portfolios will not have the resources for big pharma–level corporate licensing schemes or litigation challenges from biotech goliaths. It is, however, anticipated that these issues are temporary until more iPSC technologies are ready for commercialization. As a field matures, industry partnerships and buyouts typically consolidate IP and provide necessary resources.

Most collaborative efforts have addressed 'open science' sharing of research materials and data but have neglected to address a need for better transparency in licensing practices. Although it is unlikely that patent holders will altruistically donate patents to a true open-source licensing collective, other commercially reasonable alternatives exist to foster the iPSC business community. Transparent commercial licensing practices could be established through the creation of online regional registries or databases, a global IP exchange or, more comprehensively, informal 'clearinghouses' for holders of stem cell–related patent to register ownership and its nonconfidential trading activity[2,3]. The clearinghouse model has been implemented in the public sector for agricultural biotechnology[2]. New licensing models such as the 'Easy Access IP' initiative (http://www.easyaccessip.org.uk/) may be suitable for smaller biotech collaboration with universities[22,23]. Other innovative life science platforms also exist for easy adaption to create an IP registry and exchange market (for example, http://www.bioinnovit.com/).

As the wider IP life-sciences landscape shifts to accommodate genomics and regenerative medicine, other forms of IP are surfacing as alternative sources of commercial value beyond patents. Trade secrets and access to corporate biobanks may become the IP concerns for the future of iPSC innovation and public health.

The lengthy regulatory path to market for cell therapies may cause patents to expire before they can be commercially exploited. Trade secrets prevent the sharing of knowledge but circumvent patent expiry and uncertainty issues. Consequently, trade secrets on improved techniques and technical know-how may become the more viable alternative and are appearing as an IP instrument in current industry practice. Cellular Dynamics International, for example, is a leading assignee of iPSC technology and supplies iPSC lines. The company has adopted trade secrets as a vital part of its IP portfolio[24].

Conclusions

Unlike human embryonic stem cells, the pivotal impending legal concern for iPSC technology is not patentability. Instead, it is the potential formation of a patent thicket and mismanaged licensing practices in a field that has begun to privatize at an early preclinical phase. The likelihood of these potential challenges occurring is uncertain. Innovative IP licensing solutions, industry growth cycles and the promise of next-generation breakthroughs suggest that such issues should resolve themselves; however, this *laissez-faire* approach may come at too high a risk for the industry and for global health.

Undeniably, the requisite conditions for patent-thicket formation exist. The complex landscape lends credibility to concerns that it is becoming increasingly difficult to navigate and negotiate access to core technologies from dispersed patent holders. This is exacerbated with uncertain validity of overlapping claims by often still-pending patents. As the technology matures, this should be less of an issue.

A pervasive multisector and multinational collaborative culture has already begun within the iPSC community[25]. The damaging IP barriers that potentially loom in the near future could be avoided if stakeholders could equally embrace collaboration (beyond biobanks and data sharing) around IP. A collaborative approach to innovation could be achieved through well-managed IP-exploitation companies or through informal pooling of interrelated patents for certain core technologies through a

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clearinghouse. These actions would go far to remove the perceived threat of IP barriers and better serve public health.

Encouraging low licensing fees cultivates mutually beneficial trading partners. Government and not-for-profit institutions are well positioned to lead the way for iPSC technologies in discouraging obstructive practices. This should include terms and conditions, such as for funding or material transfer agreements, which prohibit or create disincentives for exclusive licensing, trade secrets and unreasonable access fees for biobanks. The implications of current licensing practices are only now beginning to surface. Negotiating cumulative licensing schemes from splintered ownership will become increasingly difficult without collaborative efforts to consolidate and ensure an affordable, transparent approach to innovation.

ACKNOWLEDGMENTS

The authors thank B. Larner, F. Wattler and J. Evans (Thomson Reuters) for their invaluable assistance; A. Carr (University of Oxford) and J. Karp (Harvard University and Brigham and Women's Hospital) for their invaluable support and insights; and R. Barker (the Centre for the Advancement of Sustainable Medical Innovation (CASMI)) and M. Morys (CASMI) for their support of the CASMI Translational Stem Cell Consortium. The authors wish to express sincere thanks to the following organizations that have contributed to the consortium as funding and events partners: Centre for the Commercialization of Regenerative Medicine; Celgene Cellular Therapeutics; Cell Therapy Catapult; CIRM; Eisai; GE Healthcare; Lonza; SENS Research Foundation; TAP Biosystems (now Sartorius Stedim); MEDIPOST Co., Ltd.; MEDIPOST America Inc.; the New York Stem Cell Foundation and the US National Institutes of Health Center for Regenerative Medicine. Additionally, CASMI is a past recipient of funding from the UK Technology Strategy Board to support an investigation into cell therapy regulation. The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.B. is subject to the CFA Institute's codes, standards and guidelines and as such, must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available at http://www.nature.com/doifinder/10.1038/nbt.2975.

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Supplemental Information

1. Patent Search Methodology

Thomson Innovation and Thomson Data Analyzer software were utilized to perform patent data mining. The search includes both granted patents and published patent applications. Keyword searches were performed of a patent's title, abstract and claims sections across a complete global dataset of 50 patent authorities. All searches were performed for the time period of September 1, 2006 – December 27, 2013. (Supp. Table 2) The applicant and inventor data was cleaned to remove duplicate entries arising from spelling errors, initialisation, international variation (Ltd, Pty, GmbH etc) or equivalence (Ltd, Limited, etc).

A characterization of the datasets would be that the initial dataset is the most inclusive of the wider range of possible iPSC patent technologies, including all generation, cell culturing, miscellaneous patents, a large sampling of differentiation patents and some over-inclusion of ESC-related patents due to overlap in terminology. The first cleaned dataset comprised 1,015 applications and granted patents. It represents the compromise position which was later further cleaned to begin to hone in on those patents related to iPSC-production technologies. Harvested documents may include invalid, discontinued or denied applications. At random manual review of harvested documents was performed to further clean subsets of denied or irrelevant patents.

Filtering Search (Derwent Manual Code)

All searches were filtered to limit results to two general Derwent manual code taxonomies within which cell technologies occur: D16 (concerned with the fermentation industry including microbiology, antibody production, and cell & tissue culture and genetic engineering) and B04 (concerned with biotechnology for natural products and polymers including testing of microorganisms for pathogenicity, testing of chemicals for mutagenicity or human toxicity and fermentative production of DNA or RNA) (Derwent class codes: http://images.webofknowledge.com/WOK48B5/help/DII/hcodes_classes.html#class_d, accessed 12/29/2013). This filtration was performed to prevent keyword searches including results from unrelated fields such as electrical engineering or botany.

Keyword search stream

A number of keyword search streams were performed and at least the first 100 documents were manually reviewed to compare relevancy. (Supp. Table. 1) Resulting datasets were compared when a search yielded less documents than the previous search by reviewing at least the first 100-300 documents omitted to ensure relevant patents were not removed.

Cleaning the dataset

The documents yielded by the search terms were further cleaned by sub-searching terms and through further manual review of those sub-search results to remove unrelated or denied patents to compile a cleaner dataset, erring on the side of over-inclusive (Supp. Table 1)

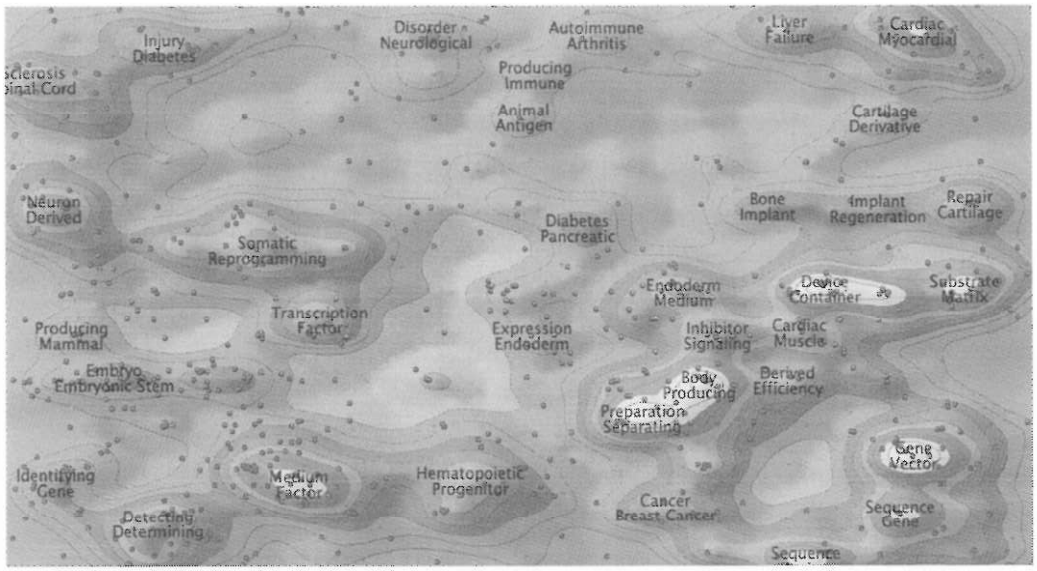
Technology areas within the PSC landscape

Patents within the broad PSC landscape in Supplemental Figure 1 were sub-searched to discern the numbers of patents related to different technology focus areas (Supplemental Table 1). These results are overly inclusive and may capture some unrelated patents. In particular, the estimation of the number of differentiation patents versus cell-culturing techniques is difficult to discern based on keyword sub-searches because of shared common terminology.

Nonetheless, the figures provide an approximation. The number of total PSC granted and pending patent applications breakdown by: technology category (generation, differentiation, cell-culturing,

other), cell source (fibroblast, adipose-derived, cord blood) and cell product (cardiac, neural, hematopoietic, ophthalmic). The different cell types are a good indication of the most active therapeutic areas of medicine in which research was conducted. The leading areas for PSC research broadly divide among the following: cardiovascular, ophthalmic, cancer and neurological which can be seen best by the peaks on the patent map at Supplemental Figure 1.

2. Figures



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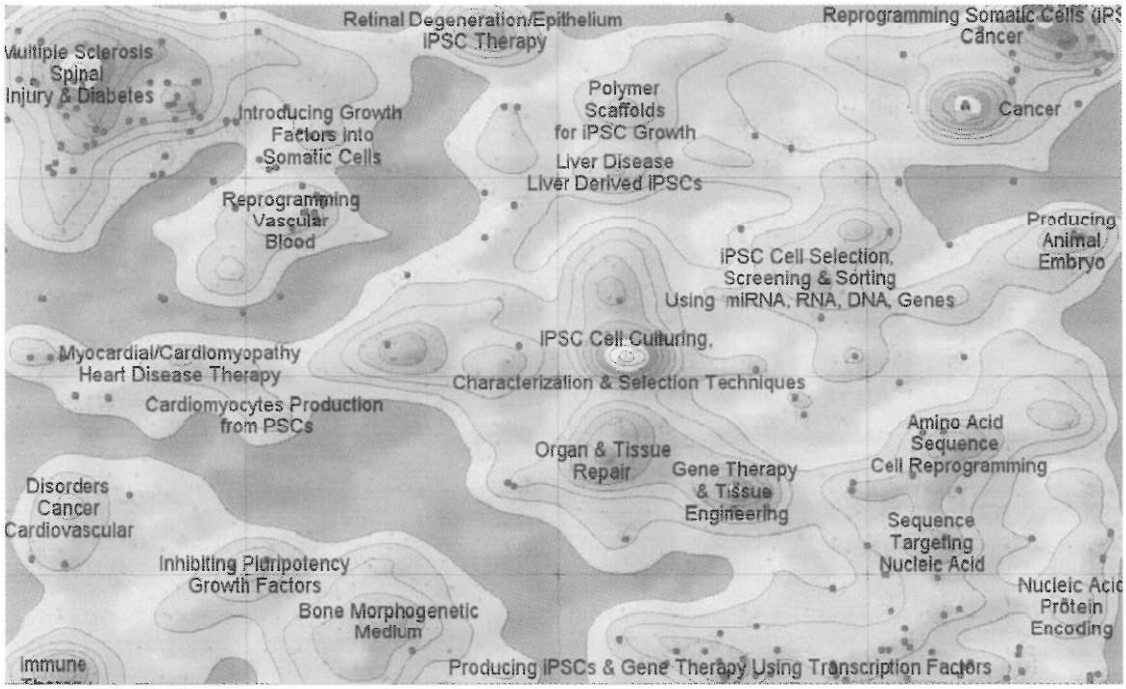
Supplemental Figure 1 Broader Pluripotent Stem Cell Patent Map
The map is a visual representation of the broader pluripotent cell landscape including patents relating to ESCs and iPSCs. It serves as a macroscopic snapshot that places the more specific iPSC field within its wider context. These PSC-related patents cite pluripotency as an aspect of the patent whether ancillary or otherwise. The dots represent patents and are clustered together according to similar terminology in the title and abstract. The more similar the patents' terminology then the more elevated the cluster. White snow-capped peaks represent the areas of highest patent density. The landscape is comprised of 2,797 patented inventions with 9,189 documents searched from September 2006 through 2013 inclusive. This number is based on a keyword search of a patent's title, abstract and claim sections for variations of the word "pluripotent" (and filtered to retrieve results only in the related field of mammalian cells). For illustrative purposes the red dots are 2,057 patents that contain the phrase "potency determining factor" in the title or abstract.



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Supplemental Figure 2 iPSC Patent map displaying 'reprogramming' patents in red
The broad iPSC-related technology dataset is comprised of 1,388 iPSC-related patented inventions (families), combining published patent applications and granted patents from September 2006 - December 27, 2013. Here, the map displays the spread of patents related to cellular 'reprogramming' technologies with red discs, showing a wide distribution across the map and concentrating in the following areas: producing animal embryos, liver disease, retinal epithelium cells, cardiomyocyte production and antineoplastic research. The different therapeutic indications named in several peaks, from liver disease to spinal cord injury, also depict a broad range of research using differentiation techniques for specialized cell and tissue types.

3. Tables

Supplemental Table 1 Keyword Search Streams

PSC dataset	pluripoten*
Broad Initial iPSC dataset	CTB=((((induc* ADJ pluripotent ADJ stem ADJ cell*) or (induc* NEAR3 pluripoten*) or ((reprogram* or re-program* or dedifferentiat* or de-differentiat*) NEAR2 (somatic or cell*))) AND (pluripoten* NEAR8 (dedifferentiat* OR retro-differentiat* or retrodifferentiat* OR de-differentiat* OR induc* OR *2program* OR generat*)))) AND DC=(D16 or b04) AND DP>=(20060901) AND DP<=(20131231);

Scientific Literature Search	(induced ADJ pluripotent ADJ stem ADJ cell*1) OR (INDUC* NEAR5 PLURIPOTEN*)) and (produc* or generat* or reprogram* or program*)) NOT SSC=("PHYSICS" OR "BEETLE" or "COMPUTER SCIENCE" OR "ENGINEERING") *844 additional publications if include "iPS" which were manually reviewed and 62 relevant publications selected and merged into final workfile of 3312 documents; 9 publications were added from the following search (with a total 3992 documents): (induced ADJ pluripotent ADJ stem ADJ cell*1) OR IPS) and (produc* or generat* or reprogram* or program*)) NOT SSC=("PHYSICS" OR "BEETLE" or "COMPUTER SCIENCE" OR "ENGINEERING")
Exemplar Search Stream reviewed, compared and eliminated	(CTB=(((((induced ADJ pluripotent ADJ stem ADJ cell*) OR (iPS*2 NOT (ipsa OR ipsen OR IPSS OR Ipse OR IPSP OR insect* OR pest*1 OR computer OR islet ADJ producing OR ipsi OR IPSO OR sexual OR plant OR (interrogation ADJ position*) OR film OR saccharide OR optical OR sensor OR (idiopathic ADJ parkinson* ADJ syndrome) OR (IPS ADJ receptor) OR (immun* ADJ privilege* ADJ site))) OR (iPS ADJ cell*)) NEAR10 (((pluripotent ADJ stem) OR iPS) ADJ cell*)) AND (*5different* OR production OR producing OR produce* OR obtain* OR induc* OR *2program* OR derive* OR generat* OR engineer*))) AND DP>=(20030101)) AND (DC=(B04 or D16));
Other keywords for iPSC creation searched (results compared to ensure relevant patents were not excluded)	induc* Near8 pluripoten* (4136 total documents) vs. induc* AND pluripoten* (6080 documents)
	-induced type stem cell (iPS cell)
	-production OR producing OR produce Near5 pluripoten*
	-artificial Near6 stem adj cell or artificial Near8 stem adj cell or artificial Near3 pluripoten*
	-human parthenogenetic stem cell
	-induc* pluripotency
	-induc* Near3 stem cell
	-deriv*/derivation Near6 pluripoten*
	-*5differentiat* Near6 pluripoten* (ie retro-differentiate)

Supplemental Table 2 Dataset Summary

	Initial Dataset	Cleaned Dataset 1	Cleaned Dataset 2
Number of Patent Families (ie Total Number of Patented Inventions):	1,905	1015	901
Number of Patent Publications	6,335	3,323	–
Number of Granted Patents	444	131	115

Peak Patent Publication Year	**2012**	**2012 [256 inventions]**	**2012 [228 inventions]**
Search Date Range of Published Patents (Incl.)	**(Sept.) 2006 - 2013 (Dec.)**		
Top Inventor Country	**US**		
Top Patent Issuing Country:	**US**		
Top Patent Assignee:	**University of Kyoto**		
Date of report creation	**27-Dec-13**		

Supplemental Table 3: Keyword Clustering of PSC Patents

TERM	NUMBER OF PATENTED INVENTIONS CONTAINING TERM FROM TOTAL (2,841 FAMILIES OF 9,504 PATENTS)
differentiat*, differentiat*	1,300-1,400*
cell culturing	820
iPSC generation	650*
scaffold, matrix, apparatus/device	40-60
cord blood cell*	40
adipose-derived or adipose	200
cardiomyocyte	250
cardiomyocyte*, cardiac, coronary	1,313
Fibroblast or dermal fibroblast	850
hematopoietic	470
neural or neuron*	750

*The estimate is based on a keyword subsearch and manual review of the first 150 documents yielded. The estimated generation of iPSCs includes culturing techniques, growth factors and other essential steps. Estimates do not account for invalid, discontinued or denied applications.

Please cite this article in press as: Silva et al., Generating iPSCs: Translating Cell Reprogramming Science into Scalable and Robust Biomanufacturing Strategies, Cell Stem Cell (2015), http://dx.doi.org/10.1016/j.stem.2014.12.013

Cell Stem Cell
Forum

Generating iPSCs: Translating Cell Reprogramming Science into Scalable and Robust Biomanufacturing Strategies

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http://dx.doi.org/10.1016/j.stem.2014.12.013

Induced pluripotent stem cells (iPSCs) have the potential to transform drug discovery and healthcare in the 21st century. However, successful commercialization will require standardized manufacturing platforms. Here we highlight the need to define standardized practices for iPSC generation and processing and discuss current challenges to the robust manufacture of iPSC products.

Introduction

Induced pluripotent stem cells (iPSCs) are powerful tools for research and drug discovery and may provide regenerative therapies for diseases that conventional medicine cannot cure presently. While methods for generating iPSCs are continually evolving in the laboratory, and there is substantial growth in patent activity in the global iPSC landscape (Roberts et al., 2014), significant hurdles remain for successful commercial translation, such as global harmonization of the regulatory landscape and attitudes to clinical adoption. A fundamental requirement for successful commercialization is the ability to translate iPSC science to the biomanufacturing community to create robust and consistent high-quality iPSC products at desired quantities that display acceptable levels of comparability across multiple lines.

As "living" products, cells pose a range of biomanufacturing challenges. Variability in starting materials, process reagents, microenvironmental fluctuations, and stochastic events within a cell population, such as spontaneous cell cycle arrest, create inconsistencies that are challenging to control in manufacturing processes. The challenges for creating iPSC-based drug testing platforms or therapeutics are particularly significant because there are multiple methodologies for reprogramming cells to create iPSCs. From a biomanufacturing perspective this creates significant variability in input materials along with process variability that could translate to the iPSC product that is generated. Subsequent processing to derive differentiated target cell types that are comparable would consequently be affected.

The need for stratified therapies is driven by the heterogeneous nature of patients, not just in terms of disease status but also genetic background. With global efforts to generate large repositories of iPSCs, effort is required to ensure that the critical quality attributes of the resulting iPSCs meet consistent high quality. If different reprograming methodologies are used for producing iPSCs across different repositories (and within a single

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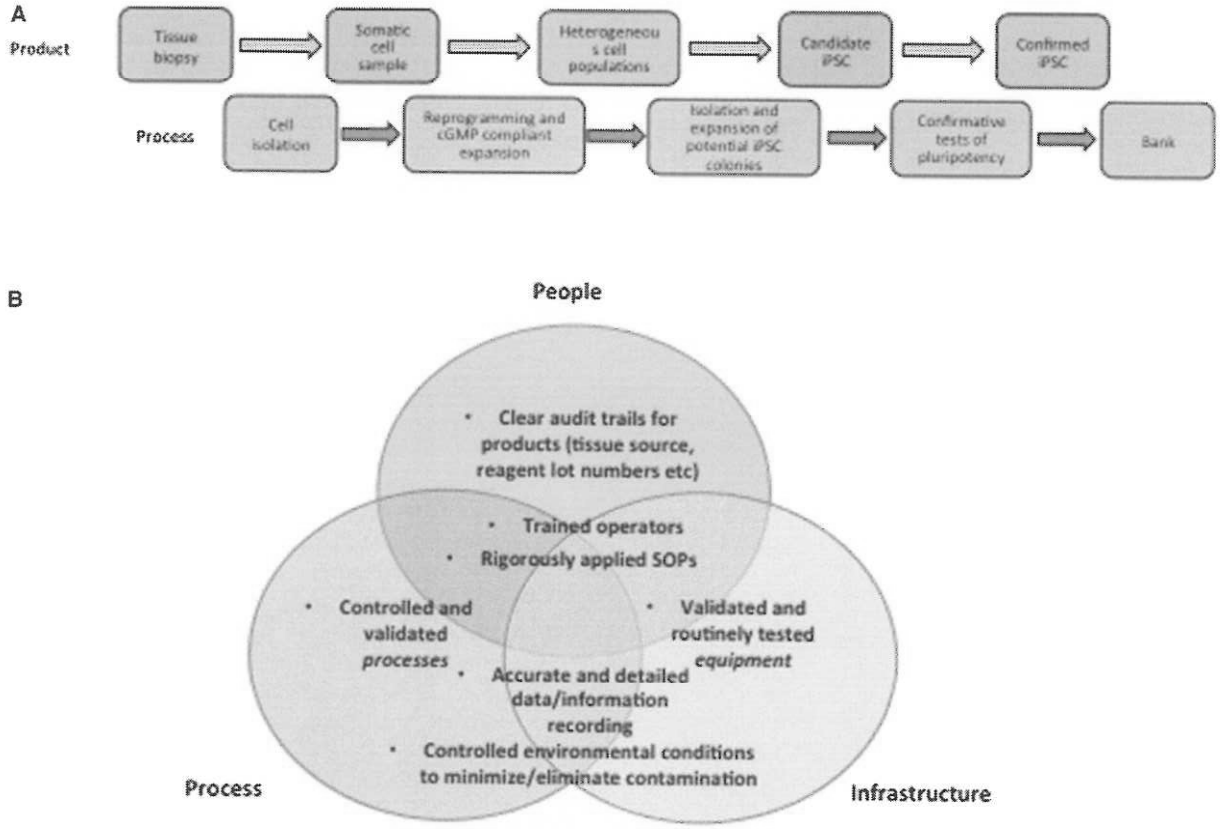

Q1 Figure 1. ■■■

High level process map (A) outlining the transition of cell samples from raw input material to final product. In the case of the iPSC product, it is then itself an input material for differentiation processes. The process is then presented below to highlight the unit operations required to deliver the downstream product. The relationship between operators, process, and infrastructure (B) is critical in the development of robust, standardized manufacturing strategies that reproducibility yield material of consistent quality.

repository), then comparing cell products from different sources may be challenging. Such discrepancies are problematic because different cell product characteristics arising from multiple genetic backgrounds need to be understood from a stratified medicine perspective independent of any product variation arising from technical input variability. Therefore, a robust and standardized methodology will reduce the impact of technical variability on the iPSC product. A solid understanding of the manufacturing processes and the relationship between key factors and their impact on the cellular product is thus needed (Figure 1).

Compared to protocols established in individual research groups, stricter standards are needed to develop and validate manufacturing processes and the associated iPSC banks (Turner et al., 2013). In particular, there remains uncertainty around the manufacturing and regulatory challenges concerning human leukocyte antigen-matched (HLA) master cell banks, in addition to regulatory and social uncertainty around this new class of drug discovery platform and therapeutic. With many different methods available to generate iPSCs, it is increasingly important to define optimal manufacturing platforms to meet the regulatory and quality assurance demands of the biomanufacturing industry while also minimizing cost of goods. To this end, we highlight here various aspects of iPSC generation and processing that must be considered for developing standardized iPSC products.

Current Technologies for iPSC Generation

Significant global effort has been made to develop methods to generate iPSCs more rapidly, safely, and efficiently. Increasingly, such scientific advances are yielding commercial products and services; notably, Life Technologies (now acquired by Thermo Fisher) has licensed assay technologies for efficient generation (CytoTune-iPS 2.0) and characterization/validation (TaqMan hPSC Scorecard) of iPSCs.

Today, multiple methods can be used to generate iPSCs (Figures 2 and S1) and key publications of factors delivered are reviewed elsewhere (Theunissen and Jaenisch, 2014). Creating iPSCs that are fit for purpose, either drug discovery or, more challengingly, therapeutics, will require a wide understanding of the biological characteristics and process conditions. Critical considerations to meet cGMP guidelines include cell line derivation, potential contaminants and adventitious agents, desired features and how

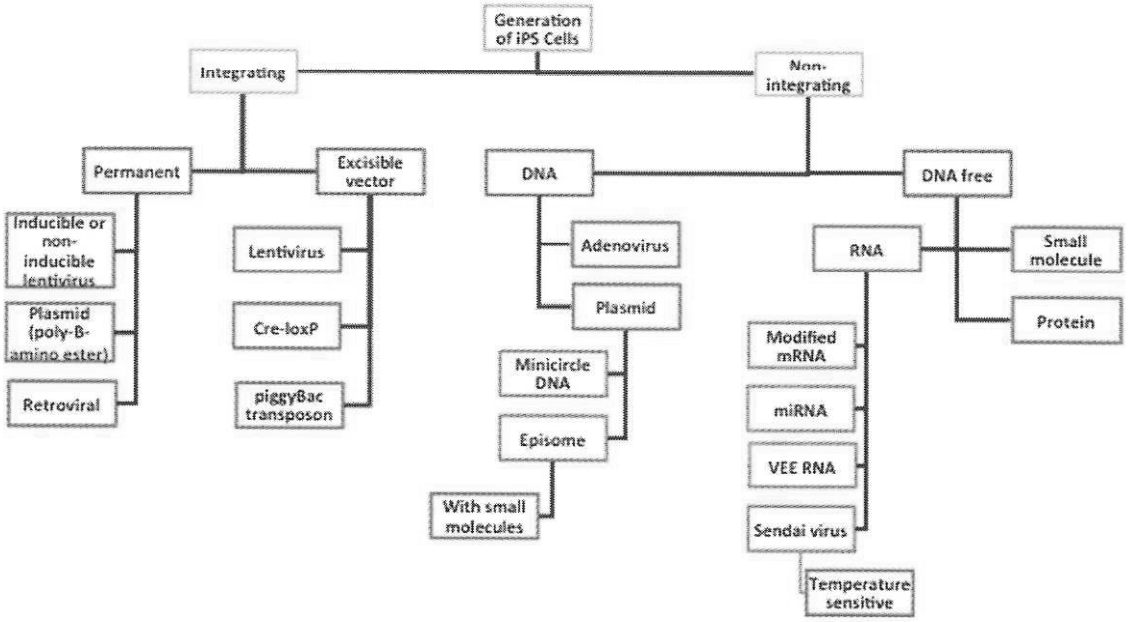

Figure 2. Delivery Methods for Molecular Reprogramming of Cells in the Generation of iPSCs
Numerous candidate technologies have potential applications in the manufacturing pathway to create iPSCs.

these features can be assayed, and reliability/reproducibility in the generation of a safe and efficacious end-product. The first major consideration for generating iPSCs is, however, the choice of primary cell source for reprogramming.

Cell Material

Because primary cell "input" material is typically heterogeneous, each single reprogrammed "output" cell might differ. Reducing or eliminating heterogeneity in the input material by pre-selecting a particular cell subset (e.g., selecting mesenchymal cells on the basis of a panel of surface epitopes) could create a more robust product. Although the field has not yet settled on the optimum starting cell for iPSC products, convincing arguments have been made for using multipotent stem cells, particularly those from cord blood, which are highly unlikely to have accumulated epigenetic changes, point mutations, or chromosomal damage typical of older cells (Jacoby et al., 2012). For the generation of disease-specific cell lines for research purposes, however, blood may be a better candidate due to broader patient accessibility.

Aside from biological considerations, the choice of source material will be influenced to a large degree by the ease with which it can be obtained from the donor with informed consent for tissue/cell removal, reprogramming, expansion, and storage. The legal requirements to cover ethical and regulatory standards must be met before source tissue/cells can be obtained—including informed consent based on the understanding of the full scope of iPSC generation including commercial opportunities.

Cell Reprograming

Advances in reprograming methods now provide multiple vectors for gene delivery, techniques that avoid the use of oncogenic transgenes, and even DNA-free methods (Figures 2 and S1).

Fundamental for manufacturing cell therapies is product stability, which in part underpins clinical safety. While phenotypic stability will be challenging to gauge when initially generating iPSC banks, any measurable characteristics of iPSCs that indicate genomic stability and phenotypic fluctuations would greatly facilitate future development of iPSC-derived products. This is where a clear distinction is drawn between integrating vectors and non-integrating vectors and DNA-free methods. Unlike integrating vectors, non-integrating vectors achieve reprogramming without inserting material into the host genome and thus avoid the risk of insertional mutagenesis.

Non-integrating episomes can achieve reprogramming within 30 days, and methodologic improvements that bypass the need for serial transfection (Yu et al., 2011) have created one of the simplest processes with minimal manual processing that could be translated to automated platforms with ease. Minicircle vectors are episomes that lack plasmid backbones, making them potentially advantageous in terms of safety. However, overall reprogramming efficiency of episomal methods is low compared with other non-integrating methods such as Sendai virus or mRNA transfection.

The Sendai virus is also popular as a non-integrating reprograming vector because the method is simple and, when temperature-sensitive Sendai viruses such as that already used for c-*myc* (Ban et al., 2011) are adopted, removal of Sendai RNA from iPSCs by a temperature shift will be possible. Also based on the Sendai virus, the CytoTune 2.0 kit (Life Technologies) is available off-the-shelf with validated protocols for generating stable transgene-free iPSCs with little cytotoxicity and much more rapid virus elimination than that enabled by previous kits. Such methods are not only very

Please cite this article in press as: Silva et al., Generating iPSCs: Translating Cell Reprogramming Science into Scalable and Robust Biomanufacturing Strategies, Cell Stem Cell (2015), http://dx.doi.org/10.1016/j.stem.2014.12.013

amenable to process development but would, if adopted as part of cGMP protocols, also satisfy regulatory requirements for therapeutics, where full removal of viral material will be desirable or necessary. The cost, however, remains high.

Direct delivery of mRNA or microRNA (miRNA), which eliminates the use of DNA and viruses, has been developed as a safer reprogramming strategy. Exogenous mRNA can be modified to dampen cytotoxicity and antiviral defense mechanisms in the cell (Warren et al., 2010). This method can achieve one of the highest reprogramming efficiencies among non-integrative techniques. Current methodologies require daily transfection but may be easily automated, making it an exciting candidate for routine biomanufacture. Yet, work remains in confirming the reproducibility and mitigating commercial risks before this methodology can serve as a viable tool for manufacturing iPSCs.

Total removal of nucleic acids for reprograming by using peptide-based delivery of transcription factors or small molecules instead could utilize established biomanufacturing pathways to generate the reprograming material. From a bioprocessing perspective, small molecules are easier to define and control for platform standardization and regulatory approval.

Process Optimization for Reprograming iPSCs

In any stem cell manufacturing endeavor, cost of reagents and media typically represents the most substantial fraction of total production costs. Furthermore, bioprocessing operations traditionally rely on iteratively optimizing each stage, which adds significant cost and off-process analysis requirements. Process optimization using small-scale, high-throughput testing devices that require microliter quantities of culture media yet allow standardized comparative assessment of cell product quality would greatly contribute toward a commercially viable process. Although still in the early stages of development, such devices can provide real-time or rapid readouts of cell product attributes, using minimal cell numbers and media in microbioreactor arrays. These microdevices can be multiplexed, permitting multiple bioprocessing parameters to be assessed in factorial or combinatorial manners, and are being used to address gaps in our knowledge of each process step, such as the impact of media exchange and shear stress, media composition and timing of factor provision, and paracrine/autocrine signaling on cellular behaviors and quality (Titmarsh et al., 2013). Due to their flexibility and portability, such microdevices have utility for pre-screening multiple cell inputs and reprogramming reagents for the optimal reprogramming regime that delivers the most consistent quality product in terms of transfection efficiency and yield, which can subsequently be mathematically modeled as part of Quality by Design engineering approaches to optimize larger scale operations for subsequent clinical-scale iPSC expansion. Finally, they would facilitate standardized product testing of iPSCs from diverse genetic backgrounds and could provide a platform to perform comparability studies with genetically diverse cells versus gene-edited single pluripotent cell lines that are not confounded by diverse genetic backgrounds.

iPSC Selection and Validation

The cell reprogramming process is not 100% efficient and consequently a heterogeneous mixture of iPSCs, partially reprogrammed cells, and partially differentiated cells is produced. Therefore, iPSCs must be isolated from the mixed population for further use. Many cell-sorting methods, particularly those depending on a single parameter, such as morphology-based colony picking, may not discern between partially reprogrammed cells and iPSCs. Ideally, an industrial-scale selection process would have the capability to be replicated robustly and the capacity to screen thousands of cell lines with very high accuracy.

Selecting colonies based on morphology is an option favored at lab-scale due to the ability of well-trained operators to identify appropriate colonies. It may even be the best method for generating different iPSC lines in parallel, given that large numbers of cell lines need to be generated from multiple primary sources to cover the immunological variation among patients. However, operator bias is difficult to control and manual picking is labor-intensive and, thus, prohibitive at large scales (Meissner et al., 2007). Algorithms for automated colony selection based on morphology could remove operator bias but would require significant validation against the gold standard: the eyes and expertise of a skilled operator.

Incorporation of a reporter or selection tool (e.g., antibiotic selection) to positively select iPSCs is typically considered a more accurate alternative to colony picking. However, adding a reporter/selection tool may introduce additional risk, particularly in cells intended for therapeutic use. Downstream elimination of reporters/selectors, using principles similar to the temperature-sensitive Sendai virus, may lower such risks, albeit with higher process complexity.

The most accurate method for iPSC identification is immunoselection based on cell surface antigens using fluorescence- or magnetic-activated cell sorting. These methods enable multiparametric selection to a very high purity. Removal of the selection antibodies will be important for ensuring that iPSCs are biologically functional for subsequent processing and directed differentiation. Even if clinical-grade antibodies are used, removal of sorting antibodies from the final product may be required, especially in clinical applications, and the additional processing will almost certainly impact cell quality. The application of existing clinical-grade cell sorting (e.g., Miltenyi CliniMACs) offers a very sound platform for selection, purification, and validation of iPSCs and provides automated, closed-system, minimal handling capacity.

True confirmation of pluripotency typically uses an in vivo teratoma assay, regarded as the best validation method for human iPSCs at present. However, this gold standard is an expensive and laborious assay, taking 2–3 months to perform, and it's hardly practical for scale-up or high-throughput adoption. In vitro assays that can conclusively confirm pluripotency would substantially streamline manufacturing of iPSCs. Recent Q-PCR-based methods offer rapid throughput and further analysis of differentiation and are now possible using the standardized *TaqMan* hPSC Scorecard (Life Technologies) by comparing transcripts to a reference standard. In vitro embryoid-body-based assays that assess differentiation toward specific lineages under optimized conditions are also better suited to high-throughput,

with measurement of protein and tissue induction in addition to that of gene transcripts. However, in vitro gene transcription and directed differentiation assays may not be sufficient in the present regulatory environment. Recent developments such as a novel in vitro teratoma assay may offer unique solutions (Whitworth et al., 2014).

Establishing robust standardized assays to adequately characterize iPSCs currently presents one of the biggest obstacles to commercialization due to the quantity and complexity of tests required. The overarching goal of biomanufacturing is to streamline validation processes by reducing the number of assays, improving assay efficiency without compromising safety, or developing standardized assays to improve reproducibility between different manufacturers. As our understanding of iPSCs increases, the possibility to rethink validation procedures will advance, making the creation of production platforms for cell banking more feasible. Critically, we need to define a robust set of criteria to ensure that a consensus standard of quality is achieved for cell therapy and drug discovery applications.

Bottlenecks and Next Steps

Ultimately, the goal of generating iPSCs is the identification and development of novel therapies. Economically sound platforms are necessary to give a high degree of reproducibility for the production of multiple iPSC lines. This would enable the establishment of cell banks with quality-assured, off-the-shelf iPSC products for multiple applications, while covering the immunological diversity of the patient pool. Current progress in this direction is notable, though a substantial change is still required in standards, cell line manufacturing, and validation to support an effective transition from research to generation of clinical-grade iPSCs. For production of universal iPSC banks, process maps and product critical quality attributes must be clearly defined. This remains the main bottleneck in advancing iPSC banking because reprogramming and validation methods are currently varied and consensus is lacking. Outlining appropriate regulator-informed process maps that incorporate defined and controllable process parameters at every possible step will help to shape a biomanufacturing platform that delivers a robust iPSC product of consistent quality. In creating large iPSC banks, fundamental science would benefit substantially from the standardization of reprogramming methods early on so that consistency and reproducibility in the generation of iPSC products can be achieved, both of which are critical for successful commercial translation.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes one figure and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2014.12.013.

ACKNOWLEDGMENTS

I.W. and H.W.K. acknowledge support from the Priority Research Center Program (2009-0093829) of the Korea Research Foundation.

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Author Insights — Exclusive App-only Content

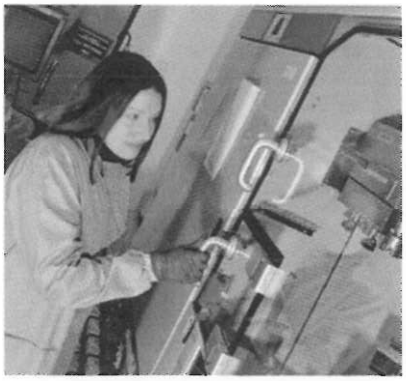
Automation of Cell Therapy Biomanufacturing

Minimizing Regulatory Risks and Maximizing Return on Investment

by David A. Brindley, I.B. Wall, and K.E. Bure

Biomanufacturing automation is an established mission-critical step in the commercialization pathway for conventional therapeutics, including small molecules and monoclonal antibodies (MAbs) (1). The prospect of a potential biologic progressing into late-stage clinical trials without a robust biomanufacturing strategy to support at least pilot-plant scale bioprocessing is simply unthinkable. Conversely, the cell therapy industry (or at least a significant proportion of it) regard this as a trend that is unlikely to be mirrored as the industry develops.

The aim of this piece is to assess the risks and benefits of the automation of cell therapy biomanufacturing by focusing in particular on the feasibility of process automation and its impact on regulatory compliance and return on investment. Interestingly, the authorship — composed of academia and industry — spans the product development pathway. One author will make the case that in some respects it is challenging to translate lab-scale processes into automated large-scale manufacturing strategies and advocate delaying automation and any costs incurred until later in the development cycle. Another — a leading supplier of automated biomanufacturing technologies, with significant experience automating cell therapy bioprocesses — will justify a strong belief that cell therapy process automation is a critical and wholly achievable product development goal, best addressed as early as possible in the translation pathway. Finally, an author positioned at the interface between academic biomedical research and finance will evaluate the prospect of biomanufacturing automation from the viewpoint of potential investors, eager to ensure that value is created and protected as efficiently as possible. It should be an interesting tussle.



TAP Biosystems automation in place at Loughborough University (WWW.LBORO.AC.UK).

Feasibility: Barriers to Cell Therapy Automation

Manual bioprocessing techniques (notably, cell culture) are critically important in terms of skill development for employees in industry and students within academia. Such skills provide a foundation for navigating future automation and operation strategies such as cell characterization studies (2). Further, in addition to capital investment costs, the management of automated biomanufacturing equipment in academic settings can be challenging. For example, access to resources must be shared amongst multiple parties with different work schedules, funding structures, and process materials.

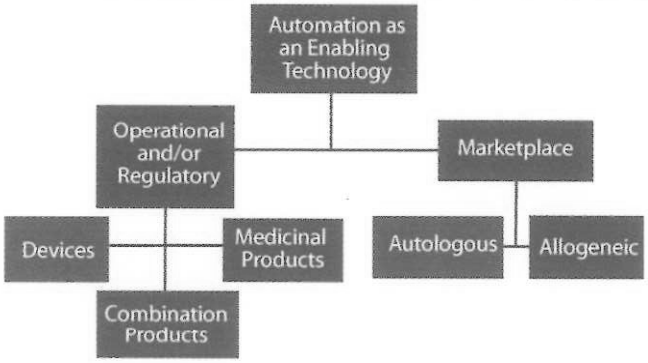
In some situations (e.g., autologous cell therapy production), manufacturing limitations render automation extremely challenging, in part due to inherent interdonor source material variability. For example, populations of bone-marrow–derived mesenchymal stromal cells (BM-MSCs) from different individuals (where the start population of cells comprises a heterogeneous mix of subclones) will age at different rates and have variable replicative lifespans. This is due largely to intrinsic telomere dynamics, difference in donor ages, oxidative stress status, and stochastic events (3, 4). A single defined set of automated process parameters for cell expansion will not discriminate among individual samples. Consequently, products will exhibit different source material characteristics after amplification of the start population.

Further, the start material will exhibit some variability if it is in the form of a tissue biopsy obtained by a

Table 1: Value of automation in other industries

Organization and/or Technology	Issue Addressed	Methods Used to Resolve Through Automation
Model T motorcar, Ford Motor Company (Dearborn, MI, USA)	High cost of goods in automotive manufacture restricting technology adoption	Introduction of world's first mass production line, reducing cost of goods and increasing throughput (28)
Personal electronics, Dell Inc. (Round Rock, TX, USA)	Established industry business model, selling to consumers through retailers, added additional cost to the value chain and inventory costs limited capital efficiency and incurred risks relating to technology obsolescence	Introduced just-in-time (JIT), highly automated manufacturing strategies to reduce inventory costs and focused on sales direct to consumers (29)
Motorcars, Toyota Motor Corporation (Toyota, Aichi, Japan)	Need to achieve consistently superior product quality to increase market share in overseas markets dominated by established large local companies	Automation is at the heart of the acclaimed Toyota Production System (TPS) contributing to reduced product variability and decreased manufacturing downtime (30)

Figure 1: Multidimensional nature of cell therapy biomanufacturing as an enabling technology



clinician. This is a consequence of the physical nature of the tissue being subject to variability between donor sites in terms of accessibility, tissue quality, surgical/sampling accuracy, and the exact quantity of tissue removed (5). Therefore, skilled technicians will isolate and plate cells from tissue biopsies and conduct morphological assessments to evaluate the likely risks and benefits arising from processing a particular patient sample.

Any suitable automated biomanufacturing platform requires significant process flexibility to accommodate unique constraints of individual cell populations, in many respects similar to the flexibility required historically in MAb manufacturing strategies to accommodate variability in product titres and glycosylation profiles (6). For some cell lines that are particularly unamenable to automation, however, there has to be a tipping point at which costly process development is pushed aside in favor of focusing on first-to-market advantages that such highly unique therapies offer.

Adding automation into long-term scale-up plans introduces another significant factor into scientific, technological, financial, and regulatory considerations. The selected automation approach should be viewed as a long-term component of a scale-up strategy that will deliver financial benefits over relatively long time periods. However, any equipment personalisation to accommodate unique product characteristics is likely to impact potential resale values. Further, well-trained operators and efficient scheduling will be required to minimize downtime due to maintenance.

Despite these hurdles, automated bioprocessing holds considerable promise for reproducible manufacturing ensuring comparability across multiple processing sites. This is achieved principally by removing manual tasks that potentially introduce high cellular variability in part due to the exposure of cells to poorly controlled bioprocess forces (5). Short-term investors may advocate more affordable manual processes and accompanying flexible staffing options; but long-term investors — including ultimate acquisition partners such as large pharmaceutical firms — will almost uniformly favor automation and scalable processes.

The adoption of cell therapy biomanufacturing automation will be limited unless product developers are able to convey their benefits and acknowledge any shortcomings. Such communication must be provided in an accessible manner to the research and small and medium-sized enterprise (SME) communities.

Evaluating Automation Success

Evaluating your automation strategy success requires that you assess

- the extent of process automation
- the extent to which automation enables and captures a market

Value of Automation in Other Industries

From personal electronics to high-end jewelry, automation is integral for producing consistently high-quality products that address a market need, at a price the market can afford, and in sufficient volume to satisfy market demand (Table 1). Subsequently, two key metrics can be used to evaluate the success of any such automation strategy ("Evaluating Automation Success" box). One is the extent of any such process automation (on a spectrum from entirely manual to

Figure 2: Particulate levels in a functionally closed robotic processing chamber

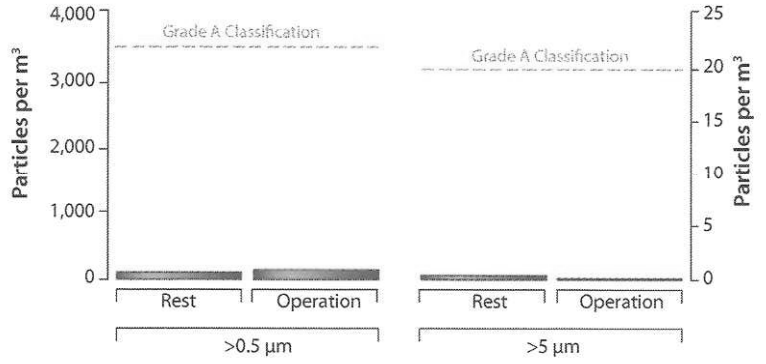
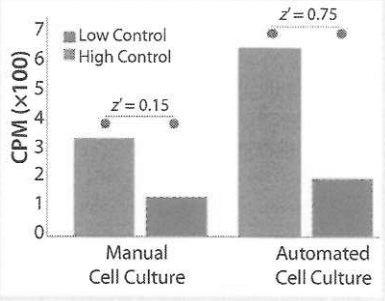


Figure 3: Enhanced assay capability through automated cell culture



fully automated). The other is the extent to which an automation strategy enables a market (to the benefit of the entire subsequent industry) and captures a market (to the benefit of manufacturers and users of such technologies).

Automation as an Enabling Strategy

From a strategic viewpoint, automation is an enabling strategy. It enables the creation of markets and the commercialization of products and services in those markets. However, equally self-evident is that complete automation is not universally appropriate in all scenarios. Financial cost and process complexity are frequently cited as factors that discourage automation, particularly at small scales (7). In truth, however, these are frequently superficial observations. To understand why, consider the process of enablement itself.

The dictionary definition of *enablement* has two aspects — which for the purposes of bioprocessing we can use as a proxy for a factor with two dimensions (Figure 1). Firstly, it means an action or series of actions that makes something possible; for example, making a device or system operational — often within a specified system. Secondly, *enablement* means granting someone or something the authority or means to undertake an action or a series of actions.

Regulatory Compliance Benefits

In satisfying the regulatory aim of safe and efficacious therapies, automation aids in the control of sterility and particulates, error reduction, increased productivity and enhanced comparability (8, 9) ("Automation Benefits" box).

Bioprocessing Automation Benefits

Benefits of automation = improved quality + increased productivity + ease of regulatory compliance

Sterility and Particulates: Cell therapy products cannot undergo late-stage purification or sterilization. Consequently, some manufacturers are understandably concerned about potential particulates that can be introduced during open-culture manipulations (10). For example, particulates could potentially affect the efficacy of a cellular product and/or influence the choice of administration route(s) (11, 12).

Manual handling of high-touch processing steps inevitably introduces fibers, plastic debris, and other exogenous materials into the process from gowning materials, laboratory plasticware, liquid storage bags, imprecise movements, and cleaning regimes (12). Of even greater concern is the possibility of particulate introductions by technicians themselves or surrounding environments, which could potentially compromise products — and consequently, patients' safety.

Robotic handling under aseptic conditions greatly reduces the level of possible particulates and contaminants introduced through manual culturing (13). As Figure 2 shows, the level of particulates in functionally closed robotic processing chambers is approximately 100-fold lower than requirements for a Class A enclosure. Therefore, in addition to reducing particulate burden, robotic handling reduces the likelihood of failed batches due to contamination events from standard operating procedure (SOP) breaches (14).

Error(s): Although a reduction in the likelihood of human errors is a self-evident advantage of process automation, it is especially critical in the manufacture of cellular therapies. The production process includes a large number of process steps and carries potential serious clinical risks arising from cross-batch contamination during autologous product manufacturing (13). In addition, regulatory restrictions surrounding the need for patient confidentiality make manual bioprocessing, in particular record keeping and retention, challenging (15).

Manual record keeping is poorly amenable to incumbent regulations relating electronic drug authentication at all points in the chain of custody to patients (16, 17). Manual record keeping, given labor constraints alone, is also likely to generate fewer data points for analysis and dynamic process optimization studies than automated online technologies (18). Therefore, this capability can be particularly advantageous when seeking to automate and scale-up manual laboratory-scale processes (19).

Productivity: The consistency of robotic handling supports the development and maintenance of optimal cell-processing conditions

Figure 4: Autologous scale-out suite cost comparisons

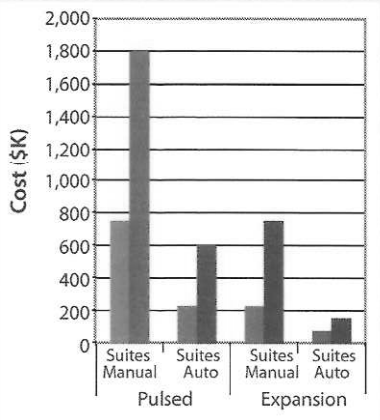
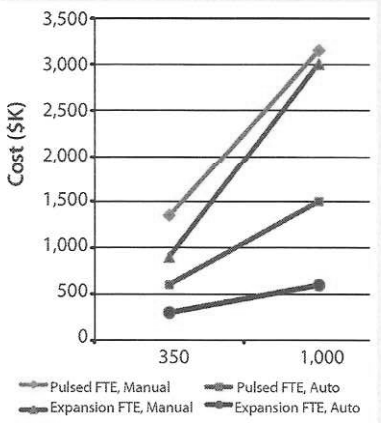


Figure 5: Autologous scale-out FTE cost comparisons



Hierachy of Comparability

- Comparability to optimal in vivo conditions
- Intrabatch comparability over multiple processing steps
- Interbatch comparability over long periods and between multiple processing sites
- Comparability in final product CQAs despite patient source material heterogeneity
- Comparability throughout chain of custody inc. distribution – cell viability
- Comparability in patient dosing and administration

over long periods. Further, the smaller footprint of automated systems compared with manual systems increases productivity per unit facility floor area.

In terms of labor requirements, the linear relationship between labor availability and maximum theoretical facility productivity for manual processes is invalid in the context of automation. A single employee and/or team of employees can operate a number of automated systems simultaneously. Therefore, the automation of repetitive tasks increases the number of tasks completed per unit time and per unit full time employee (FTE) resource (20), supporting rapid process scalability without the need to train new staff in manual processes. Automation also supports a decrease in requirements for staff training to maintain quality management systems and good manufacturing practice (GMP) compliance as a large number of associated manual tasks are permanently automated (21).

Comparability: Achieving and demonstrating comparability in critical quality attributes (CQAs: identity, potency, purity and safety) throughout all stages of cell therapy biomanufacturing is understandably a key regulatory requirement (22, 23). It is useful to understand key drivers for the regulatory needs for comparability and ways in which biomanufacturing automation may support regulatory compliance ("Hierarchy of Comparability" box).

Even the best intentions to strictly follow SOPs cannot remove the inherent variability amongst different technicians performing the "same" actions of a multistep process. Typically during manual bioprocess passaging of cells, environmental parameters such as temperature, duration of exposure to proteolytic enzymes, hydrodynamic forces, and fluid shear/stress expanded during cell resuspension are all subject to interbatch and interoperator variability (24). Such variability can detrimentally affect the consistency of CQAs and therein final products. Automation can remove the "art" of highly skilled staff with precise robotic movements and accurate timings. Such changes can improve intrabatch and interbatch comparability within and across globally located sites.

Bioprocess automation can also enable access to a greater number of techniques and tools to generate the data necessary for proving comparability in regulatory submissions. For example, due to the inconsistent cellular quality of manually cultured cells for a drug discovery assay, it was not possible to perform the radioligand binding assay depicted in Figure 3. However, this assay was successfully performed using automated techniques — further improving the dynamic range of the assay and making differentiation of the controls possible. Higher cellular reproducibility could increase the effectiveness and scope of similar types of product-release tests, thereby providing additional comparability data for regulators and improving confidence in product CQAs.

Potential Payback Timelines for Autologous Products

To demonstrate the cost benefit of transitioning from manual to automated culture, we investigated two models of common autologous cell therapy processes — pulsed and expansion. Pulsed models aim to simulate processes used in dendritic cell therapies in which patient immune cells are exposed to tumor lysate, peptides and/or antibodies, priming them for attack upon reintroduction (25–27). Expansion processes are similar to those generally used for mesenchymal scale-up. We modeled process flows within standard industry suite space and assessed the necessary full-time employee (FTE) requirements for two annual production scales at 350 and 1,000 patient doses. These two process scales can then be extrapolated for escalating commercial market penetration and/or expansion to multiple sites.

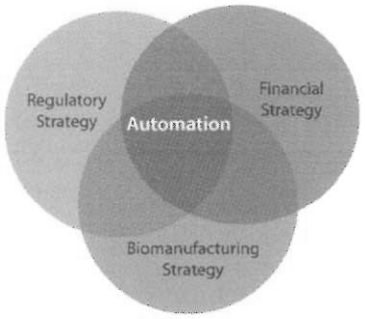
Respectively, Figures 4 and 5 show suite space and FTE costs incurred in each production model. As seen in both models, increases in the number of patients has a direct FTE impact in manual processing and a more gradual impact in automated processing, which has a lower labour requirement. The pulsed process included an additional manual interaction due to an unavoidable centrifugation step, which slightly limited the automation

Table 2: Calculation of payback timelines from savings conferred by automation versus manual processing

	Number of Patients	Estimated Suite Cost Savings[a]	Estimated FTE Cost Savings[a]	Estimated Total Gross Cost Savings[a]	Estimated Automation Cost[b]	Automation Investment Payback Period (Months)
Autologous pulsed models	350	$525,000	$750,000	$1,275,000	$2,000,000	18.8
	1,000	$1,200,000	$1,650,000	$2,850,000	$2,000,000	8.4
Autologous expansion models	350	$150,000	$600,000	$750,000	$1,600,000	25.6
	1,000	$600,000	$2,400,000	$3,000,000	$3,000,000	12.0

[a] Prices are in US dollars per annum [b] As one-off capital expenditures in US dollars

Figure 6: Venn diagram outlining the interdependence of regulatory strategy, financial strategy, biomanufacturing strategy and automation



benefit. The expansion process alleviates staff from repetitive tasks although the lengthy culture time requires additional automation systems, therein making the net benefit relatively similar.

Additional manual process hindrances include the need to ensure the separation of patient samples and the resultant large "footprint" of suite space required. Separate suites and lengthy cleaning regimes between each patient are typical in manual culture. Subsequently, the number of patients that could be processed during normal working hours was considerably lower. Automated solutions avert this setback — either through the use of plastic tube welding or functionally closed processing. Further automation advantages include improved consistency of products within a site as well as amongst decentralized sites and full audit trail of product handling, both of which would aid in expediting validation.

As Table 2 shows, although automation requires significant upfront capital expenditure (an oft bemoaned complaint of SMEs), it is clear from the estimated payback periods for each process that the savings over manual quickly outweigh the risks, especially as patient numbers increase. It is important to be mindful that these savings do not account for the additional direct automation benefits of lowered product loss due to quality or contamination issues nor the reduced FTE cost effects that arise from staff illness, transition, or retraining.

The Best Path Forward

The "process is the product" is a mantra that has informed the cell therapy bioprocessing community perhaps more than any other. But, to date, it has also been applied as a misnomer.

In the cell therapy industry, the strong interrelationship between regulatory strategy and financial success is undeniable. Rather less appreciated, yet of particular importance, is that "the [biomanufacturing and regulatory processes] are the product."

The regulatory environment is driven by developments in fundamental science, just as automated processing technologies respond to needs in the translation pathway from scientific innovation to affordable and efficacious patient benefits. This triumvirate is tangible, with significant implications for industry development – positive (if managed) and negative (if continued to be neglected) (Figure 6).

Basic scientists have valid concerns surrounding the applicability of automation in all cases, in part due to its perceived dissimilarity to optimized manual processes. Regulators are charged with the remit of protecting public health, while at the same time not hindering innovation. Investors seek the most cost-effective strategy to ensure regulatory compliance and maximize financial returns. Subsequently, the developers of automated biomanufacturing technologies face the highly formidable task of demonstrating value to all parties in the translation pathway from academic scientists to potential acquirers of a technology.

The nub of the matter is clear: Even if we are able to develop robust manual biomanufacturing strategies to enable the early stage cell therapy industry of today, will these same strategies be sufficient to enable the commercial cell therapy industry of tomorrow? There are growing signs that the financial and compliance benefits of automated biomanufacturing at production scale offer the best path forward for the sector's success.

Therefore, it's time to acknowledge the latest dichotomy for the cell therapy industry — beyond "autologous or allogeneic," "transient or permanent," "fresh or cryopreserved," "centralized or decentralized" — and now include "automated or manual" bioprocessing. In all cases, decisions will be made severally; assessing multifactorial risks and benefits on a product-by-product basis. The most important step is to appreciate that multiple paths exist to market and the establishment of a sustainable cell therapy industry.

After all, as George Keith Funston, past head of the New York Stock Exchange said, "Automation does not make optimism obsolete!"

Acknowledgments

The authors thank Richard Barker (CASMI), Christopher Bravery (Consulting on Advanced Biologicals), Andy Carr (NDORMS), Osnat Hakimi (NDORMS), Joe Gold (Stanford), Zuzana Kalivodova (NDORMS), Pierre-Alexis Mouthuy (NDORMS), Brock Reeve (HSCI), and Dave Thomas (TAP Biosystems).

Disclosures

The content outlined herein represents the individual opinions of the authors and may not

necessarily represent the viewpoints of their employers. D.A.B. gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA, USA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that amongst other services provides cell therapy biomanufacturing, regulatory and financial advice to clients in the cell therapy sector. D.A.B. has received hospitality C/O TAP Biosystems within the past seven years with a cumulative value of less than $10,000. D.A.B. is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such, the author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. K.E.B is an employee of TAP Biosystems (Royston, Hertfordshire, UK), which supplies automated bioprocessing solutions to the cell therapy sector. I.B.W. is a member of the World Class University Programme (Grant No. R31-10069) funded by the National Research Foundation, Ministry of Education, Science and Technology, South Korea. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed apart from those disclosed.

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Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence

A Concise Review

by David A. Brindley, Anna L. French, Ricardo Baptista, Nick Timmins, Thorsten Adams, Ivan Wall, and Kim Bure

The cell therapy industry is undergoing a natural evolution from scientific curiosity into a commercially and clinically attractive opportunity (1). This evolution is by no means complete, and growing evidence suggests that its progression is driving significant developments in cell therapy bioprocessing — notably, convergence.

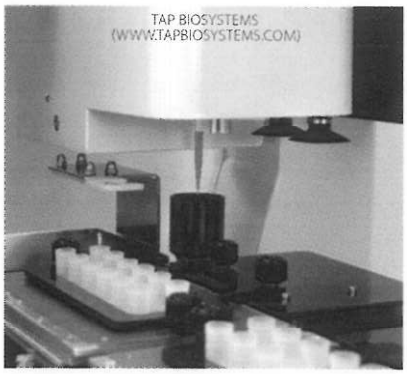
Progressively, bioprocessing technologies primarily used in production of noncell-based products are being evaluated for cell therapy bioprocessing applications (2). Consequently, this process of convergence is leading to an increasing proportion of the total portfolio of such bioprocessing options involving technologies that have previously been used in other biomanufacturing applications — such as production of recombinant proteins.

Technological convergence is not unique to cell therapy biomanufacturing (Table 1), or indeed to bioprocessing (Tables 2 and 3). This process shares similarities with technology repurposing; however, the key distinction is that convergence describes the tendency for heterogeneous technological systems to evolve toward performing similar tasks. One example is the convergence of digital audio, data and video tools. Similarly, the trinity of process engineering, commercial considerations, and regulatory requirements drives the convergence of cell therapy bioprocessing technologies.

Fundamentally, bioprocess engineering encompasses the design, operation, control, and optimization of biochemical processes to efficiently produce a range of products at requisite scales. This remit is achieved through application of intellectual and physical tools, the selection of which is driven by unique properties of the bioprocess materials involved. In cell therapy bioprocessing, the primary influence is the high sensitivity of cells to their bioprocess environment (3, 4).

Unique Characteristics of Cells as a Bioprocessing Material

In production of existing biologics such as monoclonal antibodies (MAbs), cells are used as an expression system that secretes target therapeutic products into their culture media unless products are retained within them and removed through mechanical and/or chemical means. At some point in the downstream biomanufacturing process of such biologics, the interdependence of a cellular expression system's critical quality attributes (CQAs) and those of the therapeutic product can be separated from one another (5, 6).



Critically, however, that is not possible with cell therapies because the cells themselves are the product that will be administered (6). Thus, end-product CQAs and the bioprocess environment experienced by therapeutic cells are interdependent and require concomitant optimization, control, and monitoring. The situation applies to not only cell culture operations, but also the full manufacturing process from entry of raw materials through final product formulation.

Industrial cell lines typically used to produce biologics exhibit substantially more physicochemical stability during bioprocessing than "biologically dynamic" therapeutic cells, whose fate is dependent upon their bioprocessing environment. For example, many therapeutic cells exhibit a high degree of sensitivity to their environment, such as

• complex nutritional demands
• dependence on exogenous growth factors
• responsiveness to endogenously produced growth factors
• differential behaviors in response to varying pH, dissolved oxygen (DO), and osmolality
• responsiveness to mechanical forces
• (in a number of cases), dependence on adhesion-associated signaling (7, 8).

Those limitations may be surpassed by the discovery of molecules and/or biomaterials that can manipulate intracellular signaling and the cells' microenvironment (9) — or by coculturing cells with biocompatible functionalized materials (8). However, the list of unique demands contribute to limitations in the direct transferability of existing bioprocessing technologies to use in cell therapy bioprocessing.

Existing cell-expansion technologies, for example, frequently require significant adaptations of cells to accommodate their increased sensitivity to environmental stress (e.g., mechanical forces and reactive oxygen species) and to provide appropriate control over differentiation outcomes and maximize differentiation efficiencies. Nevertheless, existing technologies and know-how from the biopharmaceutical industry can revolutionize cell therapy bioprocessing by facilitating integrated process monitoring and control, informing media development and feed optimization, providing cost-effective means for scaling up or out, and ultimately helping to industrialize cell therapy manufacture. Conversely, the needs of cell therapy bioprocessing are transforming existing technologies with sophisticated monitoring and control approaches, an increasing need for scale-out solutions, and a heavy focus on integrated single-use technologies for implementation throughout the entire manufacturing process. Ultimately, the previously disparate fields of biologics production and cell therapy manufacturing will converge upon more sophisticated and highly controlled bioprocesses.

Although it is apparent that a wide range of bioprocess technologies are available for cell culture operations (Figure 1), options for downstream processing of cell therapy products are currently limited. This perhaps reflects the current stage of industry development, which has so far focused on simply growing sufficient cells to meet clinical trial demands — without substantial investment in optimization of the entire manufacturing process (including downstream processing). Furthermore, it is during downstream processing that typical biopharmaceutical processes diverge sharply from cell therapy because they remove cells as by-products. However, much of the knowledge and technologies involved in biopharmaceutical downstream processing by biopharma can be applicable to cell therapies.

Table 1: Examples of bioprocessing convergence

Technology	Original Application(s)	Contemporary Bioprocessing Application(s)
Bioreactors	Brewing	Cell expansion and biologics production
Homogenizers	Dairy bioprocessing	Cell lysis
Fine filters	Air conditioning systems	Filtration
Steam sterilization	Canning	Sterilization in place (SIP) and clean in place (CIP)
Plasticized polyvinyl chlorine (PVC) bags	Blood storage and transportation	Rocking motion bioreactors for cell expansion
Counterflow centrifugation	Blood bioprocessing	Therapeutic cell concentration
Ultrasonic lysis	Communications and imaging	Cell lysis
Lyophilization (freeze drying)	Serum distribution	Biologics manufacturing, food manufacturing, hydrocarbon analysis

Table 2: Examples of nonbioprocessing technological convergence

Technology	Original Application(s)	Contemporary Application(s)
Teflon polytetra-fluoroethylene (PTFE)	Pipe joint sealant	Cookware, communications wiring
Electrospinning	Scientific apparatus — evaluation of magnetic and electrostatic phenomena	Textile and medical device manufacture

Table 3: Examples of technological convergence in biomaterials (adapted from personal communication with R. Langer and J. Karp)

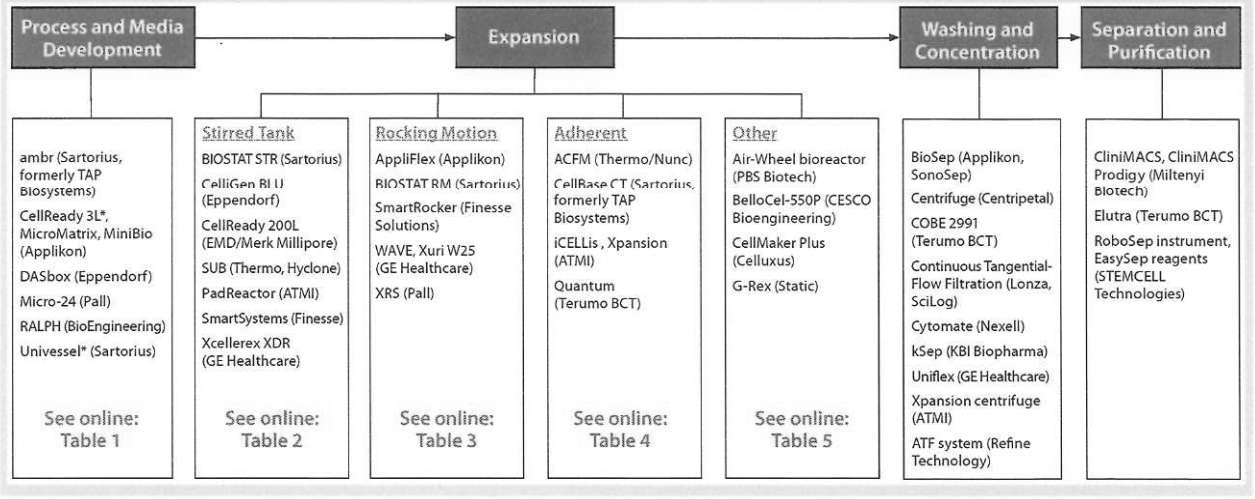
Polymer	Original Application(s)	Medical Application(s)
Polyether urethane	Ladies' girdles	Artificial heart
Cellulose acetate	Sausage casing	Dialysis tubing
Dracon	clothing	Vascular grafts
Polyurethane	Mattress stuffing	Breast implants

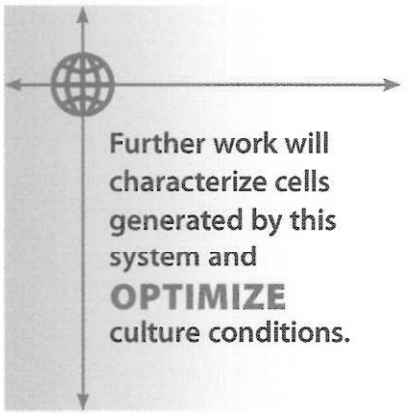
Ideal Characteristics of Cell Therapy Bioprocess Technologies

At all process scales, it is essential that the bioprocess solutions selected not only meet the specific demands of manufacturing cells as products, but also satisfy the regulatory, commercial (demand and cost of goods, CoGs), and infrastructural requirements of the cell therapy industry (10). The relative importance and burden of those challenges is likely to vary throughout product development. For example, academic developers are likely to be constrained by physical and financial resources, so they will place greater emphasis on capital and operating expenditures (11). Conversely, industrialists will focus on regulatory compliance — driving demands for in-line process analytics — and commercial drivers, including CoGs at commercial scales and material-supply risks involved when bespoke consumables are required.

Regardless of scale and target-product characteristics, a number of process technology features are desirable

Figure 1: Overview of commercially available single-use cell bioprocessing technologies





for ensuring robustness of bioprocesses with maximum flexibility and amenability to short-term manufacturing demands and long-term product development strategies (12). These include minimization or (preferably) elimination of manual operations; operator ease; (functionally) closed systems wherever possible; single-use components; scalability (up and out); ease of technology transfer between manufacturing sites; regulatory compliance; a range of in-line process analytical technologies; ease of process optimization; and high-productivity with maximum process efficiency.

A key differentiating feature among cell therapy bioprocessing technologies is their relative automation capabilities. In the academic environment, automation is of limited utility and only a limited number of systems will be in use simultaneously. But industrialization of autologous cell therapies will lead to creation of "bioreactor farms," where operators must handle dozens or even hundreds of bioreactors at a time — one for each patient — followed by separate downstream processing flows for each patient lot.

Effective cell therapy bioprocess automation also requires enhanced process-control capabilities to enable effective material and patient sample tracking; scheduling optimization; and execution of patient-specific processing protocols (if applicable). Those essential features typically extend beyond the automation regime implemented in conventional biologics production process automation. Additionally, from a risk-management perspective, effective bioprocess automation should reduce patient lot mishandling, including interpatient contamination risks.

Concise Review: Methodology, Implications, and Caveats

We compiled a list of key cell therapy bioprocessing technologies through expert-user interviews; reviews of trade and industry literature; and discussions with technology manufacturers. Thereafter, we obtained technical specifications from publicly available documents and (whenever possible) confirmed them with the technology manufacturers (see Acknowledments)to ensure their accuracy.

It was not possible in all cases, however, to make contact with some manufacturers for corroborating publicly available data or obtaining complete data for all technology features sought. Additionally, our data presented are agnostic to performance for particular cell types, are restricted to single-use technologies, and do not reflect the impact of operator skill and/or regulatory restrictions on technology performance. Due to the significant technological heterogeneity in downstream processing technologies, our discussion is restricted to upstream bioprocess technologies concerning cell culture process and media development. We also omitted the impact of cell characterization and testing technologies that may be used alongside those technologies discussed.

Collation of these data clearly demonstrates the convergence of "traditional" biopharmaceutical technologies with the emerging cellular therapies industry. High-level technical specifications are not always easily obtainable. Technology manufacturers are hesitant to definitively state typical operating ranges for reasons of commercial confidentiality. Potential inter–cell-type idiosyncrasies can also make a difference, as well as as-yet limited user experiences and optimization case studies in which cells are the product. In five electronic-only tables accompanying this article online (www.bioprocessintl.com/bpiextra), we provide an overview of the most common technologies for rapid and straightforward comparison of available options to guide readers' identification of technologies for further investigation. Online Table 1 details process and media development options listed in Figure 1. Online Table 2 details stirred-

tank cell expansion options listed in Figure 1. Online Table 3 details rocking-motion cell expansion options listed in Figure 1. Online Table 4 details adherent-cell expansion options listed in Figure 1. And online Table 5 details other cell expansion options listed in Figure 1.

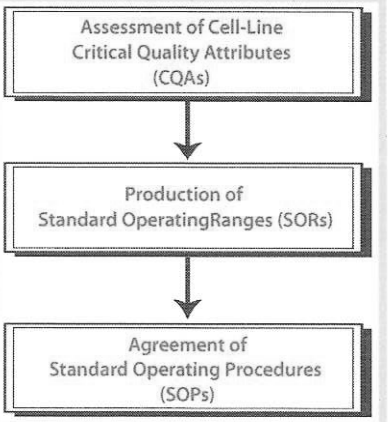
Process and Media Development

For this analysis, we combined technology options for both process and media development into a single subgroup. However, although some technologies may be suitable for both functions, others will not be. For example, it is likely that the Pall Micro system is suitable for media development but not for process development because of its small working volume. Similarly, Univessel (Sartorius) and/or Celligen (Eppendorf) systems are likely to have excessively large working volumes for most media-development operations. The key differentiator among technologies for process development and media-development operations is probably the design space for final production-reactor volumes in terms of classical process parameters: mixing time, pH, DO, volumetric power input, and so on. In particular, a large process design space probably is more advantageous for allogeneic (rather than autologous) therapies that necessitate larger process volumes.

The importance of cell culture media on cell CQAs and process performance follows from heterogeneity in the physiochemical properties of individual cell lines (13, 14) and the close relationship between the cell bioprocessing environment and cell fate (Figure 2). Consequently, significant efforts are used in cell line specific media optimization both specific and nonspecific to cell lines in cell therapy bioprocessing.

Process and media developments that are not cell-line specific focus on achieving regulatory compliance for early stage technologies, at which point a disparity in expectations exists between academia and industry. For example, to mitigate supply and contamination risks, it is essential to ensure that all process and product components are xeno-free wherever possible. That necessitates removal of xeno-cell feeder layers that have been used to provide physicochemical support to certain cell types as well as removal of animal-derived sera in favor of defined media (15, 16).

Figure 2: Typical cell biomanufacturing process and media development pathway



Therefore, the key differentiators among technologies available to support process and media development are the working-volume range; the number of vessels that can be used in parallel (in some cases each with alternative reaction conditions); the range of "off-the-shelf" and standard components (including impeller types); and the extent of liquid-handling automation. Wherever possible, automated liquid-handling functions are preferred for maximizing throughput and minimizing interoperator variability. Furthermore, process control and in-line analytics are critical to development of robust data sets that support process development and regulatory compliance.

Cell Expansion

For this review, we restricted our consideration of cell-expansion technologies to single-use systems only. This constraint reflects market trends that are driven in part by the desire to minimize contamination risks, ease regulatory compliance, maximize flexibility, and accommodate unique challenges posed by recipient-specific manufacturing strategies (17). Of all unit operations we investigated, it is evident that expansion technologies have been subject to the greatest research and development (R&D) efforts for cell therapy applications thus far, having the most significant body of user experience as well.

Despite significant differences in operating principles and construction, the four main types of expansion technologies we assessed share similar features and specifications, as delineated in the "Value Differentiators" box. Expansion technology choices are principally driven by cell-type attributes (e.g., adherent or nonadherent cells) (18), and the stage of product development (e.g., low capacity and ease of operation for early stages or high capacity and robustness for late stages).

Similar to process and media development technologies, provision of in-line process analytics is critical to cell expansion technologies. It is particularly true for autologous therapy biomanufacturing, in which variable starting-material volumes and CQAs must be accommodated in manufacturing consistent products. Additionally, a range of gas and liquid lines is important for process monitoring and control (19). This may be challenging for proprietary expansion technologies with operational characteristics that can vary substantially to conventional stirred-tank reactors (STRs) hindering performance comparison and evaluation.

One of the most critical properties of single-use cell-expansion systems (as well as single-use media storage and preparation technologies) is the material choice for the disposable components. If selected inappropriately, they can pose a risk of releasing potentially toxic or inhibitory substances. Such leachables are chemical compounds, namely additives to polymers used to manufacture bags and/or other substances generated during gamma irradiation and storage. Hammond and coworkers (20) identified such a compound that can be present at impermissibly high amounts in some single-use bags currently offered in the marketplace. Leachable compounds can migrate from plastic materials to cell culture media — and consequently to cells in culture. The release of cytotoxic compounds under process conditions is particularly undesirable because such chemicals negatively affect cell growth and viability (21).

For cell therapy applications in which downstream processing steps are fairly limited, it is important to prevent cytotoxic effects arising from leachables and extractables. Therefore, it is essential to select suppliers who can understand, specify, and control additive formulations in their disposables as well as in their manufacturing processes (22) to secure patient safety.

One neutral source for such evaluations is a pair of recently published round-robin experiments by the Dechema (23). In these interlaboratory trials involving several large biopharmaceutical companies, bags from all major suppliers were subjected to media and water-for-injection (WFI) extraction followed by a standardized cell culture trial to assess growth. Several bags showed impaired growth compared with controls; others reproducibly supported cell growth without any restrictions. We encourage every scientist using single-use products in the field of cell therapy to enter into a discussion with his or her suppliers on the performance of their respective products during these trials.

Increasing growth for cell bioprocessing technologies is currently met by a combination of cell-specific and non–cell-specific technologies adapted from other industries (particularly biologics manufacturing). It is likely that the latter technologies, representing convergence, will continue until the unique physicochemical demands of cells contained in process fluids necessitate significant adaptions to existing (if not entirely new) technologies. Developments in downstream cell bioprocessing lag behind those in upstream bioprocessing, where the engineering community has sequentially approached production bottlenecks.

We hope that this clear overview of commercially available cell therapy bioprocessing technologies — particularly the online materials —provides a useful resource for both technology users and developers. It highlights implications of the important trend of technological convergence. For readers of the classics, we pose the parting question of, "To what extent does technology repurposing and adaptation represent a Theseusian Paradox?" (24).

Key Value Differentiators in Expansion Technologies

- Dependency on other technologies (e.g., microcarriers)
- Capital expenditure
- Productivity per unit footprint
- Monitoring and control capabilities
- Rheological properties (e.g., shear forces generated)
- Amenability to a range of cell types
- Interbatch consistency
- Construction materials (rig and reactor)
- Range of working volumes available
- Expansion modalities (e.g., batch or fed-batch operation)
- Compatibility with "generic" consumables
- Ease of sterilization including minimization of "process downtime"
- Graphical user interface (ease of operation)
- (Functionally) closed
- Data "audit trail" for use in regulatory compliance and multiparametric process optimization
- Operational costs
- Ease of multisite comparability
- Efficient gaseous exchange
- Heat monitoring and exchange
- Potential for application of "artificial intelligence" and/or dynamic feedback in bioprocess control
- Ease of maintenance

Acknowledgments and Disclosures

This work is supported by the CASMI Translational Stem Cell Consortium. The authors express their sincere thanks to the following organizations that have contributed to the consortium as funding and events partners — without whom the consortium and the benefits it will bring to stem cell translation would be unacceptably constrained: GE Healthcare, CCRM, TAP Biosystems, Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, and NIH Centre for Regenerative Medicine. The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers.

Vendors that contributed information to this study include ATMI (Jose Castillo, Matthieu Egloff, Matt Niloff, and Brent Todd), GE Healthcare (Emanuela Costigliola), Sartorius Stedim Biotech (Don Traul, Joseph Jirka, Andre Grebe, Christel Fenge), and Stem Cell Technologies (Mike Jones). And the following individuals supported in the production of the manuscript: Andrew Carr (NDORMS, Oxford), Richard Barker (CASMI), and Dave Thomas (TAP Biosystems/Sartorius Stedim Biotech).

David A. Brindley gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA, USA). He is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that among other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. Brindley has also received hospitality from TAP Biosystems over the past seven years with a cumulative value of <US$10,000. He is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such must stress that this article is provided for academic interest only and must not be construed in any way as an investment recommendation.

Kim E. Bure and Thorsten Adams are employees of TAP Biosystems (now Sartorius Stedim Biotech), which supplies automated bioprocessing solutions to the cell therapy sector. Ivan B. Wall is a member of the World Class University Programme (Grant No. R31-10069) funded by the National Research Foundation (part of South Korea's Ministry of Education, Science, and Technology). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials addressed herein.

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Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence

A Concise Review

by David A. Brindley, Anna L. French, Ricardo Baptista, Nick Timmins, Thorsten Adams, Ivan Wall, and Kim Bure

Methodology, Implications, and Caveats

We compiled a list of key cell therapy bioprocessing technologies through expert-user interviews; reviews of trade and industry literature; and discussions with technology manufacturers. Thereafter, we obtained technical specifications from publicly available documents and (whenever possible) confirmed them with the technology manufacturers (see Acknowledments)to ensure their accuracy.

It was not possible in all cases, however, to make contact with some manufacturers for corroborating publicly available data or obtaining complete data for all technology features sought. Additionally, our data presented are agnostic to performance for particular cell types, are restricted to single-use technologies, and do not reflect the impact of operator skill and/or regulatory restrictions on technology performance. Due to the significant technological heterogeneity in downstream processing technologies, our discussion is restricted to upstream bioprocess technologies concerning cell culture process and media development. We also omitted the impact of cell characterization and testing technolcgies that may be used alongside those technologies discussed.

Collation of these data clearly demonstrates the convergence of "traditional" biopha-maceutical technologies with the emerging cellular therapies industry. High-level technical specifications are not always easily obtainable. Technology manufacturers are hesitant to definitively state typical operating ranges for reasons of commercial confidentiality. Potential inter–cell-type idiosyncrasies can also make a difference, as well as as-yet limited user experiences and optimization case studies in which cells are the product. In these electronic-only tables, we provide an overview of the most common technologies for rapid and straightforward comparison of available options to guide readers' identification of technologies for further investigation.

Online Table 1 below details process and media development options listed in Figure 1 of the accompanying article (1). Online Table 2 below details stirred-tank cell expansion options listed in Figure 1 (1). Online Table 3 (next page) details rocking-motion cell expansion options listed in Figure 1 (1). Online Table 4 (next page) details adherent-cell expansion options listed in Figure 1 (1). And on ine Table 5 (next page) details other cell expansion options listed in Figure 1 (1).

Reference

1 Brndley DA, et al. Cell Therapy Bioprocessing Technologies and Indicators of Technological Convergence: A Concise Review. *BioProcess Int.* 12(3) 2014: S##–S##.

ONLINE Table 1: Process and media development (M = manual, A = automated)

				Impeller Types			Control						Liquid Handling		
System	Supplier	Working Volumes	Vessels	Rushton?	Marine?	Gases	Temperature?	pH?	DO?	Gas Flow?	Stir Speed?	Liquids/Vessel	Bolus	Drip	Sampling
Micro-24	Pall	3–7 mL	24	No	No	3	18–45 °C	3.5–8.0	0–100%	0–20 sccm	0–800 rpm	**	M	—	M
ambr 15	TAP Biosystems (Sartcrius Stedim)	10–15 mL	24, 48	No	Yes	3	20–40 °C	6.5–7.5	0–100%	0–1 mL/min	300–2000 rpm	***	A (20 µL–4 mL)	—	A
DASbox	Eppendorf	60–250 mL	4	Yes	Yes	4	10–60 °C	0–14	0–400%	0–25 sL/h	20–3,000 rpm	2	A	A	M
ambr 250	TAP Biosystems (Sartcrius Stedim)	100–250 mL	12, 24	Yes (2)	Yes (2)	3	18–55 °C	2.0–8.5	0–200%	0–75 mL/min	150–4500 rpm	4***	A (30 µL-10mL)	A (10 nL/hr to 120 mL/hr)	A
MiniBio	Applikon	50–800 mL	1	Yes	No	4	Yes	Yes	Yes	Yes	50–2,000 rpm	6	A	A	M
Univessel*	Sartorius Stedim	600–2,000 L	1–4	No	Yes (2)		5–50 °C	6.0–8.0	0–100%	—	—	—	M	—	M
CellReady 3L*	Applikon	1,000–2,400 mL	1	No	Yes	3	Yes	Yes	Yes	Yes	Yes	1–3**	M	—	M

* Single-use vessels that can be integrated with multiple vendor controllers, therefore specifications depend on chosen controller ** Alkali addition *** Limited only by available reagent space

ONLINE Table 2a: Stirred-tank bioreactors for cell expansion (specifications)

					Impeller						Control					
System	Supplier	Working Volumes	Vessel Shape	Sparger	Disk?	Pitched?	Paddle?	Packed Bed?	Agitation Speed	Power Number (n^3)	pH	DO	Temperature	Gas Flow	Gases	Peristaltic Pumps
CelliGen BLU	Eppendorf	1.25–40 L	Cylinder	Static	No	Yes	No	Yes	25–200 rpm	1.3	2–14	0–200%	Ambient + 5–40 °C	0.002–7.5 SLPM	8	3
CellReady 200L	Millipore	10–200 L	Cylinder	Static	No	Yes	No	No	0–350 rpm	3.2–4.0	—	—	—	—	—	—
PadReactor	ATMI (Pall)	3–1,000 L	Cube	Dynamic	No	No	Yes	No	*	*	*	*	*	*	*	*
BIOSTAT STR	Sartorius Stedim	12.5–2,000 L	Cylinder	Ring, microsparger	2 × 6	2 × 3	No	No	10–240 rpm	1.3–3.2	5.5–8.5 (single use) 2–14 (reusable)	0–100%	CW + 8–40 °C	0.01–400 L/min	6	2 or 3

* Open architecture — dependent on the controller chosen

ONLINE Table 2b: Stirred-tank bioreactors for cell expansion (benefits)

			Automation Capabilities								Sensor Technologies/PAT						GMP Compliance		
System	Supplier	Performance (CHO maximum density)	Process Parameters	Trends	Temperature Control?	pH Control?	DO Control?	Agitation Control?	Gas Mix?	Media and Supplement Addition?	Analog Inputs	Analog Outputs	Traditional pH?	Single-Use Optical pH?	Conventional DO?	Single-Use DO?	Weighing Scale?	Vessel Material (USP Class VI or higher)	SCADA	Validation Packages
CelliGen BLU	Eppendorf	8.58×10^6	32	8	Yes	Yes	Yes	Yes	3–4	Yes	7	7	Yes	Yes	No	Yes	Yes	Polycarbonate	BioCommand	Yes
CellReady 200L	Millipore	$>20 \times 10^6$	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PadReactor	ATMI (Pall)	$10–20 \times 10^6$	—	—	Yes	Yes	Yes	Yes	No	Yes	—	—	Yes	Yes	Yes	Yes	No	TK8	—	Yes
BIOSTAT STR	Sartorius Stedim	160×10^6	unlimited	16	Yes	Yes	Yes	Yes	Yes	Yes	4	4	Yes	Yes	Yes	Yes	Yesccccc	ultra-low density polyethylene (ULDPE)	BioPAT MFCS	Yes

* No data available

ONLINE Table 3a: Rocking-motion bioreactors for cell expansion (specifications)

						Control								Liquid Handling	
System	Supplier	Working Volumes	Weight Measurement?	O_2/Air	CO_2/Air	Rocker Speed	Rocker Angle	Rocking Control?	pH?	DO?	Temperature	Gas Flow	Gases	Pump Flow	Pumps
WAVE 2/10	GE Healthcare	0.1–5 L	Yes	0–50%	0–12%	2–40 rocks/min	2–12°	No	Yes	Yes	0–50°C	—	—	—	—
XRS	Pall Life Sciences	2– 20 L	No	—	—	1–35 rpm	—	Biaxial	6–8	0–200%	Ambient +8–40° C	—	3	—	3
Xuri W25	GE Healthcare	0.3–25 L	0.5–25 kg	0–50%	0–15%	2–40 rpm	2–12°	Yes	6.0–8.0	0–100%	20–40 °C	0–1,000 mL/min	—	0.07–100 mL/min	—
BIOSTAT RM	Sartorius Stedim	0.1–300 L	Yes	0–100%	0–100%	2–42 rpm	4–10°	Yes	6.5–8.5	0–100%	CW + 8–40 °C	0.02–10 L/min	4	0.01–180 mL/min	4
WAVE 200 and 500/1000	GE Healthcare	10–500 L	No	0–50%	0–15%	4–25 rocks/min	0.5–9°	No	Yes	Yes	5–40°C	—	—	—	—

ONLINE Table 3b: Rocking-motion bioreactors for cell expansion (benefits)

			Performance (maximum CHO density)			GMP Compliance								
System	Supplier	Footprint		Rocking Profiles?	Automated Perfusion?	Vessel Material (USP Class VI or higher)	On-Board Control?	Remote PC Control?	Units Linked to One PC	SCADA	User Access Levels	Alarms	OPC	Validation Packages
WAVE 2/10	GE Healthcare	489 × 330 × 200	10×10^6	Yes	Yes	ethylene vinyl acetate (EVA)/low density polyethylene copolymer	X	No	0	—	No	No	No	Yes
XRS	Pall Life Sciences	*	*	*	*	*	*	*	*	*	*	*	*	*
Xuri W25	GE Healthcare	475 × 430 × 60; 800 × 610 × 260	—	Yes	Yes	Yes	No	Yes	32	UNICORN DAQ	Yes	Yes	Yes	Yes
BIOSTAT RM	Sartorius Stedim	—	—	Yes	2	Yes	Yes	Yes	16	BioPAT MFCS	Yes	Yes	Yes	Yes
WAVE 200 and 500/1000	GE Healthcare	—	—	No	No	8	Yes	No	—	—	No	No	No	NO

* No data available

ONLINE Table 4: Adherent-cell technologies for cell expansion

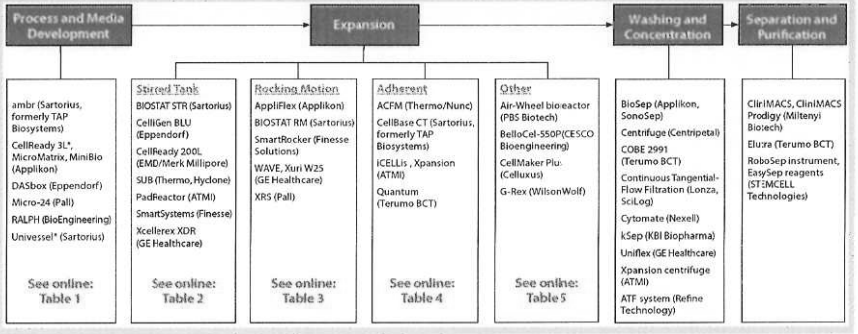
									Control							Detection			
System	Supplier	Surface Area	Labware	Material	Closed?	Perfusion?	Pumps	Agitation Speed	pH	DO	Temperature	Media Flow	Gases	Cell Density	Growth Curve?	Morphology	Control	GMP Compliant?
Quantum	Terumo BCT	21,000 cm^2	Proprietary Bioreactor	Hollow-fiber	Functionally	N/A	1	NA	N/A	N/A	—	—	1	—	—	—	Touchscreen	Yes
iCELLis	ATMI (Pall)	53–50,000 cm^2	Fixed-bed, microfibers	USP class VI rigid plastic	Yes	Yes	1–5	0–1,500	6.0–9.0	0–100%	15–40	—	4	—	—	—	PC	Yes
ACFM	Thermo/Nunc	75,840–101,120 cm^2	Cell Factory 10 (4 × 3), Cell Factory 40 (4 × 1)	USP class VI polystyrene	Yes	N/A	1	NA	—	—	—	—	—	—	—	—	On-board	Yes
Xpansion	ATMI (Pall)	6,120–122,400 cm^2	Proprietary plate	USP class VI polystyrene	Yes	Yes	2	5–250 rpm	6.0–9.0	0–150%	0–50	1–5 mm/s	4	Holographic microscope	Yes	Holographic microscope	PC	Yes
CellBase CT	TAP Biosystems (Sartorius Stedim)	75–157,500* cm^2	T75, T175, Triple, HYPER*	USP class VI polystyrene	Functionally	N/A	10	NA	N/A	N/A	30	N/A	1	Trypan Blue	Essen Incucyte	Essen Incucyte	PC	Yes

* Based on research-grade experience

ONLINE Table 5: Other technologies for cell expansion

System	Supplier	Technology
CellMaker Plus	Celluxus Ltd.	Airlift
BelloCell-500P	CESCO Bioengineering	Microcarrier
Air-Wheel bioreactor	PBS Biotech	Air-Wheel
G-Rex	Wilson Wolf	Static

Figure 1: Overview of commercially available single-use cell bioprocessing technologies



"Cell Therapy Manufacturing: Identifying and Meeting Demand"

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For submission to:

Wiley-Blackwell Life and Earth Sciences

Alain A. Vertès, Nasib Qureshi, Arnold Caplan and Lee Babiss (Eds): Stem Cells in Regenerative Medicine: Science, Regulation and Business Strategies

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Abstract

The commercialization of cell-based products presents new manufacturing challenges compared to more traditional pharmaceuticals, or even biopharmaceuticals. The development of clinical-grade, viable, cell-based products will require some sophisticated scientific innovations. Exciting process techniques and technologies have already paved the way for novel cell-based products to debut on the market. This chapter addresses a range of unique challenges facing developers of cell-based products as well as the introduction of innovative technologies that address these hurdles. Finally, the chapter concludes with some commentary on the future of cell-based products and the role optimized manufacturing paradigms will play in the commercialization of these ground-breaking products. As with other ground-breaking therapies that came of age before cell-based therapies, with manufacturing innovations and more products entering the market, cell-based products will become affordable, and attainable for most patients who stand to benefit from them.

Key Words

Cell therapy; definition of cell therapy; value; business models; commercialisation; commercialization; timeline; reimbursement; funding; translation; marketing; clinical trials; manufacturing; bioprocessing; bottlenecks; future trends; regenerative medicine.

1.0 INTRODUCTION AND BACKGROUND

1.1 Rationale

The fundamental research that underpins the cell therapy industry (Mason et al., 2011) may represent a selection of the 21st century's scientific greatest achievements. Advances in cell culture, developmental biology, and molecular techniques have all paved the way for exciting opportunities in the development of cell-based therapies. However, a number of hurdles still to this date separate basic scientific discoveries from their broad clinical implementation, including additional laboratory studies, almost a decade of clinical trials, funding challenges, and the unique, and to some extent unquantifiable risk, that a given therapy will fail to demonstrate its safety and efficacy in vivo. Furthermore, even when such issues have been overcome, the product must demonstrate commercial viability, generating sufficient financial returns to reward stakeholders, and to trigger additional investment into future innovations.

As in the case of monoclonal antibodies when this technology was still emerging, at the heart of the quest for the commercial viability of cell based therapies is manufacturing (Williams, 2011). Without robust and scalable manufacturing techniques and technologies, lifesaving products cannot be accessed by the greatest number of patients. Therefore, bioprocessing is an essential task on the critical path to delivering safe and efficacious cell based therapies to patients worldwide.

The topics that will be covered in this chapter include the opportunities and challenges of establishing best practices for the manufacture of cell based therapies at commercially meaningful scales. One important aspect of cell therapy development and manufacture, which will be emphasized, is the need to maintain the critical quality attributes (CQAs) of cell-based products, and to do so at costs that worldwide public and private healthcare payers can afford. As the cell therapy industry matures, and as bioprocessing capabilities meet the new demands posed by these products, the manufacturing costs should decrease sufficiently for cell-based products to be attainable for a wider portion of the population.

1.11 The Cell Therapy Industry: 'An Overview'

While the global healthcare sector generates significant societal benefit, it must also generate investor value. Therefore, the ability to manufacture revolutionary cell based therapeutics alone is insufficient to sustain the burgeoning cell therapy industry (Mason et al., 2011). Rather, the capability and capacity to manufacture cell therapies in a *commercially viable manner and scale,* is a mission-critical step towards the goal of a competitive and sustainable 21st century industry (Brandenberger, 2011). This ethos needs to be in the mind of industry pioneers as the industry ushers exciting pre-clinical findings in academia toward translation into cell-based products (Cooksey, 2006, McKernan et al., 2010, Lysaght, 2006, Mason and Manzotti, 2010b). This transition is undoubtedly

exhilarating; however, the seemingly slow rate of translation from discovery to therapy can be frustrating for patients with few alternative treatment options. In addition, the sluggish pace of progress for cell therapy products in clinical development can be unnerving for investors, especially if they recall the financial challenges faced by tissue engineering developers at the turn of the Millennium (Mason, 2007, Lysaght, 2006, Williams and Sebastine, 2005).

However, it must be stressed that cell therapy product development is, by and large, distinct from tissue engineering and regenerative medicine (Mason et al., 2011). The majority of cell-based products are intended to transiently persist in the patient, secreting factors that then allow the patient's body to heal; the cells are subsequently eliminated from the body. This is a fundamentally different therapeutic modality compared to most tissue engineered products. Typically, cell-based therapeutics are administered as single cell suspensions. Therefore, the cells will ideally need to be prepared such that cell viability is preserved and cell clumping is minimized, with the final container amenable to use with intravenous technologies. Furthermore, it is likely that unique manufacturing platforms, in addition to novel commercialization strategies, will be required to create a successful, sustainable cell therapy industry (Rao, 2011). Indeed, exciting innovations in cell therapy manufacturing have already been deployed and efficiencies observed in the commercialization of cell-based products. Examples include ultra dense HYPERStack platforms (Corning, NY, USA) and microcarriers for adherent cell culture, and new purification options such as the

kSep centrifugation system (KBI Biopharma, Durham, NC, USA) and tangential flow filtration; progress compared to the blood processing equipment the industry started with. Moreover, there has been a widespread shift in industry to implement scalable manufacturing systems that are completely closed from the environment (James, 2012), with companies such as Miltenyi Biotec (Teterow, Germany) offering a 'plug and play' process with their CliniMACS® Prodigy. With such developments, the promise of cell-based therapies is increasingly becoming reality, with patient outcomes rivalling and/or besting those of established pharmaceuticals (eg AMI, GVHD), biologics and medical devices for conditions such as AMI and GVHD (Mason et al., 2011). As more therapies become commercially available, and manufacturing infrastructure is able to meet the anticipated demand, a broader base of patients will be able to, affordably, benefit from these therapies.

1.12 Importance of Manufacturing: Translating Great Science into Great Business

Due to the long duration of the drug development pathway [Figure 1.0], and the large number of stakeholders it unites, the need for a robust manufacturing strategy is fundamental in the development of successful therapeutic products (Archer and Williams, 2005).

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Despite past experience, the commercialization of novel biomedical innovations repeatedly follows the same trend, where initial public hype concerning the promise of a new scientific discovery gradually turns into frustration as years pass and a limited number of products reach the marketplace; cell therapy is not immune to the Gartner curve effect (Fenn and Raskino, 2008). The reasons for such slow progress are numerous, and often the rate of product development is delayed by the inability of contemporary manufacturing strategies to meet the challenges of groundbreaking new products. This paradigm is perpetuated by an industry eager to get to market and unable to afford the time and money required for rigorous process development.

The majority of cell therapy products in clinical development are spun out from academia. Indeed, clinical materials for first-in-man/phase I studies are often generated in academic cell processing labs, with academic funding. Biotech companies developing cell therapy products, usually small start-up companies, often struggle to raise funds to support full clinical programs. Furthermore, the high degree of risk associated with emerging technologies and early clinical development mean that such companies rarely have the capital required to build a facility in which to manufacture their novel products, thus much production tends to occur in academic labs. Contract manufacturing organizations (CMOs), such as Lonza Inc , afford therapeutic developers the ability to leverage existing facilities, quality systems, and in-house expertise for the manufacture of therapeutic products (e.g. cell therapies, biologics, and small molecules). By

partnering with a CMO, cell therapy developers can unburden themselves from the costs and risks associated with establishing infrastructure, regulatory compliance, and manufacturing experience.

1.2 Manufacturing Challenges Unique to the Cell Therapy Industry and their Commercial Implications

Compared to existing therapeutic platforms, including mAbs and small molecules, cell therapies have a number of unique attributes that significantly impact the nature of their manufacturing strategies. Therapeutic cells must be formulated as live-cell preparations, they are not amendable to filter sterilization, and they must be stored and shipped in liquid nitrogen to ensure product integrity. The unique interdependency of cell therapy manufacturing and product quality is well noted and often expressed by the mantra: "the process is the product (Mason and Hoare, 2007). " However, while the relationship between a product and its manufacturing process is widely understood, it is also important to appreciate the interdependency of a selected manufacturing strategy and its commercial implications.

1.21 'Lessons from Predecessors:' Whole Cell vs. mAb Therapy Manufacturing

A number of comparisons, including commercial and manufacturing, have been made between the cell therapy and the mAb industries (Jones, 2012). An overview of fundamental manufacturing similarities and differences is provided

subsequently in this chapter as well in in a later chapter, "the history of the development of mAbs.".

Before discussing the various manufacturing paradigms and manufacturing challenges associated with cell-based products, it is useful to note the commercial implications of key cell therapy product attributes which can impact manufacturing [Table 1]. Donor sourcing (allogeneic vs. autologous), and fresh vs. cryopreserved, are two key features of cell-based products that significantly impact the manufacture of these products. Fully understanding the challenges presented by a particular type of cell-based product will facilitate the selection of an optimal manufacturing process from both a bioprocessing and commercial perspective.

<Table 1.0 – see rear of doc>

1.22 Patient-specific (Autologous) vs Universal Donor (Allogeneic)

Allogeneic = Universal Donor

Universal Donor: "Where donor and recipient are different individuals." This characteristic is the concept behind the development of allogeneic products that model a conventional biomanufacturing approach, akin to non-cell-based pharmaceuticals (BSI, 2006). Cells are grown aseptically at a large scale, the product is subsequently harvested, washed, concentrated, formulated, filled in vials and stored until the product is tested for quality and released for

distribution. As bioprocessing innovations are being adopted, new technologies are enabling the large-scale culture and processing of cells, a paradigm that has allowed the industrial scale production of allogeneic cell-based products to realize the benefits of economies of scale. In addition, QA/QC evaluations and their associated costs can beh applied on a per-batch basis, thus a larger batch size can drastically reduce the testing costs per unit dose.

Though the production of allogeneic products is more akin to conventional pharmaceutical manufacture and business models, from a regulatory and risk management perspective they can be more challenging than their autologous counterparts, as a greater consistency in product attributes is expected (Brandenberger et al., 2011). These products present immunological challenges for the patient (recipient), as the donor and recipient are often not immuno-matched. This can lead to complications associated with immune rejection, and in the worst case scenarios, graft versus host disease (GvHD). However, as the majority of allogeneic products are derived from mesenchymal stromal cells (MSCs) they are, by their inherent (and often therapeutic) nature, immune suppressive. These cells are often indicated for their ability to dampen the recipient's immune response, thus the chance of the patient mounting a response to these products is real, yet extremely remote (Fairchild, 2010, Shi et al., 2010, English et al., 2013).

Autologous = Patient Specific

An autologous product can be defined as a product "Where donor and recipient are the same individual." (BSI, 2006). Autologous cells offer a number of benefits to patients, including the potential for personalized medicine(s). Patient material (usually blood, bone marrow, or tumor tissue) is brought into the manufacturing facility. The product cells may be extracted and/or expanded and/or enhanced, and then re-administered to the same patient. In addition to self-to-self, these products adhering to this manufacturing paradigm can also be patient-specific, meaning that the donor is not "self" but rather the material (e.g. cord blood) is from a histocompatible donor. These "patient-matched" products are processed in a similar manner to autologous products, i.e. a single product is intended for a single patient, and are therefore grouped together as "patient-specific" products.

Patient specific therapies originated as point-of-care blood products, the basic principle being that a tissue/blood sample is taken, separated in order to isolate a target cell type, and re-administered into the target patient. For this type of procedure, the industrial step consists of separation, which is often conducted with commercially available equipment. In this basic example, the cells may be classified by regulatory agencies as having been minimally manipulated. However, for some therapeutics, the cell dose needed may be greater than can be obtained from a single isolation procedure. As a result, a culture expansion step becomes required. In order to maximize space efficiency it may be necessary for multiple lots originating from different patients to be manufactured

in the same manufacturing space. In this case, great care must be taken to ensure that cross contamination between patient lots does not occur. Wireless tracking of all raw materials, equipment, and consumables for each patient lot will be vital for minimizing the risk of cross contamination between lots (Brindley, 2013).

From a biomanufacturing perspective, autologous therapies bring new challenges compared to their allogeneic counterparts as these products require a 'scale out' rather than scale-up approach. Since these products typically involve the manufacture of a single patient-specific dose per lot, the percentage of product and cost of quality testing and release of the product tends to be orders of magnitude greater than the testing associated with allogeneic products, where one lot produces many hundreds of doses. For instance, Dendreon has an autologous dendritic cell product for the treatment of prostate cancer in which each dose is derived individually . In fact, the scale-out of autologous cell-based products represents a radically different manufacturing and testing paradigm than previously experienced, as the testing required per batch remains similar, but the number of batches greatly increases [Figure 1.1] (Rowley, 2011). Therefore, testing costs represent a significant proportion of the cost of manufacture and thus selling price of an autologous product (Jones et al., 2012).

<Figure 1.1 – see rear of doc>

A crucial aspect of the manufacture of patient specific therapies is segregation of product lots. Thus, the culture equipment required typically consists of cell flasks or cell factories for adherent cells, or sterile bags for non-adherent cells, which should be meticulously tracked and labelled to minimize the risk of breach in chain of custody Therefore, manufacturers of autologous products will need to have quality systems in place that ensure good product segregation (FDA, 2008b).

<Figure 1.2 – see rear of doc>

1.23 Fresh Versus Cryopreserved Product Doses

Fresh

The designation of "fresh" cell product is typically applied to products that are administered within 48 hours of the completion of manufacturing. The major benefit for the patient conferred by this type of product is that the cells are likely of very good health and viability. From a manufacturing standpoint, fresh products present a logistical challenge, as they should be transported from the manufacturing facility to the patient in a timely manner and without temperature fluctuations. Furthermore, these products, often autologous, are typically derived from limited starting material and there is an incentive to administer as much of the product back to the patient as possible. This does not leave much material

porcine trypsin. Alternatives to xenogenic trypsin (such as recombinant or plant-derived trypsin) are also available, and gaining traction in the field (Manira et al., 2013). Care must be taken when using trypsin as a processing agent; prolonged exposure to a digestive enzyme such as trypsin can damage and/or kill the cells. Furthermore, once harvested, the cells must typically be washed in order to reduce the presence of trypsin in the final product to below allowable levels (FDA, 2008b).

The basis for many adherent cell-based therapies is a planar surface, and various technologies have evolved from this principle (Smalley et al., 2006, Chen et al., 2013). The smallest of these manufacturing devices is the T-flask: it is a small vessel with a defined area for cell growth that is commonly used in laboratory-based research. It is not applicable to the manufacture of therapeutics as it is labor intensive, generates only small quantities of cells and requires open system processing. The smallest vessel that enables closed system processing is the cell factory, which is a single vessel containing several layers of a cell culture surface. Cell factories of various sizes are used, starting with processing units as small as one layer and as large as up to 40 layers per culture vessel (632 cm2/layer for cell factories and 636 cm2/layer for cell stacks). Each 40 layer cell factory provides a significant growth area of more than 25,000cm^2, however, at this scale other limitations arise. For example, the protocol may dictate the need for active gassing to ensure a homogeneous environment within the vessel. In addition, the substantial weight of a 40-layer cell factory filled with cells and

media requires specialized automation equipment to operate. To overcome this, the Automatic Cell Factory Manipulator (ACFM) (Nunc, Rochester, NY, USA) has been developed to provide a robot programmed to perform all necessary cell culture operations, including inverting the system to remove all media. The ACFM can process simultaneously up to four 40-layer cell factories; however, this piece of equipment requires a significant amount of floor space to operate.

Hyperdense platforms constitute another manufacturing solution enabling larger surface areas. Advances in the role of materials in cell culture have facilitated the implementation of gas-permeable plastics, which remove the need for airspace above each layer, thereby enabling the vessel to be completely filled with media; more layers in the same footprint (Titus et al., 2010). As a result, triple the number of layers, and subsequently 3 times the surface area available for growth, can be achieved in the same volume as a conventional cell stack or factory. These 'hyperstacked' vessels start at 12 layers, with a slightly smaller footprint than a 10 layer cell factory, and can be scaled up to 120 layers using the same volume of media (6 liters) as a 40-layer cell factory (www.corning.com). Additionally, the manipulation of 120 layers also may be automated using the newer versions of the ACFM.

Other culture vessels based on planar technologies include the Cell Cube™ (Corning, NY, USA) and the Xpansion™ bioreactor (ATMI, Danbury, CT, USA). The Cell Cube™ operates with growth plates positioned perpendicularly to those found in cell factories. Each unit comprises either 10 or 25 layers and is continuously

perfused with media. Up to four units can be stacked to save floor space, representing a maximum number of 100 layers. What is also unique about this technology is that cells are able to grow on either side of a plate, thus effectively doubling the available surface area. However, cell seeding in this system is technically more challenging; as a result, it can be difficult to achieve consistent seeding densities across each layer.

On the other hand, Xpansion™ (ATMI, Danbury, CT, USA) is a cylindrical multiplate bioreactor. The bioreactor is actively gassed and media is perfused; this design enables a small headspace above each plate of just 1.6mm (compared to approximately 15mm for a cell factory). Each unit is fitted with disposable sensors that link to a controller, which is able to monitor and adjust crucial cell culture parameters including pH, temperature and dissolved oxygen tension, as well as other variables such as agitation rate and media flow rate. The Xpansion™ system is available in 3 sizes: 10-, 50- and 180–layers. It is recommended that the 10- and 50-layers be used as a seed train to the larger reactor. However, the system enables one to mimic the microenvironment of other planar systems, and is sufficient to generate enough cells to seed the 180-layer in a more cost effective manner.

Aas the limits of planar culture are being reached, other options need to be explored, including hollow fiber technologies as found in the Quantum system (Terumo BCT, Lakewood, CO, USA). The Quantum system is a functionally closed, automated hollow fiber bioreactor system designed to grow both adherent and

suspension cells. It essentially acts as a 'black box', where seed cells are attached via a sterile welded bag, and expanded cells are collected in a second sterile welded bag. As the system is fully automated, the labour requirements are minimal (principally consisting of setting up the system and attaching the sterile bags). When properly operated, the rate of contamination is very low (BCT, 2012). However, the system is expensive and can only handle one sterile hollow fiber cartridge at a time, thus the only way to increase scale and throughput is to add more units.

Another system for cultivating adherent-cells that is not based on planar culture is based on the microcarrier technology. Microcarriers are water-insoluble polymers to which adherent cell types attach and are able to grow to high densities (Martin et al., 2011, Oh et al., 2009, Phillips et al., 2008, Tatard et al., 2005). They are used in various sizes and types of vessel and have the potential to provide an extremely large surface area for culture (hypothetically thousands of liters of microcarrier-laden cells are possible, though in practice this has not yet been achieved). Several different types exist with different applications; for example carriers with an adherent surface and a solid core tend to be used more in batch culture, whereas macroporous fully adherent carriers are more suited to perfusion culture. Microcarriers are typically composed of polystyrene or dextran and may be coated with compounds such as proteins, gelatin, or silica glass to facilitate cell binding (Inc., 2013, Sciences, 2012). A common microcarrier system currently used in the culture of pluripotent cells is matrix-coated beads in

a Wave bioreactor (Åkerström, 2009) (for more information on WAVE please see (Healthcare, 2012)). Microcarriers are easily passaged via the removal of microcarriers from the culture media and the addition of fresh microcarriers, to which cells have been shown to migrate. It is also possible to differentiate cells that are still bound to the microcarriers. However, technical problems have been encountered with this system, including the efficient harvesting of the cells and subsequent removal and purification from the spent microcarriers (Zweigerdt et al., 2011, Timmins et al., 2012). Particularly, product yield and viability can be compromised if the process to release cells from the microcarriers harms the cells or is incomplete. Additionally, carry-over of micricarriers into the final product is a common concern since the purity of the final product would not be guaranteed and those residual molecules could pose safety risk.

Non-Adherent (Suspension) Cell Cultures

Non-adherent cells, including hematopoietic stem cells, do not stick to a surface but instead grow in suspension in the medium. Culture vessels for this cell type can be as simple as the bags used in blood collection. However, as the size of the bags increases, it is crucial that no air or nutrient gradients are created and that these parameters remain constant throughout the bag, such that no 'dead zones', hypoxic or nutrient-depleted areas, are not created, since such heterogeneities' would result in the production of a heterogeneous population. Homogeneity is typically achieved by incubating the cell culture bags on a device which supports movement of the bag in order to ensure that nutrients and air are consistently

redistributed throughout the vessel. Alternatively, cells cultivated in suspension can be grown in spinner flasks or stirred tank bioreactors; vessels in which a moving part (often called an impeller) keeps the culture moving to ensure continuous exposure to nutrients and adequate gas exchange for the cells in culture. In these latter vessels, large volumes can be incubated, though there is a risk that the impeller that is used to stir the contents may damage the cells.

It is worth noting that while the technologies discussed above are not yet widely implemented, they nevertheless constitute off-the-shelf options. More recently, companies such as Invetech (Melbourne, Australia) and The Technology Partnership (Royston, Cambridge, UK) offer bespoke mechanisms of automation and process improvement to meet the unique needs of individual cell therapy developers.

3.6 Current Downstream Manufacturing Technologies

The majority of downstream manufacturing technologies are based on those previously developed for processing blood or purifying proteins from a microbial fermentation mixture (Bailey and Ollis, 1986). The use of certain pieces of equipment is based on many variables such as product type or batch size; over the years of experience and as the number of product units has increased, these incremental changes have resulted in significant know-how and productivity gains (Patasseril et al. 2013). The most common downstream manufacturing technologies are described below.

The convention, in cell processing, has been to employ centrifugation as the basis for volume reduction and purification. For example, the Elutra® Cell Separation System (Terumo BCT Inc, Lakewood, CO, USA) is type of processing equipment used to separate cell populations into multiple fractions by size and density based on 'counter-flow centrifugal elutriation' (Pattasseril et al. 2013). This functionally closed system enables cell enrichment, depletion, concentration and washing. This technology can be valuable for cells grown in suspension and on a fairly small scale; it is typically used for patient-specific products. Similarly, the Cell Saver® (Haemonetics, Braintree, MA, USA) was originally designed to return lost blood to patients during surgery. It is thus useful for manufacturing operations at the patient-specific scale. This very well established system has thus been applied to cell therapy purification, particularly of blood products, both remotely and at the point of care.

For large-scale cell processing, other centrifugation-based systems are more appropriate. For example, the kSep® (KBI Biopharma Inc. Durham, NC, USA) is a single-use closed centrifugation system that has been designed to impart low shear onto cells during processing. The kSep® can be used to wash and concentrate large volumes, processing volumes of up to 720L/hour of cells in suspension (Systems, 2012). Due to its relatively larger scale, kSep® tends to be most applicable for allogeneic products though it is amenable to some autologous cell processing as well. It can also be used for performing perfusion and to ensure retention of microcarriers. Likewise, the Centritech® Cell II (Centritech, Cuyahoga

Falls, OH, USA) is based on a similar concept, in that it is a single use centrifugation platform, which is also applicable to perfusion culture.

As the industry develops, alternatives to cell processing by centrifugation are beginning to emerge. Examples of such techniques include tangential flow filtration, where cells and media flow parallel to a filter in order to concentrate and purify the product (Pattasseril et al. 2013).

3.7 Quality Systems

Quality systems is a term that describes the oversight of the methods, facilities, and controls instituted in the design, manufacture, and distribution of clinical material intended for use in humans. Quality assurance relates to governance of the quality system: the procedures and controls in place to safely and effectively manufacture and test products intended for human use (FDA, Revised 2012). Regulatory oversight necessitates quality systems to ensure and demonstrate that a robust and reproducible production process has been implemented, and thus that the commercial product is consistent in terms of safety and efficacy to the product that has been validated during the clinical trials (FDA, 2002).

3.71 Quality Control of Cell-Based Products

During quality control testing, the product quality is assessed at several stages throughout the process by analysing critical attributes; these are established following current good manufacturing practice guidance (cGMP) (FDA, 2008b):

- *Identity - To confirm that the final product contains the intended cellular and non-cellular components*
- *Potency - To confirm that the product possesses the inherent or induced biological function(s) that is relevant to treating the intended clinical indication*
- *Purity - To confirm that the product does not contain undesired components, such as contaminating cell types or residual process reagents*
- *Safety - To confirm that the product is not contaminated with microbes or adventitious agents, and, if appropriate, does not have tumorigenic potential*

These characteristics can be translated into end product release criteria as both the manufacturing process and the assays themselves mature. Often more than one assay is used for each attribute. To this end, a testing matrix is typically recommended to ensure that all adequate parameters are tested prior to final release of production lots (Carmen et al. 2012).

3.72 Quality Assurance

The quality of a process relates to how robust, reproducible, and compliant it is relative to cGMP standards. Quality assurance is used as a tool to ensure the safety and efficacy of methods, facilities, and controls implemented in the manufacture (and all processes therein eg raw material testing, packaging) and distribution of product intended for human use (FDA, Revised 2012). Notably, from raw material to final product dose, the manufacture of clinical grade products should comply with cGMP regulations. Furthermore, due to the delicate nature of cell therapy products, the need for validating the cold storage chain by which a product is transported, delivered, and stored at the point of care is crucial to help ensure a safe and efficacious product.

Validation can be achieved through several means, including temperature mapping of both culture conditions and transport conditions, as well as by demonstrating operational and performance qualification. Supervising in-process monitoring conditions and operational limits of key variables are aspects of the quality monitoring process. Other quality assurance measures include indirect methods for improving the industrial robustness of the manufacturing process, including staff training and appropriate gowning validations. Finally, the use of electronic 'tagging' and labelling of products in manufacturing represent forward-looking practice in bioprocessing. This will be particularly important for patient-specific therapies.

4.0 PERSPECTIVES

In this chapter, a number of unique characteristics of cell therapy products have been discussed, including manufacturing processes and challenges posed by their commercialization. As a sector that is still emerging, industry best practices and platform technologies have yet to be firmly established. Until it finally matures, the cell therapy industry of today will undoubtedly undergo numerous changes, particularly gained through the experience curve.

As new processing technologies evolve, it is likely that industrial scale platform biomanufacturing processes will emerge, thereby reducing the process and commercial risks of cell-based products, as well as reducing their production costs. Presently, however, the majority of cell therapy products are still in an early stage clinical setting, where the focus is on translational medicine to accelerate the development of products to meet urgent unmet medical needs, rather than optimizing the long-term commercial viability of the new products.

Historically, cost of goods (COGs) have been high for the first generation of products developed in a new industry. Furthermore, as cell-based products must be maintained and delivered as live cells, the costs associated with manufacturing and delivering these products will likely remain high relative to existing biologics, including monoclonal antibodies.

As the portfolio of commercialized cell therapy increases, and as manufacturing costs decrease, the cell therapy industry is likely to be able to support more chronic indications, particularly using allogeneic products. Until

then, the new cell therapies that enter the market are likely to initially primarily address acute indications for which no appropriate alternative exist. Once more cell-based products enter the market, a broader base of patients should have access to the new therapies as their production costs decrease; this may be particularly true for products that are intended to treat chronic diseases as these will need to be less expensive, especially in instances where patients will require multiple doses. Process developers and contract manufacturing organizations thus hold a critical piece of the regenerative medicine development puzzle.

The optimal path to success is to fully understand the manufacturing needs for developing a live, cell-based product. Developers should understand the logistical issues associated with autologous versus allogeneic products, those associated with fresh versus cryopreserved product, or those associated with adherent cell culturing versus suspension cell culturing. Notably, none of these product types is superior to the others, as each exhibits a specific set of positive and negative attributes. Crucially, the better characterized a given product, the more effectively product developers can identify and manage product risks, thus maximizing the probability of commercial success and delivery of therapeutic products to the market.

The goal of the pioneers of the global cell therapy industry is to develop solutions that are affordable for the greatest numbers - to improve healthcare outcomes for patients and to deliver a fair return on innovation for all

stakeholders, including academia, investors, industry, and payers. The establishment of best biomanufacturing practices is a mission critical step towards the achievement of this transformational goal.

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undergo rigorous assessment prior to the generation of MCB. The relationship between MCBs and WCBs is illustrated in Figure 3.0.

In order to meet the manufacturing demands of this system, a seed train is often used to scale up from the number of cells in a WCB vial to the number of cells required for commercial production. This process has been in routine use to produce biologics, and its usefulness to support quality and reproducibility has been well documented (Bailey and Ollis, 1986)

<Figure 3.0 – please see rear of doc>

3.4 Current Upstream Manufacturing Technologies

3.41 Adherent vs. Non-Adherent (Suspension) Cell Culture

Adherent Cell Cultures

Adherent cells, such as MSC, bind to a solid surface such as tissue culture-treated plastic. This characteristic is convenient because it enables culture media to be exchanged without disturbing the cells. In some cases, the growth surface needs to be treated or coated with a matrix (such as gelatin or fibronectin) to facilitate cell adhesion(Brindley et al., 2011). Cells can be grown on large surfaces in plates, or on microcarriers in bioreactors (Park et al., 2013, Yuan et al., 2012). When harvesting cells, chemical or mechanical forces are required to liberate the cells from whatever they are bound to (Mulhall et al., 2011). Typically enzymatic removal of cells from a plastic surface is performed using bovine or

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Acknowledgements

We wish to acknowledge Jon Rowley (Independent Consultant), Christopher Bravery (Consulting on Advanced Biological Ltd.), and Wouter Van't Hof (Cleveland Cord Blood Center) for thoughtful discussions on the importance of the minimum effective dose.

FIGURES AND TABLES TO INSERT

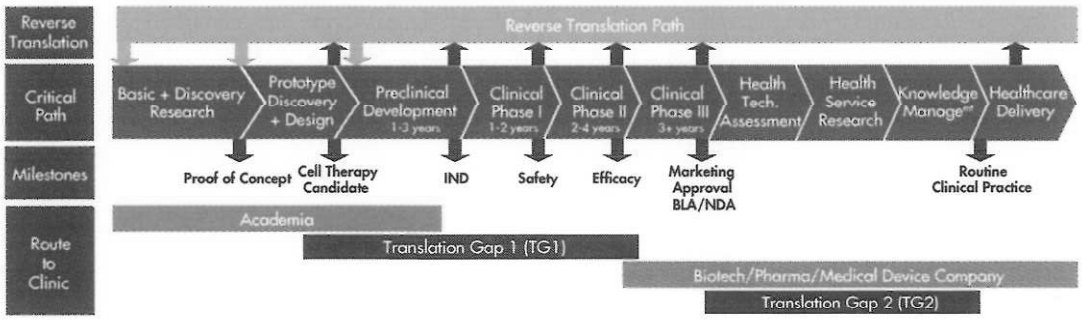

Figure 1.0: Cell Therapy Development Pathway (Mason and Manzotti, 2010b) [Has a formal permission to republish been obtained?]

In this figure is depicted the typical clinical development pathway, from laboratory bench to market, that most therapeutic products will take on the path to commercialization. The figure also highlights 'translation gaps'; key points in the cell therapy development pathway that are particularly resource-constrained in terms of both financial and intellectual capital.

	mAb	***Cell Therapy***
Start and End Points	*Start Point:* Cells from cell bank. *End Point:* Protein-based product, ready (or minimal processing required) for intravenous infusion	*Start Point:-* Allogeneic therapy: Master cell bank. Autologous therapy: Patient material *End Point:-* *"Live" cell products: ready for injection or implantation into the patient.* *Cryopreserved products may require post-thawing processing prior to administration to the patient*
Product	*Dose:* Multiple doses over long time period. *Product Nature:* labile, inert *Heterogeneity:* various glycoforms may be present.	*Dose:* One to few doses may be required *Product Nature:* Live, dynamic and responsive to stimuli. *Heterogeneity:* Various cell types may be present
Single Use Components	Single use components for seed stages; but stainless steel at large scale.	Single use components are dominant.
Process	*Process Automation:* Largely Automated *Platform Process:* Generic processes dominate *Process Delays:* Little impact, Stable product	*Process Automation:* Partial automation: labor intensive. *Platform Process:* Product-specific processes in use. *Process Delays:* High Impact, dynamic product.
Key Sources	Product titers vary with cell	Donor variability impacts allogeneic

of Variability	line.	product (master cell banks) as wel as autologous products (patient starting materials)
Cell Culture and Media	Defined, animal-free media.	Complex media containing supplements, many contain animal-derived raw materials
Recovery and Purification	Dominated by chromatography operations.	Volume Reduction and Washing, open processing for small-scale, closed processing for large-scale
Transportation and Storage	Can be frozen and stored for several months.	Cryopreserved or fresh. Fresh products have a limited shelf life

The Table needs to be reformatted

Table 1.0: 'Key Cell Therapy Manufacturing Decisions'

Presented in this table is a comparison of various typical product characteristics of monoclonal antibodies (mAbs, a segment of the pharmaceuticals that are designated as "biologics") and cell-based products. The advent of cost-effective and industrially robust manufacturing processes for biologics has helped to set the precedent for some of the unique attributes associated with cell-based products. Cell-based products are most similar to biologics, when compared to more traditional therapies such as small molecules.

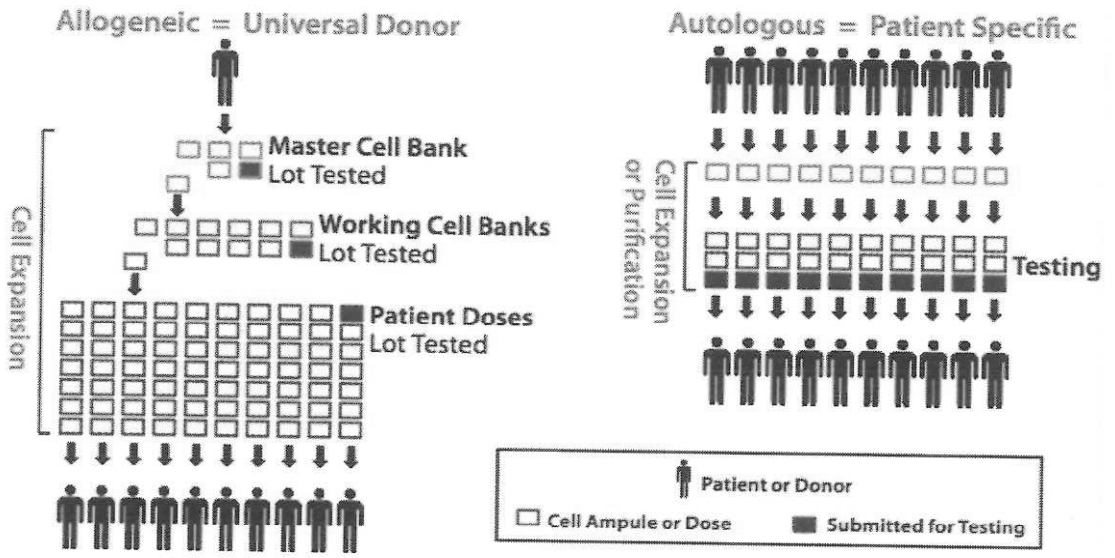

Figure 1.1: 'Testing Challenges in Cell Therapy Manufacture' (Brandenberger, 2011).

A simple depiction of the major differences between the manufacturing and testing paradigms associated with allogeneic and autologous cell-based therapies. Allogeneic products are typically manufactured in a "scale-up" approach, similar to that of traditional therapeutic products. In the scale-up approach one large batch/lot is manufactured from which multiple doses will derive enabling treatment of many patients from one sample of starting material. Likewise, samples reserved for testing represent a small fraction of the total manufactured material. Autologous products employ a "scale-out" approach in which multiple lots are generated, with each lot yielding one (or a few) doses intended for one patient. This indicates that a greater percentage of the autologous products will be dedicated to testing, and that a greater number of lots will be manufactured.

Therefore, a greater number of Quality Assurance and Quality Control tests will need to be run for a particular product. Acknowledgement(s): This figure is reprinted with permission from BioProcess International, March 2011, pages 30-37.

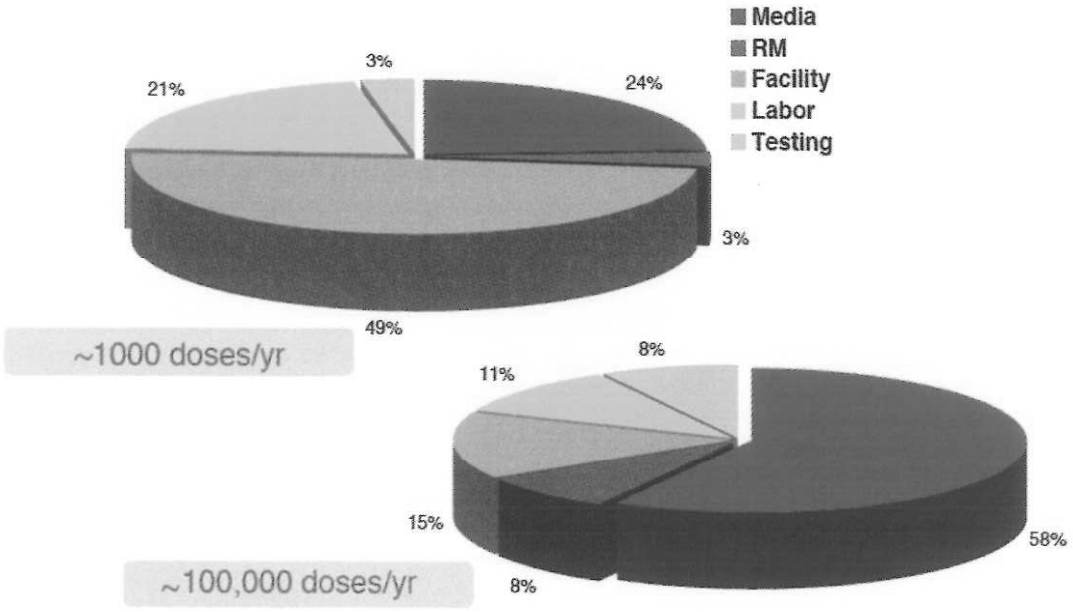

Figure 1.2: The impact of process scale on cost bottlenecks

The pie chart in the top of the figure depicts the cost breakdown of a typical allogeneic cell-based product in phase II, the phase in which most cell therapy products currently exist. The bottom pie chart represents an estimate of cost for the same cell therapy product when manufactured at commercial scale. In clinical development, the costs to manufacture of an allogeneic product are dominated by the costs associated with using and maintaining a cGMP facility. At commercial scale, the costs of the cGMP facility become dwarfed by media and growth factors, raw materials used in the manufacture of cell-based products.

Serum-dependent	Serum-free
Limited supply	Readily producible at scale using GMP manufacturing
Undefined, high batch-to-batch variability	Defined, reproducible material
Potential for pathogen transmission	Reduced potential for pathogen transmission
Animal welfare considerations	Animal-free
Current material of first choice for basic research due to knowledge base	Transition to serum-free may require resource-intensive optimization
Provides growth factors and hormones, lipids, trace elements and other nutrients	Requires the addition of growth factors, hormones, lipids etc
Provides attachment factors (fibronectin, laminin)	May require the addition of attachment factors for culturing on surfaces
Intrinsically contains differentiation factors	Easier control of differentiation by the addition (or not) of appropriate factors

Table 2.0: A comparison of serum-dependent and serum-free culture systems.

In this his Table, a summary of some of the key characteristics associated with serum-dependent and serum-free (also known as chemically-defined) culture systems is provided. Most cell-based products employ serum-dependent culture systems. However, the use of animal serum in the processing of cGMP-grade products presents unique challenges, including the risk of zoonotic diseases, as well as supply chain risks. Nonetheless, the use of chemically-defined media also presents challenges: these media are usually more expensive, and require a thorough characterization of the growth requirements of the cell-based product for which it is intended.

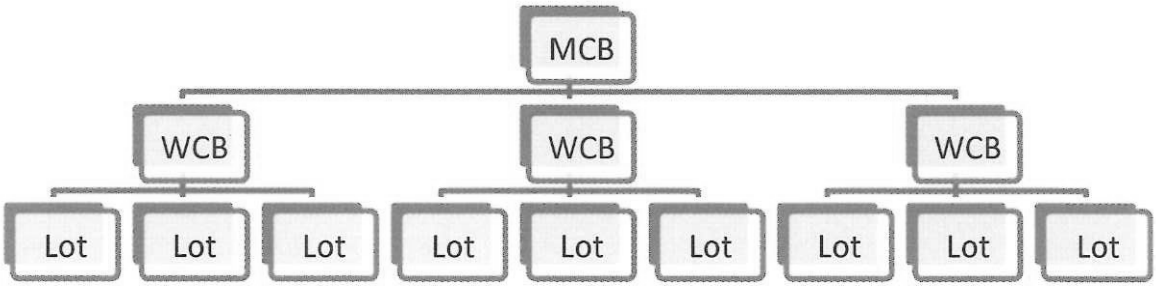

Figure 3.0: The relationship between working and master cell banks in cell therapy manufacture. [The top of the Figure needs some fixing as some lines are not straight]

A typical manufacturing cell banking strategy for allogeneic cell processing is presented here. The initial cells isolated from an appropriate clinical sample are expanded, formulated, filled, and cryopreserved as a master cell bank (MCB). The MCB is subsequently subjected to significant sterility tests (including adventitious viruses), purity, and activity. From each vial of MCB, cells may be expanded, formulated, filled and cryopreserved in order to generate working cell banks (WCB). One (or more) vial of the WCB can be thawed and expanded as necessary for manufacturing one product lot.

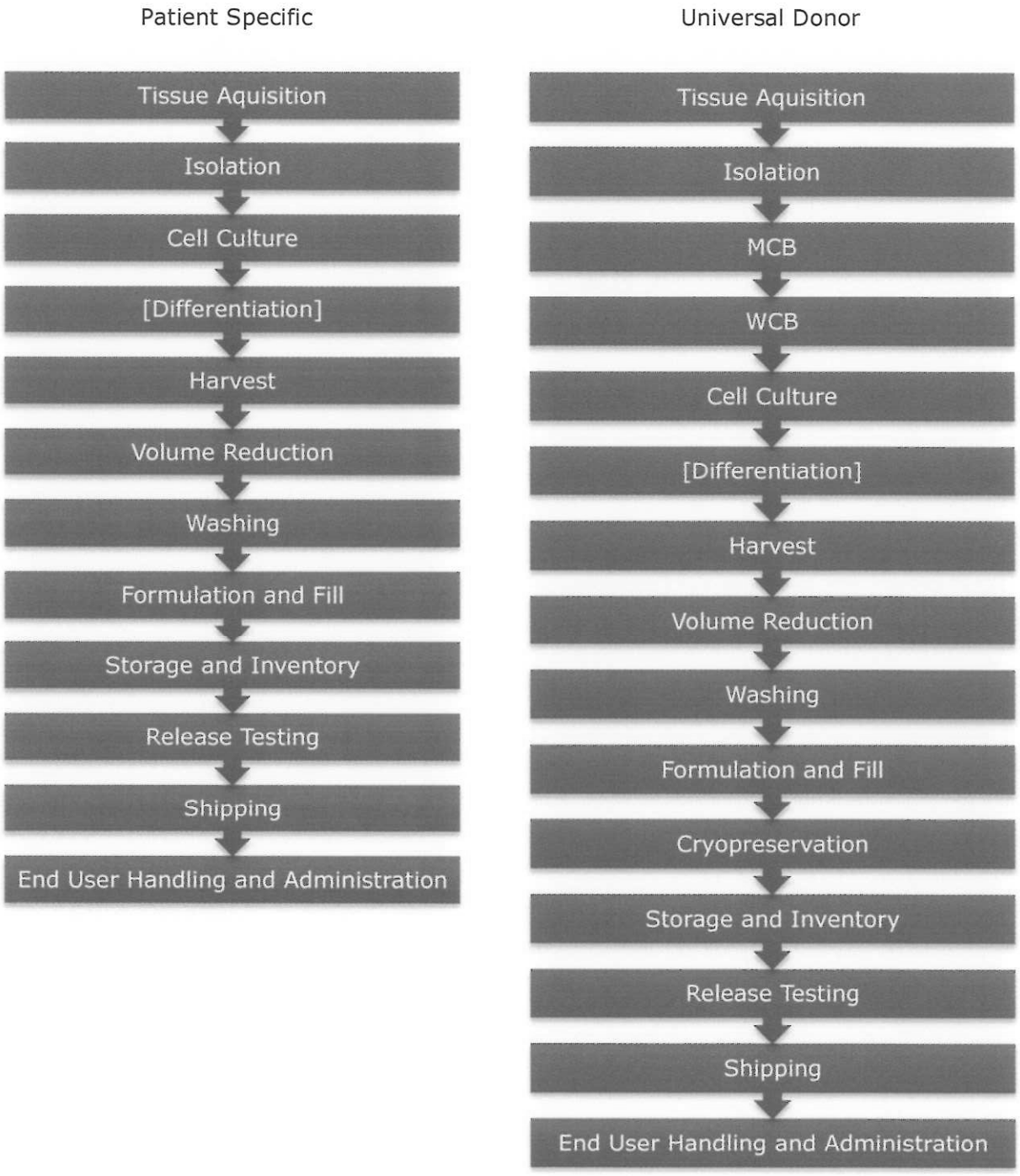

Figure 2.0. Typical processing steps for the manufacture of patient specific and universal donor derived cell therapies (applicable to both adherent and non-adherent cell types).

Cell Therapy Biomanufacturing Risk Management

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Introduction, overview, and defining risk

In virtually any modern industry informed management of risk (and associated uncertainty) plays a central role in the successful production of a product or service (Haimes, 2011; Pons, 2010). The increasing complexity, decentralization and heterogeneity of modern industrial (bio)processes, alongside growing demands for quality assurance and operational throughput, expose such operations to a substantial degree of outcome risk (Haimes, 2011; Miller, 1992; Pons, 2010). This reality is especially emblematic of biopharmaceutical manufacturing, in which lengthy, intricate, and dynamic process chains can often define the quality of the end product (Ratcliffe et al., 2011, PMID21852279). Without leveraging sophisticated risk analysis and management tools to manage these process pathways, biomanufacturers thus face the prospect of (potentially elevated) risks and uncertainties along developmental, production, regulatory, and economic dimensions.

Understanding such risk management methods requires first a definition of what exactly constitutes risk. Described here, as per the ISO (International Organization for Standardization) Standard, is 'the negative role of chance on objectives within a systemic process' (2009), risks can pose a threat to a manufacturer in a manner that can appear highly unpredictable. Notably, risks are distinct from hazards, the latter being defined as the actual sources of these negative effects that are triggered by risk (Figure I) (Waring and Glendon, 1998). Risk is also formally distinct from uncertainty, for whereas 'risk' is composed of known unknowns, 'uncertainty' deals with unknown unknowns, that is outcomes that are intrinsically unpredictable (Miller, 1992). Because of this distinction, risk, unlike uncertainty, is a threat that can be predicted and ultimately managed. The discipline of risk management aims to equip manufacturers with the tools, frameworks, and techniques necessary to optimize strategies for successfully dealing with and mitigating risk (McNeil et al., 2010; Waring and Glendon, 1998). Appropriate application of risk management principles allows industries to turn risks into opportunities, meaning that understanding and successfully managing risk can prove the decisive factor between industrial success and failure. Risk management therefore is experiencing a strong period of growth and increasingly attracting the interest of executives from across a range of industries (Dionne, 2013).

[insert Fig.1]

Initially, risk management emerged as a discipline following the Industrial Revolution of the 1800s, in response to the growth in both scope and magnitude of hazards posed by industrial-scale technologies (Bernstein and Bernstein Peter, 1996; Crockford, 1982; Vesper, 2006). Owing its roots to the early work of statisticians during the Renaissance, modern risk management began to take shape following World War II, coinciding with the peak of American manufacturing during the post-war industrial boom. Though the field began as a largely theoretical discipline, with a particular emphasis on financial and insurance management (i.e., "pure risks"), it has since evolved to incorporate a more applied set of methodologies (Bernstein and Bernstein Peter, 1996). A number of successful applications of risk management techniques in a wide variety of industries are described in Table I.

Today, risk management encompasses an array of analytical, optimization, and modeling techniques including Failure Mode and Effects Analysis (FMEA), Preliminary Hazard Analysis (PHA), Pareto Analysis, Multicriteria Decision Analysis (MCDA), Design of Experiments (DoE), Monte Carlo Analysis, and Quality by Design (QbD), among other methods (Ericson, 2005; van Leeuwen et al., 2009, PMID19640668; Mavris and Bandte, 1995; Nutt et al., 2010, PMID21036393; Tummala and Schoenherr, 2011; Yu, 2008, PMID18185986). These techniques range from qualitative to quantitative in scope, and offer a distinct set of advantages (strategic, operational, and analytical) for conceiving of, managing, and optimizing for risk. In practice, successful risk management involves a combinatorial application of such techniques, as tailored to the industry, product, and process at hand (Pons, 2010).

[insert table I]

Despite the clear abundance of successful applications of risk management in a variety of industries, the discipline remains under utilized for a number of manufacturing paradigms, including cell therapy. A rapidly advancing field, cell therapy involves the administration of living cellular material for therapeutic benefit (Jing et al., 2013; Mason et

historically remained limited. This is in part because of a lack of understanding of the key critical process parameters, product critical quality attributes (CQAs), and process analytical technologies necessary to drive clinical-stage quality increases in biomanufacturing (Halme and Kessler, 2006, PMID17050899; Kessler et al., 1993, PMID8377782). Despite this, risk management methods gain increasing significance as biologics become ever-more vital diagnostic and therapeutic tools, and the need to enable scaling of these technologies becomes critical (Mason et al., 2011, PMID21548728). Recent advances in the risk management literature have allowed for deeper insights into how these optimization techniques might be successfully applied to cell therapy.

For this reason, in this chapter, we outline existing work on this "unsolved" problem to answer a central question: how can risk management principles be effectively applied for cell therapy biomanufacturing? This question is explored in stages that are defined by their position along the bench-to-bedside translational product development pathway. Primarily, we examine risks found in manufacturing itself, through inputs and the process chain. Secondly, we outline commercial risks facing cell therapy manufacturers, including those in the marketplace alongside those derived from regulatory pressures. We also explore clinical risks, both those posed to the patient and to society at large. At each stage, we discuss the principal techniques available to manage, mitigate, and optimize these core risks (Figure II).

[insert Fig. 2]

Manufacturing risk

Manufacturing risks form the core of a cell therapy manufacturer's risk profile, and can ultimately can be tied back to the principal commercial challenges facing cell therapy products: assurance of a high quality therapeutic, consistency in finished product output, avoidance of contamination, and cost-effective scaling of production (Ratcliffe et al., 2011, PMID21852279). As product and process are effectively equivalent for cell therapy, risks within the manufacturing sphere are often derived from or closely interlocked with corresponding risks in the marketplace (Davie et al.). Risk management, when grounded by

al., 2011, PMID21548728). Cell therapy encompasses a broad range of cell and tissue types, processing techniques, treatment methods and disease applications. Three broad categories can be identified with regard to donor type: autologous (where cells are harvested and administered to the same individual), allogeneic (where the donor and recipient are genetically different), and xenogenic (cells are obtained from another species) (Brandenberger et al., 2011; Brindley et al., 2013; Kirouac and Zandstra, 2008, PMID18940729). Activity in therapeutic xenogenic approaches has diminished over the last decade in accordance with the advancement of human cell-based technologies (Edge et al., 1998, PMID9853581). In general, cell therapies can be categorized into four main groups in terms of cell type: adult stem cells (such as mesenchymal and hematopoietic stem cells); cells derived from pluripotent stem cell sources (both embryonic stem cells and induced pluripotent stem cells), cells harvested from neonatal tissues (e.g. cord blood or placental tissue) and differentiated cell types harvested directly from a donor (e.g. T lymphocytes and fibroblasts). Cell therapies typically leverage three main mechanisms of action: 1) *cell replacement* in which the administered cells functionally compensate for diseased or damaged tissue; 2) *trophic effects* through juxtacrine, paracrine, and/or endocrine interactions with host cells to elicit endogenous repair and regeneration; and 3) *immunomodulation*, in which the administered cells regulate the immune response (Hentze et al., 2007, PMID17084475; Rayment and Williams, 2010, PMID20333747; Strong et al., 2009, PMID19231235). The range of cell types and proposed mechanisms of action highlights the diversity in cell therapy.

Risk management is a compelling, and increasingly critical, optimization tool for cell therapy and cell therapy manufacturing, which represents a novel therapeutic paradigm (Lopez et al., 2010, PMID20723148). Unlike traditional pharmaceutical drugs such as small molecules which can purified, extensively characterized and that demonstrate strong stability profiles, cell therapy involves a complex and dynamic living product (Brindley et al., 2013; Lopez et al., 2010, PMID20723148). Therefore, there exist inherent limitations in the ability to characterize the major physiochemical and functional parameters for cell therapies, and cell products have the potential to change in response to internal and external stimuli. Not only does this make manufacturing cell therapies at scale much more risk-sensitive, it opens up a number of unique challenges. For instance, while

pharmaceutical batches tend to be fairly stable and consistent across production lots, cell therapies can vary enormously in quality, consistency, and therefore presumably therapeutic potential between batches (Brindley et al., 2013; Herberts et al., 2011, PMID21418664; Rayment and Williams, 2010, PMID20333747). Nor are cell therapy products physicochemically static in the same way that pharmaceuticals typically are (Brindley et al.).

These complicating factors and their downstream risks are visible throughout a given cell therapy biomanufacturing process. Considering a hypothetical, generic bioprocessing pathway, along each step a challenging set of risks unique to cell therapy production emerge. For example, source material risks from donor tissue pose potential contamination risks which may compromise the long -term clinical and regulatory suitability of an allogeneic cell bank (Ratcliffe et al., 2011, PMID21852279). In a second example, the enriched or purified product may encounter the risk of low yields (Brindley et al., 2013; Davie et al.). In culturing cells *en masse*, it becomes challenging to maintain particular cellular phenotypes and culture conditions (e.g., changes in cytokine production); moreover, technologies that could enable sufficient in-process quality control may not currently exist (Davie et al.; Ratcliffe et al., 2011, PMID21852279; Ungrin et al., 2012, PMID22139975). Even after traversing the bioprocessing pathway, end user and post-manufacturing risks, such as during a surgical procedure, can ultimately damage the cell therapy product (Foley and Whitaker, 2012, PMID23197823; Hentze et al., 2007, PMID17084475; O'Cearbhaill et al., 2014; Strong et al., 2009, PMID19231235). These risks, outlined in full in Table II, represent just an illustrative subset of the many that plague the cell therapy bioprocess chain.

[insert Table II)

The prevalence of these risks throughout the cell therapy biomanufacturing pathway suggests that risk management methods are critical for development of this therapeutic class. However, while risk management techniques have been exploited successfully for pharmaceutical products, and are currently required by the FDA under GMP guidelines, the use of these methods in bioprocessing strategies for cell therapies has

rigorous science and when approached with an active consideration of both commercial and clinical contexts, allows for a proactive approach in isolating, controlling, and navigating these manufacturing hazards, thereby serving as a powerful tool for informed decision-making and management (Lopez et al., 2010, PMID20723148).

Risk management for cell therapy begins with optimal points along a production possibilities frontier, in which tradeoffs between process parameters and relevant production outputs are evaluated to find points for optimal outcomes. To illustrate, along any given bioprocessing chain for cell therapy, there may be an intrinsic tradeoff to be struck between cell proliferation, or yield, and cell homogeneity, or quality (Kirouac and Zandstra, 2008, PMID18940729). Pluripotent stem cells, as an example, readily form teratomas upon transplantation into animal models, making critical the need for stringent characterization and/or selection mechanisms in potential therapeutic applications to remove the risk of undifferentiated cells, which increases production costs (Herberts et al., 2011, PMID21418664; Kirouac and Zandstra, 2008, PMID18940729). These tradeoffs are especially challenging to manage given the array of manufacturing risks unique to cell therapy: donor source material variability, genetic heterogeneity, and the operator error incurred by manual tissue culture operations are all examples (Brandenberger et al., 2011; Brindley et al., 2013; Herberts et al., 2011, PMID21418664).

In effect, dealing with such tradeoffs through risk management amounts to multidimensional risk optimization, in which targeted product output qualities (yield, purity, functionality, regulatory compliance, sterility, consistency, and cost) are maximized by adjusting input parameters (source materials, reagents, process time, operation) (Kirouac and Zandstra, 2008, PMID18940729; Lopez et al., 2010, PMID20723148). This form of process design has already been extensively deployed in traditional pharamaceuticals to great effect, though its use in biomanufacturing thus far has remained limited, thereby constraining the productivity at-scale of cell therapy products (Kirouac and Zandstra, 2008, PMID18940729; Lopez et al., 2010, PMID20723148). Because the clinical product effectiveness of cell therapy is directly predicated on the process by which cells are produced, regulatory agencies have begun issuing a number of compliance guidelines for biomanufactured products to promote the use of risk management tools (2012). Building on its 2004 Process Analytical Technologies Initiative and 2005

Pharmaceutical Risk Management Guidelines, the US Food and Drug Administration has issued recent guidelines on current good manufacturing practice (cGMP) and chemistry, manufacturing, and controls (CMC) as they relate to biomanufactured products, including standards on cGMP-grade cell lines, flask controls, culture protocols, and raw material origin (Deal, 2009; Halme and Kessler, 2006, PMID17050899). Though compliance with cGMP is not required at preclinical stages, the close intertwining of product and process in cell therapy provides substantial disincentives for modifying the manufacturing process in downstream development (Baum et al., 2013).

Despite the well-documented diversity in cell therapy products, there exist a series of core risks along any generalized bioprocessing framework that must be dealt with by biomanufacturers. Here, we divide these risks into four broad categories that relate to the bioprocess chain: 1) input and source specifications; 2) the process pathway; 3) storage and distribution; and 4) testing and compliance. Primarily, risk management of any bioprocess chain and its compliance with regulatory guidelines must begin with a focus on input and source specifications. Initiating a source cell line that does not meet cGMP guidelines, or prompts any degree of risk around donor contamination (via pathogenic or xenogenic materials), could in some cases lead to downstream regulatory challenges and adverse clinical effects (Baum et al., 2013; Giancola et al., 2012, PMID23738304). Additionally, within the process pathway itself, incorporating precise feedback control to regulate key quality parameters, such as pO_2, pH, osmolarity, and shear stress of the culture fluid, is of tantamount importance (Kirouac and Zandstra, 2008, PMID18940729; Rodrigues et al., 2011, PMID21726624). These conditions must be fine-tuned throughout the key segments of the process chain: isolation, production, expansion, and selection. Improper regulation of parameters can create substantial bottlenecks in process scheduling, which can prove costly, escalate the risk of operator contamination, and increase process variability (Mandenius et al., 2009, PMID19418475). Furthermore, during storage and distribution, which can involve weeks of product maintenance, these precisely defined conditions must be kept constant, particularly for "fresh" products, despite "recreation risks"—including genetic selective pressure, external contamination, cell degradation, and improper storage and handling (Ährlund-Richter et al., 2009, PMID19058776). Inter-lot contamination, too, presents a substantial risk to the viability of

cell therapy during storage (Brindley et al., 2013). Lastly, rigorous assessments of testing and compliance must be leveraged to validate the product output. This is particularly important in managing risks inherent to data security (e.g. of patient-level clinical data), as well as of regulatory compliance (e.g. ensuring full product characterization though a clearly delineated potency assay) (Carmen et al., 2012, PMID22168500). A full description of generic process pathways for manufactured cell therapy products, in comparison to typical biological products, is depicted in Figures I and III.

In achieving these goals and standards, manufacturers can leverage the array of frameworks catalogued in the literature to manage manufacturing risk. Traditionally, manufacturing risk management involved iterating through numerous permutations of a processing pathway until a configuration could be obtained that offered sufficient quality at reasonable cost-effectiveness and product predictability. The high costs of this "brute force" approach have spurred the development of numerous statistical and data-driven techniques that reduce the need for large-scale trial-and-error. Perhaps the most notable of these is QbD (Rathore and Winkle, 2009, PMID19131992; Rouiller et al., 2012, PMID22426134; Zhang et al., 2014, PMID23860745). Already established in traditional pharmaceutical manufacturing, QbD can be applied towards improving end-stage cell therapy product quality through enhanced process understanding and by building quality into the biomanufacturing pathway (Awotwe-Otoo et al., 2012, PMID22944306; Zidan et al., 2007, PMID17169518). Specifically, QbD involves the variation of CQAs within a multivariate "design space" to yield critical process parameters that define end-stage cell therapy product quality (Rathore and Winkle, 2009, PMID19131992; Rouiller et al., 2012, PMID22426134; Zhang et al., 2014, PMID23860745). As an example, to reach targeted production yield within a QbD approach, statistical analysis through a multivariate analysis (MVA) would be performed on rearrangements of key product attributes like cell number to determine the optimal ranges for each CQA. The CQA rearrangements, in turn, would be set up beforehand through a statistical DoE approach, which enables controlled experimentation on how changes in each CQA affect the Target Product Profile (TPPs) (Eriksson, 2008; Rathore and Winkle, 2009, PMID19131992). This paradigm therefore enables a manufacturer to determine at the outset what processing steps are required to reach the desired cell therapy product state; whereas traditional cell therapy

biomanufacturing assesses risk retrospectively, QbD enables risk management on a prospective basis.

In practice, implementing a QbD paradigm in cell therapy biomanufacturing involves the use of process analytical technologies (PAT). PAT are systems that allow for streamlined formulation, analysis, and management of a biomanufacturing pathway through the use of statistical DoE, Monte Carlo simulation modeling, feedback loops, and real-time assay monitoring (Bakeev, 2010; Read et al., 2010, PMID19731253). These systems take many forms, with variations that come with competing sets of strengths and weaknesses across core purpose, cost, sensitivity and specificity, assay types, purity, and statistical techniques leveraged (Reid et al., 2013). Typically, determining an appropriate PAT to utilize within a QbD framework can be aided through the use of pre-process analytical risk assessments. Taking such forms as FMEA (which provides insight into various "breakpoints" in a process chain) and Pareto Analysis (which helps identify parameters comprise the bulk of manufacturing risk), these methods provide a systematic means for identifying, analyzing, and ranking potential risk parameters and associated hazards (van Leeuwen et al., 2009, PMID19640668; Zimmermann and Hentschel, 2011, PMID22293839). Though a number of PAT are available for pharmaceuticals, PAT designed for cell therapy remain limited, while increasing in number (Varadaraju et al., 2013).

Commercial risk

In commercial terms, cell therapy is an industry yet to reach commercial maturity (Table III). Since the regenerative potential of bone marrow transplantation was first successfully demonstrated, the field has generated an explosion of scientific, industrial, and investor interest, making the transition from a purely academic discipline to one with clear potential to generate both health and wealth benefits (Davie et al.; McCulloch and Till, 1960, PMID13858509; Muller-Sieburg et al., 1986, PMID2868799; Wu et al., 1967, PMID6033948). Today, cell therapy comprises a billion dollar industry that forms a fourth pillar of healthcare, in addition to the more established areas of small molecule pharmaceuticals, biologics and medical devices (Culme-Seymour et al., 2012, PMID22817619; Mason et al., 2011, PMID21548728). By virtue of its developmental lag

behind more established industry segments, regulatory policy in cell therapy has lagged behind technological development, with substantial restrictions placed on clinical product administration (Barclay, 2009, PMID19291840). There are however thousands of ongoing cell therapy clinical trials in the US alone (Ankrum et al., 2014, PMID24561556; Culme-Seymour et al., 2012, PMID22817619).

[Insert Table III]

Still, for biomanufacturers to successfully commercialize cell therapy products—to cross the infamous "Valley of Death" that has often stymied innovations—they must first grapple with a number of risks. These risks begin as early as the product development stage. Though public-private partnerships can provide considerable advantages in bringing a product to scale, such arrangements also multiply the bureaucratic roadblocks to manufacturing, and increase requirements for information disclosure (Allarakhia and Walsh, 2011; O'Connor, 2004). Alternative models of partnership and licensing also exist and are on the increase, including a number of translation centers (e.g. the UK's Cell Therapy Catapult (London, UK) or Canada's Center for Commercialization of Regenerative Medicine (Toronto, Canada)) (Brindley et al., 2013, PMID24304079; Williams, 2011, PMID21999264). Commercialization through partnership not only requires setting up some form of shared development order, disbursing responsibility, ownership, and profit-sharing of the product across multiple actors and institutions with varying aims, but also necessitates that clear agreements regarding intellectual property (IP) be established (O'Connor, 2004). Even with a product design and development strategy in hand, developers must weigh the advantages and disadvantages of the various industrial options available for full-scale production, including the choice to pursue a retrofitted plant or to construct an entirely new one. Whereas the latter is considerably more expensive and time-consuming, which can erode a manufacturer's competitive advantage in a marketplace, it can also help avoid the contamination risks posed by the former, and provide flexibility over the medium to long term as the cell therapy industry undergoes rapid evolution.

These development-stage risks are in addition to commercial risks, inherent to cellular therapies as a product category. Firstly, as described, cell therapies exhibit remarkable heterogeneity with respect to product type. Autologous therapies, for instance, present an entirely novel set of marketing and commercialization challenges, among other risks, as compared to allogeneic products within the healthcare sector (Figure III). An autologous approach is challenging to market in a customer-inclusive way, given that product performance is predicated in large part on the individual (Brandenberger et al., 2011; Bravery, 2010, PMID20861040). There are also inherent variations in commercialization strategies for products that transiently persist, as is common with mesenchymal cell therapies, as compared to those that engraft into patient tissue, as is typically the case for hematopoietic types (Daley and Scadden, 2008, PMID18295571). Transient therapies in particular face a harder commercial "sell" as compared to conventional pharmaceuticals, in part, due to uncertainties surrounding their valuation and subsequent reimbursement (Daley and Scadden, 2008, PMID18295571). Moreover, there are also differences in cell therapies that straddle the 'drug-device divide', as well as those that have been genetically modified (Nowakowski et al., 2013, PMID23595280). The principal issue facing biomanufacturers here is complexity, especially for those that may commercially offer a portfolio of cell therapy products. The risk profile of each cell therapy subtype varies dramatically with respect to excessive cell growth post-transplant; immunological reactions; negative interactions with other medications; and/or biodegradation or mechanical instability of scaffolds or other biomaterials (Daley and Scadden, 2008, PMID18295571; Herberts et al., 2011, PMID21418664).

[insert Fig. 3]

In compliance and financing, too, cell therapy manufacturers face a distinct set of risks. Because cell therapy is relatively young as an industry, there still exists substantial variation in regional, national, and international regulatory standards, making compliance for global markets both costly and byzantine (Deal, 2009; Kessler et al., 1993, PMID8377782; Parker, 2001). This is further complicated by the impact of continued regulatory innovations, such as adaptive licensing and named patient exemptions (Eichler

et al., 2012, PMID22336591; 2011). Though these innovations may offer significant value to a biomanufacturer in the long run, they can also render compliance a prohibitively costly risk in the short to medium term. Appropriate financing vehicles can, of course, help offset cost concerns. But here as well biomanufacturers must navigate a crowded risk space. Value-based pricing, which is a strategy that sets prices on the basis of customer value as opposed to costs alone, can offer larger profit margins to biomanufacturers, but successfully implementing this strategy requires direct consumer branding and clear differentiation from competing therapeutics (Koerber et al., 2013, PMID24147530). On the other hand, tiered pricing schemes, such as those that vary between markets or at volumes, allow biomanufacturers to cater to a diverse customer base and offer products through a variety of channels (Danzon and Towse, 2003, PMID14625999). With the exception of those based principally on volume, however, tiered pricing schemes are challenging to maintain in an increasingly borderless global market, as the potential for arbitrage risk is high.

Central to the issue of establishing these financing schemes in the first place is the need to establish distribution and adoption of a cell therapy. Maintaining the "cold chain" is a central challenge to cell therapy distribution, where critical quality attributes (CQAs) must be maintained throughout the chain of custody from manufacturing facility to end patient, in a manner that can be validated from a regulatory perspective and that is accepted by the clinical community (Brandenberger et al., 2011; Massie et al., 2013, PMID22834979). Cold chain breaks are perhaps the most significant of a constellation of risks posed via supply chain disruptions, to which cell therapies face exceptional exposure given the physicochemical fragility of the product class. In parallel, these distributional risks are dovetailed by those associated with product adoption. A clear demonstration of efficacy in a clinical setting remains to be achieved by a number of cell therapy products that have entered the market, particularly for those indications where therapeutic options are available and where a current standard of care exists. Cell therapies in the US and UK have to demonstrate significant improvements, both in terms of efficacy and cost-effectiveness, over existing treatment options before they will be adopted by health systems. This is especially true in light of stringent budgetary and policy pressures being placed on government purchasing bodies like the UK's National Institute of Health and Care

Excellence (NICE), which demand exacting criteria prior to product purchasing (Coombes, 2010, PMID24690402). Curative therapies, meanwhile, are innately challenging to assess. Consider the standard measure: quality-adjusted life years (QALY). Treatments that generate maximal QALYs do not necessarily offer the optimal patient experience— one in which discomfort and pain over the long term are minimized (Gerlier et al., 2010, PMID21080737). In order to succeed, it is imperative that biomanufacturers enter these spheres armed with ample empirical data across a variety of metrics, including patient reported outcome measures (PROMS) (Dawson et al., 2010, PMID20083546).

Aggregating this data, can offer numerous benefits in commercial risk management for biomanufacturers. For one, it allows cell therapy manufacturers to take advantage of established frameworks for dealing with such risks. The unique set of commercial risks facing a biomanufacturer, can be first ascertained through a qualitative and quantitative risk identification program, in which literature reviews, targeted interviews, and process modeling can help aggregate, filter, and rank a complete list of risk attributes and scenarios (Zimmermann and Hentschel, 2011, PMID22293839). These identified risks can be further analyzed and quantified through preliminary hazard analysis and fault tree analysis, which focus on identifying the severity, frequency, and detectability of each risk (Rathore and Winkle, 2009, PMID19131992). It is important that all relevant product partners be consulted and informed throughout this process. While sharing of these plans between operational partners is rare, as an admission of risk can be perceived as a sign of weakness or failure, it is a necessary step for successfully managing the multi-actor partnership and consortia schemes that often govern cell therapy development.

Clinical and societal risks

Once commercial and manufacturing risks are accounted for, it is easy to overlook those risks that lie further downstream of the cell therapy production process—namely, clinical and societal risks. Yet these risks can ultimately define the success or failure of a cellular product. Not only are clinical and societal risks the most public facing, and therefore most subject to public backlash or reputational damage, they are also those most difficult to recover from. Inadequately controlled clinical risks in the form of adverse side

effects (e.g., formation of teratomas common to undifferentiated pluripotent stem cells), can invite regulatory backlash in the form of probationary or shutdown measures, which can cripple a biomanufacturer (Hentze et al., 2007, PMID17084475). Societal risks (e.g., large -scale adverse clinical reactions, or inaccessibility of the end product), in turn, can prompt retaliatory legal action or punishing legislation, which can extract substantial awarded damages.

Taken as a whole, clinical and societal risks can be structured within two broad categories: those internal and external to the product itself. Examples of internal risks include clinical product toxicity, lack of product viability, product procurement challenges, immune reactions to the product, and tumorigenicity (Herberts et al., 2011, PMID21418664). Because the precise mechanisms by which cell therapies act are yet to be fully uncovered, these risks remain incompletely understood, and require further preclinical studies to delineate. On the other hand, external risks include challenges with regulatory expectations, post-market surveillance, risks in the clinical operation and/or administration, cell line contamination, immunosuppression co-morbidities, or unintended clinical consequences and co-morbidities (Herberts et al., 2011, PMID21418664; Ratcliffe et al., 2011, PMID21852279). These external risks can be addressed in part through quality risk management at the process stage. However, to truly mitigate them, it is essential that robust, responsive post-market surveillance tools for cell therapy are put in place.

Despite the rapid pace of scientific development in cell therapy, and ongoing gaps in mechanistic understanding, governing these risks successfully requires conducting thorough risk:benefit analyses at the outset of product development, accounting for both predictable and stochastic risks within internal and external spheres (Halme and Kessler, 2006, PMID17050899). These frameworks can hedge off downstream risks while maintaining economic viability of the manufacturing enterprise by allowing biomanufacturers at the outset to identify the most significant clinical and societal risks, and determine for which ones the costs far exceed benefits provided. Moreover, risk:benefit assessments prompt clear risk-mitigating and risk-reactive strategies to be established prior to the start of large-scale manufacturing. Regulatory agencies in both the United States and Europe have provided guidance on how satisfactory benefit:risk assessment frameworks can be established (Halme and Kessler, 2006, PMID17050899;

Tsang et al., 2011). Still, ongoing gaps in regulatory structures imply that biomanufacturers should take a cautious approach in handling clinical risks, so as to avoid dangerous path dependency effects in the event of adverse outcomes.

Tipping this risk:benefit ratio in favor of the former also depends in part on rigorous post market surveillance strategies. Notably, autologous products present a unique set of post-market surveillance challenges. Because these therapies are heterogeneous by definition, traditional pharmaceutical and biotech frameworks for post-market reporting that function for allogeneic products need not apply (Daley and Scadden, 2008, PMID18295571; Mittra). Rather than relying on broad-based population measures, autologous products must allow for individual patients to have clear access to the appropriate routes for reporting concerns.

Addressing these unique challenges of cell therapy can be done partly by setting up clear and consistent communication channels for use by patients. Communicating these risks to patients, directly, for instance, does more than to just head off any legal or regulatory concerns given the difficulty of autologous surveillance. It also empowers patients to mitigate risks (Aym[illegible] et al., 2008, PMID18555918). Establishing an advisory vehicle for patients on issues of risk management, such as through a consulting board, can further increase the propensity for patients to report outcomes (Lee and Williams, 2010, PMID19747556). Given that a major challenge for cell therapy is enforcing patient adherence to monitoring procedures, soliciting recommendations or feedback from these interface forums can help manufacturers determine strategies for avoiding therapeutic transience. Such direct patient interaction takes a singularly significant role in cell therapy; since this therapeutic class remains heavily experimental, patient choice in opting for cell therapy treatments takes comparative precedence over clinician prescription. Making patients active partners in cell therapy use, then, can serve as a low-cost means for hedging risk, as long as all risks are actively communicated to patients throughout the process (Kim and Miller, 2014, PMID24552326).

Within the clinic, it is of utmost importance that biomanufacturers not distribute products indiscriminately, as is comparatively the case for standard pharmaceutical and biotech therapeutics. Instead, it is recommended that cell therapy developers forge trusted partnerships with proficient surgical and clinical staff who not only receive extensive

training in the various clinical-side risks that accompany the product, but can also stratify patients accordingly (Kadidlo, 2009). Such training may result in substantial decreases in clinical-side risks associated with cell therapies, such as those incurred from improper handling of immunosuppressive co-treatments; offering it up-front would reduce operator bias for meaningful clinical outcomes that will educate manufacturing iterations and future trials. This administration training can be supplied in addition to curricula on the advantages, disadvantages, and proper use of cell therapy. At scale, such a training could encompass a licensing scheme, such as through the Graduate Medical Education scheme in the United States, in which only specially certified clinicians are permitted to administer the therapy (Knoepfler, 2013, PMID23477401). Though such a scheme would certainly pose barriers to product delivery, the costs may be well worth the risk mitigation benefits—a calculus that can be made explicit through the risk:benefit frameworks described above.

One parallel class of risks facing cell therapy manufacturers is driven by the affordability, accessibility, and availability of these treatments around the world (Salter et al.). For instance, an ongoing inaccessibility of cell therapies in low-resource settings may prompt governments to cease in enforcing intellectual property (IP) protection, which, like generic drugs in the pharmaceutical industry, can foster alternatives that price traditional cell therapeutics out of the market due to extremely low R&D costs (Salter et al., 2006, PMID17465734, 2007). A lack of IP enforcement can thus financially constrain cell therapy developers; a recent example of this can be found in India's refusal to honor IP protection for high-need drugs, which has spurred a wave of generics into the local drug market (Mueller, 2007). Nor are these risks confined to emerging markets; a lack of IP protection can result in medical tourism or arbitrage opportunities that pose financial and economic risks to manufacturers in developed markets, particularly when coupled to the political risks as patients become aware of lower-cost options. Inoculating against these risks by forging partnerships with state governments and health ministries worldwide, and offering competitive pricing schemes in developed markets, is therefore advisable. Strong branding, staff training, and patient engagement services, such as those described above, can further protect against these risks.

Future directions and conclusion

Despite the powerful set of tools, techniques, and methods available for risk management in cell therapy biomanufacturing, the field remains nascent. For one, many of the standards and paradigms in the field have been adopted from applications in other industries, chiefly pharmaceuticals, and tailoring these to the unique challenges to cell therapy manufacturing is an ongoing area of research. Furthermore, the convergence of a number of recent trends in medicine, biotechnology, regenerative medicine, regulatory policy, and computational technologies are driving rapid changes within cell therapy biomanufacturing processes (Table IV). Here we discuss how risk management for cell therapy may be reconceptualized in the coming decades, and synthesize insights from the literature on how biomanufacturers might capitalize on these trends.

[insert Table IV)

Primarily, the idiosyncrasies of cell therapy as a medicinal product class leave a number of outstanding issues that are yet to be resolved by advances in risk management. Many of these barriers that are unique to cell therapy have been outlined above; as a consequence, cell therapies do not easily fit existing biomanufacturing or regulatory paradigms. In addition, there is a tendency by manufacturers to conflate risk:benefit and cost:benefit and cost effectiveness assessments of cell therapy, given the high production costs and novel nature of the product class (Bruttin and Dean, 2004; Guo et al., 2010, PMID20412543; 1998). The latter frameworks make the implementation of risk mitigation measures appear undesirable, as many of these measures are quite costly to implement without an apparently commensurate set of benefits. However, this focus on "short-term" costs ignores the "hidden" benefits of controlling for risk. On the other hand, in the sphere of clinical risks, comprehensive risk assessments are impeded by the reality that most clinical risks for cell therapy products remain ill -defined. Profiling for each cell therapy product and its associated indication could help address this need, just as the severity and likelihood of risks in a profile could dictate particular evaluation pathways for the product, similarities to known products could mitigate the need for costly randomized trials. Lastly,

cell therapy risk management is complicated by the ongoing difficulty in process automation for this product type. Manual operations confound risk management tools by inducing greater fundamental uncertainty into a process chain, and making difficult the incorporation of PAT and real-time feedback controls (Brindley et al., 2013).

Adding to these challenges are recent trends that are reshaping the landscape for cell therapy manufacturing. For example, the cell therapy industry may be undergoing the beginnings of a gradual convergence with mainstream pharma, which demands much more exacting product and process standards than the field currently exhibits (Brindley et al.; Daley and Scadden, 2008, PMID18295571). In parallel, Big Data, increasingly *en vogue*, offers novel capabilities for quantifying, analyzing, and predicting risk. For now, though, it has mostly generated 'Big Questions'. How, after all, can these abundant datasets and their concomitant noise be parsed for risk-mitigating signals? Clinically, too, advances in –omics are driving an emerging focus on "personalized" and stratified medicine that has made process-stage scaling end-stage product effectiveness assessment increasingly tricky. Fortunately for the cell therapy industry however, these changes largely play in its favor; the increased push towards personalized medicine will catalyze the development of practices that can be used to aid the development of cell therapies, a key barrier to cell therapy manufacturing. Cell therapy biomanufacturers can, accordingly, spearhead the adoption of Good Genomic Practice: standards that can help standardize and therefore proliferate techniques to optimize the use of genomic profiling (Barker et al., 2013, PMID23652098).

Ultimately, these trends build on a long tradition in risk management: leveraging data and analysis to make biomanufacturing less art and more reproducible, robust science. Though the risks and challenged posed to cell therapy manufacturers are vast, there exist ample tools by which to manage and mitigate these barriers. Capitalizing on a deep existing body of risk management success stories across industries, as well as leveraging novel tools being developed, will equip biomanufacturers with the capacity to negate these risks at the outset. For the cell therapy industry, there could be no greater catalyst.

Acknowledgements

RR wishes to acknowledge support of a 2014 SENS Research Foundation Summer Scholar grant which provided essential support towards the delivery of this publication.

We wish to express our sincere thanks to the following organizations that have contributed to the CASMI Translational Stem Cell Consortium as funding and events partners — without whom the consortium and the benefits it will bring to stem cell translation would be constrained: CCRM, Celgene Cellular Therapeutics, Cell Therapy Catapult, CIRM, Eisai, GE Healthcare, Lonza, SENS Research Foundation, TAP Biosystems (now Sartorius Stedim), MEDIPOST Co., Ltd., MEDIPOST America Inc., New York Stem Cell Foundation and the NIH Centre for Regenerative Medicine. Additionally, CASMI is a past recipient of funding from the Technology Strategy Board to support an investigation into cell therapy regulation. We also wish to extend our sincere thanks to Richard Barker and Megan Morys (both CASMI) for their support of the CTSCC, as well as to Robert Carlisle, Mark Thompson, Cathy Ye, and Aidong Yang of Oxford's Institute for Biomedical Engineering.

Disclosures and Conflicts of Interest

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B. gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that amongst other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. D.A.B. is subject to the CFA Institute's Codes,

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All other authors, do not declare any additional conflicts of interest, as defined by the journal. However, the authors are happy to respond to direct requests for confirmation; and stress that affiliations stated may or may not constitute a disclosure of employment and/or ownership of financial instruments in the named entity.

Table II. Comparison of risks between autologous and allogeneic products

Autologous Risks	Allogeneic Risks
No donor selection concerns; avoids risk of immune rejection	Donor selection risks; can trigger adverse immune response
Can avoid use of expensive and risky immunosuppression	Immunosuppressant regimen-related organ toxicity
Single-patient manufacturing; lower startup costs; limited cell line development	Dearth of scalable, cost-effective manufacturing technology for large cell numbers
Avoids toxin and pathogen transmission concerns from donor tissue	Donor tissue toxin and pathogen transmission concerns
Source material variability	Large lot quality control; consistent material
Low economies of scale	Substantial economies of scale
Difficulties in generating large cell numbers from biopsied tissue; one-patient batch size allows only scale-out	High potential for scale-up via parallel bioprocessing; universal therapies enable high patient throughput
Significant lag time before therapeutic availability	Off-the-shelf availability
Contamination risks confined to single lot	Lot-lot biocontamination
Lower regulatory hurdles	Greater regulatory hurdles
Self-derived tissue provides greater patient comfort; lower risk for consent	Bioethical and patient comfort concerns from nonself tissue; greater risk of consent
Complications from biopsy procedure	Avoids need for biopsy

Table III. Commercially available cell therapy products (Adapted from French et al., 2013 (French et al., 2013, PMID23470045))

Company	Lead product(s)	Indication	Market launch	Allogeneic/ autologous	Estimated revenue (million $/ yr)	Current Markets
Advanced Biohealing, a Shire company	Dermagraft	Diabetic foot ulcers	2001	Allo	>100	US, Canada
Dendreon	Provenge	Prostate cancer	2010	Auto	>100	US
Organogenesis	Apligraf	Venous leg ulcers/ diabetic foot ulcers	1998/2000	Allo	>100	US, Saudi Arabia
NuVasive	Osteocel Plus	Skeletal defects	2005	Allo	>50	US
Orthofix	Trinity Evolution	Musculoskeletal defects	2009	Allo	>50	US
Genzyme, a Sanofi Company	Carticel	Articular cartilage repair	2007	Auto	>10	US, EU
Anterogen	Cupistem	Crohn's disease	2012	Auto	<10	S.Korea
Avita Medical	ReCell	Burns, scars	2007	Auto	<10	EU, UK, Australia, Canada
FCB Pharmicell	Hearticellgram	Acute myocardial infarction	2011	Auto	<10	S. Korea
Genzyme, a Sanofi company	Epicel	Severe burns	2007	Allo	<10	US, EU
Japan Tissue Engineering	J-TEC Epidermis /Cartilage/ Corneal Epithelium	Burns/Cartilage repair/Ocular repair	2012	Auto	<10	Japan
Medipost	Caristem	Articular cartilage repair	2012	Allo	<10	S. Korea
TiGenix	ChondroCelect	Articular cartilage repair	2009	Auto	<10	EU

Table IV. Examples of convergence in cell therapy bioprocessing (Adapted from Brindley et al., 2014(Brindley et al.))

Technology	Original Application(s)	Contemporary Bioprocessing Application(s)
Bioreactors	Brewing	Cell expansion and biologics production
Homogenizers	Dairy bioprocessing	Cell lysis
Fine filters	Air conditioning systems	Filtration
Steam sterilization	Canning	Sterilisation in place (SIP) and clean in place (CIP)
Plasticized polyvinyl chlorine (PVC) bags	Blood storage and transportation	Rocking motion bioreactors for cell expansion
Counterflow centrifugation	Blood bioprocessing	Therapeutic cell concentration
Ultrasonic lysis	Communications and imaging	Cell lysis
Lyophilization (freeze drying)	Serum distribution	Biologics manufacturing, food manufacturing, hydrocarbon analysis

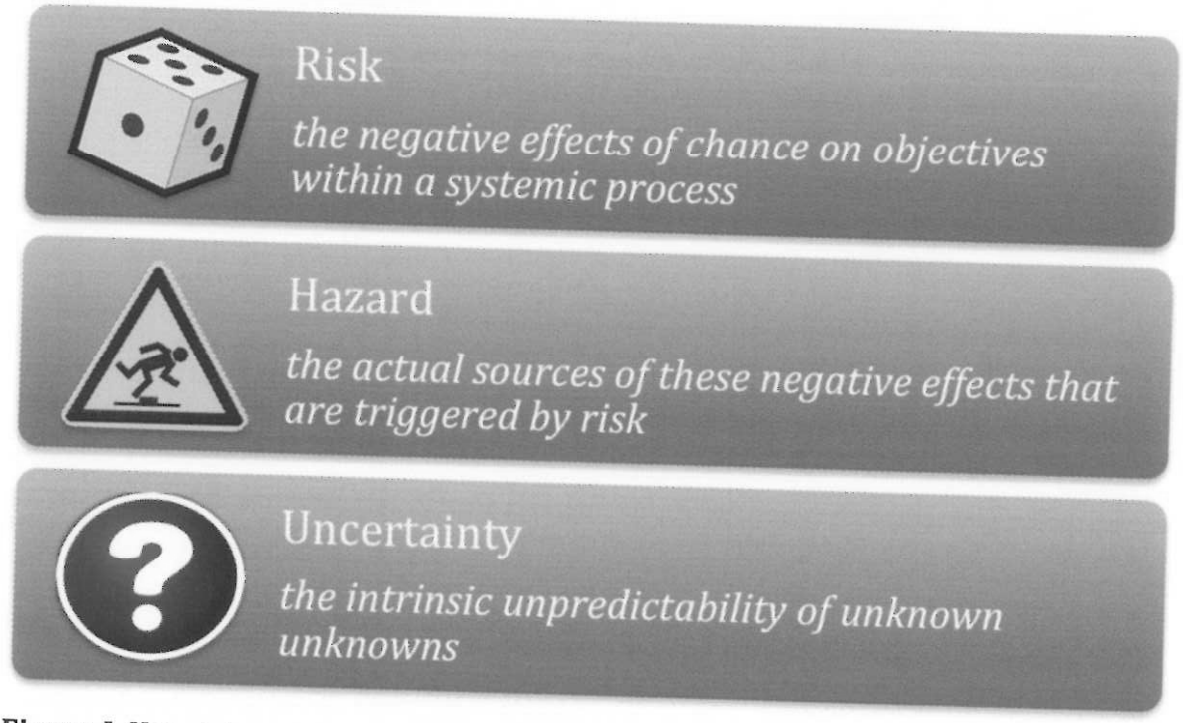

Figure I. Key risk management definitions

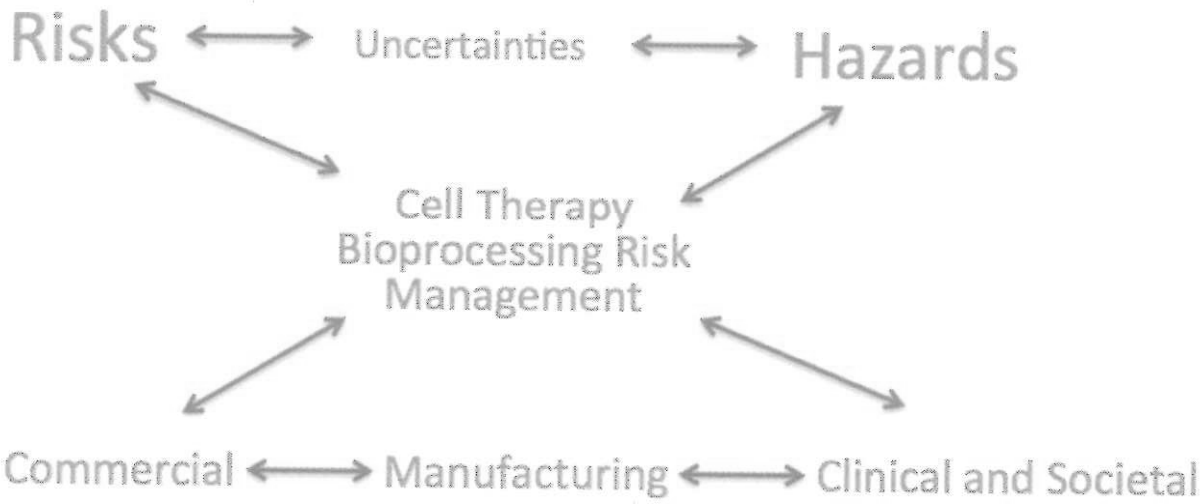

Figure II. Overview of cell therapy bioprocessing risk management

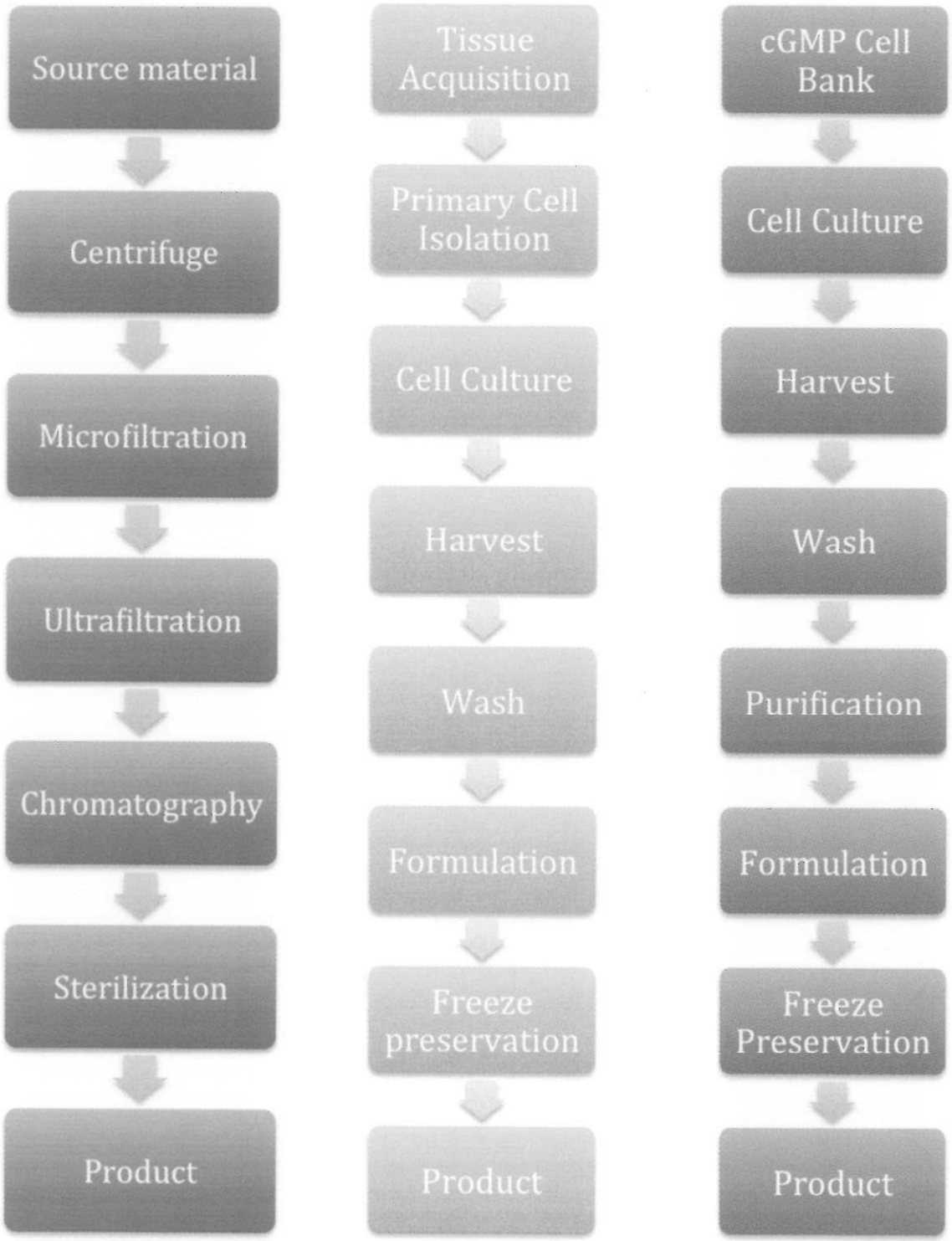

Figure III. Example of generic bioprocessing pathway for monoclonal antibody (left), autologous cell therapy (center), and allogeneic cell therapy manufacturing (right)

In this figure, the typical steps required for the processing of both patient-specific (autologous) and universal donor (allogeneic) products are shown. Overall, there are more processing steps associated with allogeneic cell manufacturing, though those allogeneic strategy typically results in a lower cost per dose of cell-based product produced.

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The Pharmacogenomics Journal (2014), 1–7
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www.nature.com/tpj

An evaluation of regulatory and commercial barriers to stratified medicine development and adoption

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Today, a range of products based on genomics, proteomics and metabolomics have facilitated the development of 'stratified' medicines and companion diagnostics. This investigation profiles a series of targeted medicines and corresponding diagnostics, and their role(s) in supporting evidence-based medicine. Despite their potential benefits we found that scientific, financial and regulatory barriers impede the development and adoption of companion diagnostics. Therefore, in order to realise improvements to the risk/benefit profiles of health-care interventions—notably reducing clinical uncertainty—conferred by the use of companion diagnostics, industry representatives, health-care providers and regulators will need a coordinated response to overcome these barriers.

The Pharmacogenomics Journal advance online publication, 7 October 2014; doi:10.1038/tpj.2014.51

INTRODUCTION

The past two decades have seen encouraging steps towards personalised or 'stratified' medicines. The completion of the human genome sequencing project,[1,2] the ENCODE project[3] and growth in next-generation sequencing technologies have enabled meaningful genome sequencing and molecular profiling at increasingly affordable levels.[4] The ability to target patient population subsets has the potential to improve treatment efficacy and minimise side effects. In addition, from a financial perspective, the cost of adverse events in the United States is estimated at $177 billion annually,[5] and this may be partially alleviated by targeting medicines to those most likely to benefit.

Some of the most well-known examples of stratified medicine can be found in oncology where target patient populations are defined by tumour histology and biology. The development of Herceptin (trastuzumab; Roche, Basel, Switzerland) a monoclonal antibody against the (breast) cancer molecular marker, HER2, is one of the earliest examples of a stratified medicine.[6,7] Since Herceptin's approval from the Food and Drug Administration (FDA) (Silver Springs, MD, USA) in 1998, other drugs have followed suit in what promised to be an age of pharmacogenomics. For example, within 5 years of the discovery of the association of ALK (anaplastic lymphoma kinase) fusion gene with a subset of non-small-cell lung cancer,[8] Xalkori (crizotinib: Pfizer, New York, NY, USA) was developed, transforming options for patients who previously had at best a 38% chance of surviving for more than 4–5 years.[9]

Despite encouraging technological developments, the number of stratified medicines has not reached expectations.[10,11] Potential causes have been discussed at length and published in at least two cross-industry forum reports: the Academy of Medical Sciences (London, UK): 'Realising the potential of stratified medicine'[12] and the Institute of Medicine workshop (Washington, DC, USA) in 2013 by the Roundtable on Translating Genomic-based Research for Health.[13] The following paper outlines key success factors for developing stratified medicines, but more importantly identifies significant barriers to their development and adoption.

CASE STUDIES OF STRATIFIED MEDICINES

To better understand what factors might be contributing to the inhibited progress of stratified medicines, we investigated a series of examples and their companion diagnostics (Table 1). These cases describe a number of indications over a period of ~15 years; although not a comprehensive list, they represent a number of leading examples of successful stratification of medicines. Unsurprisingly, a significant proportion of the cases outlined are in oncology, a therapeutic area that is particularly amenable and attractive to the implementation of stratified medicines. There has been a paucity of examples in other therapeutic areas, although it should be recognised that there is significant literature on genetic markers and the cytochrome *P*450 (CYP) genes and their role in the metabolism of drugs such as codeine, clopidogrel, warfarin and tamoxifen.[14,15]

The cases demonstrate that the timing of the decision to stratify and the level of developmental support through strategic partnership (s) are all instrumental in facilitating the approach to stratification.

We have simplified the timing at which stratification occurs to three points relative to the clinical development timeline of a medicine or diagnostic: (1) before and (2) during clinical development and (3) after marketing authorisation. We illustrate our findings with a small number of examples that fit within each category.

Before clinical development

The development of Zelboraf (vemurafenib: Roche, Basel, Switzerland), a small-molecule inhibitor of oncogenic, V600-mutated

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Received 3 May 2014; revised 1 August 2014; accepted 13 August 2014

Table 1. Case studies of stratified medicines and clinical diagnostics

Drug, diagnostic	*US approval*		*EU approval*	
	Drug	*Diagnostic*	*Drug*	*Diagnostic*
Herceptin (Roche, Basel, Switzerland), *Hercep Test* (Dako, Glostrup, Denmark)	Sep 1998	Sep 1998	Aug 2000	1999
Ziagen (ViiV Healthcare, Brentford, UK), *Genotyping for the leukocyte antigen (HLA) b allele (HLA-B*5701)*	Dec 1998	LDTs available at the time of label changes	July 1999	LDTs available at the time of label changes
Vectibix (Amgen, CA, USA), *therascreen: KRAS RGQ PCR Kit* (Qiagen, Venlo, The Netherlands)	Sep 2006	July 2012	Dec 2007	November 2007 (CE mark)
Selzentry (ViiV Healthcare), *Trofile assay*	Aug 2007	Developed as LDT during drug development, remains a LDT	Sep 2007	CE marked before EMA approval
Zelboraf (Roche), *BRAF V600E* (Roche)	Aug 2011	Aug 2011	Feb 2012	CE marked before EMA approval
Xalkori (Pfizer, NY, USA), *Vysis ALK Break-Apart FISH Probe Kit* (Abbott, IL, USA)	Aug 2011	Aug 2011	Jul 2012	Aug 2011
Kalydeco (Vertex Pharmaceuticals, MA, USA) *FDA-cleared cystic fibrosis diagnostic for presence of G551D mutation*	Jan 2012	Available unbranded test used during clinical development	May 2012	Available unbranded tests to be used
Breast cancer drugs, *Oncotype Dx* (Genomic Health, Redwood City, CA, USA)	Approved drugs	Classified as LDT in the USA	Approved drugs	2007

Abbreviations: CE, product compliance with EU legislation; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; LDT, laboratory-developed test; PMA, premarketing approval.

BRAF kinase, blocking cell proliferation and promoting cell death,[16,17] is an example of a target-driven approach from the outset of clinical development. Zelboraf's development along with the cobass 4800 (Roche) BRAF V600 mutation test represents one of the fastest FDA approvals in history (only 4 months after submission, and <5 years after first in human trials), and also represents an example where therapeutics and diagnostics received simultaneous approval (Box 1).[18]

During clinical development

Once pivotal phase III trials have commenced, companies are typically hesitant to alter development plans to stratify. In these cases, adverse events or differential responses have driven the decision to adopt a patient stratification approach. Any stratified approach at this stage would need clear mechanism of action for either therapeutic or biomarker, supported by a diagnostic with potential for clinical adoption.

Much has been made of the potential for adaptive approaches to development and licensing.[19,20] Adaptive designs are particularly amenable to stratification, and allow users to modify a trial during its progress based on interim results without affecting the integrity of the trial, and potentially permit earlier (conditional) licensing. There are very few precedents where a regulatory agency has accepted the introduction of patient stratification once

Box 1 Case study 1

Zelboraf (vemurafenib)

The efficacy of Zelboraf in metastatic melanoma was demonstrated in clinical trials in which patients whose tumours carried V600 mutations were selected using the cobas 4800 BRAF V600 mutation test.

Zelboraf showed antitumour effects in cellular and animal models of melanomas with BRAF V600E mutations and was thus selected for development using a stratified approach from the outset. This meant that for both therapeutic and diagnostic the development programmes and regulatory filings were done simultaneously and in parallel.

Lessons learned:

1. Early and integrated collaboration between the pharmaceutical and diagnostic developers helped maintain alignment across rapidly evolving and accelerated timelines for clinical trial and regulatory filings. In this case, Roche developed both the medicine and the diagnostic, highlighting the advantages of integrating therapeutic and diagnostic development capabilities.
2. Despite the integrated collaboration, the timelines proved challenging, and Roche Molecular Systems was a reluctant participant until the original Plexxikon (previously Berkeley, CA, USA; acquired by Daiichi Sankyo, Tokyo, Japan) investigator compound was acquired by Roche Pharma.[42]
3. Constructive and collaborative dialogue with the FDA on both the pharmaceutical and diagnostic sides (Center for Drug Evaluation and Research and Office of In Vitro Diagnostic Device Evaluation and Safety) laid the foundation for future companion diagnostic approvals.
4. Simultaneous approval of Zelboraf and the cobas BRAF test enabled collaboration at all levels across the commercial organisations during the launch phase.
5. Setting up testing infrastructure before launch reduced barriers to test adoption by hospital and pathology laboratories.

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pivotal trials have begun, and for such adaptive designs to be valid, specific details and decision choices need to be specified in the original study designs before commencement. The I-SPY studies in breast cancer serve as a guide to developing such trials in neurooncology with two experimental drugs passing major milestones through adaptive trial designs leveraging tissue and imaging biomarkers for stratification.[21]

Post marketing authorisation

Poor sales and/or retrospective clinical trial data may prompt a company to explore patient stratification after launch. Ziagen (abacavir) (ViiV Healthcare, Brentford, UK), is one of the earliest examples in which a genetic marker predicted drug-associated adverse events.[22,23] Ziagen represents a successful case in which researchers, industry and health-care professionals were able to build on real-world information to reduce the risk side of the risk/benefit profile. There are also examples where stratification after launch was undertaken to improve efficacy.

The development of Vectibix (panitumumab) by Amgen (Thousand Oaks, CA, USA) is an interesting case in which a stratification approach was adopted after launch to identify KRAS as a limitation of use as it was considered a negative predictor of outcome (Box 2). It was approved for the first time in September 2006 in the United States via accelerated approval as a monotherapy for the treatment of metastatic colorectal carcinoma.[24] Soon after approval, prospective–retrospective analysis from the phase III study showed an association between KRAS mutation status and treatment risk/benefit.[25]

The Vectibix case demonstrates that with adequate real-world surveillance, it is possible to identify more suitable subpopulations for a drug and regulate for its restricted use.

Stand-alone diagnostics

The ability to better understand tumour subtypes through next-generation sequencing or expression profiling may result in a delinking of the diagnostic and the individual therapy. Rather, patients will be offered a range of treatments based on the tumour profile as assessed through a 'stand-alone diagnostic'. The adoption of these stand-alone diagnostics enable significant cost savings by avoiding the use of ineffective expensive therapies and most importantly prevent needless suffering of patients who might otherwise receive aggressive treatments that can lead to adverse events.

Genomic Health's (Redwood City, CA, USA) Oncotype Dx represents this new wave of diagnostics. The prognostic test for breast cancer helps oncologists identify low-risk breast cancer patients unlikely to benefit from chemotherapy (Box 3). The test predicts the likelihood of breast cancer recurrence and benefit of adjuvant chemotherapy in node-negative, oestrogen receptor-positive and HER2− patients (roughly 60% of breast cancer patients).[26]

Tests like Oncotype Dx are complex, sometimes expensive, but most importantly enable health-care practitioners to either identify nonresponders and or those with a greater benefit/risk profile who will not benefit from intensification of treatment.

BARRIERS TO FURTHER ADOPTION OF STRATIFIED MEDICINES

Although the success factors are as diverse as the technology behind these health-care solutions, there are some common barriers that act to inhibit further development of more stratified medicines and adoption of those that are developed.

Box 2 Case study 2

Vectibix (panitumumab)

Vectibix is an example of a drug developed against a known biomarker (epidermal growth factor receptor (EGFR)), and later had its use restricted with the knowledge of another biomarker (KRAS) that identified nonresponders. In the case of EGFR detection, the Dako EGFR pharmDx kit was developed before marketing authorisation, and the use of the diagnostic was specified on the original US label. The KRAS biomarker was revealed after marketing, prompting the development of the therascreen: K-RAS RGQ PCR Kit (K-RAS Kit) *in vitro* diagnostic test intended for the qualitative detection of seven somatic mutations in codons 12 and 13 of the K-RAS oncogene. Amgen partnered with DxS (and then Qiagen) to ensure that a KRAS test kit was available in the EU at the end of 2007 and to file a premarketing approval in the United States.

Vectibix was given an accelerated approval by the FDA based on assessment of all-comers (intention-to-treat population), and a conditional approval by the European Commission based on the assessment of a KRAS wild-type subset, as its benefits outweighed associated risks and it satisfied the criteria of 'meeting unmet medical need'. Vectibix's development represents a rapid response to retrospective analysis to ensure prompt availability of a companion diagnostic.

Lessons learned:

1. Rigorous KRAS hypothesis testing was needed to demonstrate the feasibility of stratification.
2. Commitment to continue with postmarketing clinical trials to further validate the improved risk/benefit profile following testing for KRAS and the availability of KRAS data enabled a negative opinion to become a positive opinion for Vectibix in the EU.
3. The partnership with DxS (and then Qiagen) ensured availability of a CE-marked KRAS test in Europe.
4. The case represents an example where stratification leads to a restricted target population with increased benefit/risk profile without an increase in price.
5. KRAS confirming LDTs, which do not require regulatory approval, are readily available and compete for market share with Qiagen's therascreen kit.[38]

Insufficient regulatory harmonisation and limited demands for clinical utility

In the United States and particularly in Europe, the regulatory frameworks that underpin the development of therapeutic and diagnostic products are different (Figure 1). In the United States, diagnostic and therapeutic approval applications can be made simultaneously to the FDA. *In vitro* diagnostics are reviewed by the Center for Devices and Radiological Health (CDRH) in consultation with the Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER), both at the FDA. The joint approval process ensures significant scientific knowledge sharing takes place that helps to provide an effective pharma-diagnostic regulatory environment.

In Europe, the European Medicines Agency (EMA, London, UK) sits separate to the regulators of diagnostics. Clinical trial authorisation applications for diagnostics must be submitted to the European Union (EU) member state Competent Authority (the organisation within an EU member state that has legally delegated authority to authorise clinical trials), whereas manufacturing and performance standards are monitored by Notified Bodies (organisations designated by national governments of EU member states to make independent judgements on whether a product

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Box 3 Case study 3

Oncotype Dx

Oncotype Dx was developed by conducting prospective and retrospective studies on tissue archives and took 5 years to develop. As the test calculates the Recurrence Score based on an algorithm combining the expression of 21 genes, the test is conducted in the company's own facilities via the Clinical Laboratory Improvement Amendment (CLIA) regimen in the United States. Although this means that the test has so far avoided having to submit to an FDA premarketing approval review and does not require European approval, it does cost ~3000 USD per test. This means that the test has significant reimbursement hurdles despite the anticipated cost savings. These hurdles have been most difficult in Europe where payers and health technology assessment bodies either lack, or are only now building, the capacity to assess molecular diagnostics for cost effectiveness. In September 2013, the UK cost-effectiveness body the National Institute for Health and Care Excellence (NICE) recommended Oncotype Dx as an option to help doctors decide whether to offer chemotherapy to a subset of patients with early breast cancer.

Lessons learned:

1. Genomic Health identified an area of potential cost savings incurred on unnecessary chemotherapy and converted it into a business model that saved more resources than those spent on Oncotype Dx development.
2. Genomic Health has become one of the first stand-alone diagnostic companies to achieve value-based pricing supported by strong pharmacoeconomic data.
3. A strong network of research consortia enabled well timed availability of tissue sample archives.
4. Claims-backed analytical and clinical validation supported a suite of publications.

complies with essential manufacturing and performance requirements). As a consequence, no single umbrella European agency exists and therapeutic and diagnostic development often takes place independently, in silos, with little early cross-fertilisation. Considering that the most recent amendment to the European *in vitro* diagnostic (IVD) Directive 98/79/EC in 2012 does little to address this fact, it is unlikely that any pan-European body will be coregulating diagnostics and medicines in the near future.

The proposals from the European Commission do place a greater emphasis on safety by recommending a risk-based classification previously outlined in 2008 by the Global Harmonization Task Force.[27] Importantly, under this system, diagnostics that guide treatment decisions will be classified as high risk and the proposed IVD Regulation contains a requirement for the notified body undertaking conformity assessments of companion diagnostics to consult the relevant medicine-competent authority of that member state or the EMA.

The different regulatory requirements can pose challenges when it comes to the development of therapeutics and companion diagnostics that are intended to be marketed on a global scale. Harmonising the evidence gaps from one region to the other can be challenging.

In both the United States and Europe, there is an imbalance in the requirement to demonstrate clinical validity (degree to which the diagnostic can accurately predict a clinical state) and clinical utility (degree to which the diagnostic positively influences clinical outcomes).[28] In Europe, manufacturers only need to satisfy essential safety and performance requirements (clinical validity) but they do not need to establish that their diagnostics has an impact on clinical outcomes (clinical utility). Furthermore, if a similar diagnostic already exists, then the manufacturer is not required to demonstrate superior or equivalent effectiveness.[29] In the United States, manufacturers of diagnostics intended for marketing and distribution must submit a premarketing approval to the FDA and undergo evaluation for analytical performance and clinical validity. As is the case in Europe, FDA clearance does not require demonstration of clinical utility. Furthermore, laboratory-developed tests (LDTs) produced within Clinical Laboratory Improvement Amendment (CLIA)-accredited laboratories do not necessarily require FDA review.

Although the current situation provides a fast route to market, the evidence gap from performance and accuracy to actual health outcomes creates uncertainty downstream for third-party payers and health-care providers who are faced with decisions on cost and relative effectiveness.[30]

Advances in technology will also increase the complexity of the information with which regulators are tasked with reviewing. The shift to mutation-directed multitherapeutic regimens is unlikely to be facilitated by classic clinical trials. Conditional approval through adaptive licensing based on clear mechanistic evidence and early proof of concept may be a way to proceed. This will require far greater cooperation between industry and regulators. Promisingly, the EU/pharma industry-funded Innovative Medicines Initiative[31] and the Massachusetts Institute of Technology (Cambridge, MA, USA)-led New Drug Development Paradigms (NEWDIGS) initiative[32] have begun pilot programmes to explore frameworks to facilitate public–private partnerships with adaptive licensing an immediate priority.

Reimbursement is becoming a significant hurdle for higher value, higher priced diagnostics

Typically, therapeutics are priced in a value-based manner with price supporting the attrition that occurs during development. The rewards are high to reflect the high risk and development costs. Most diagnostics, on the other hand, are priced on a cost-plus.[33] The risks are lower, the development timelines shorter and the prices are much lower than their therapeutic counterparts.

Developers like Genomic Health rely upon a model in which the diagnostic is priced using a 'value-based' approach, much like the therapeutics. Although this is a novel way to address the financial imbalance with regards to diagnostic development and reward, it raises issues after approval at the reimbursement hurdle.

Stand-alone diagnostics are unlikely to have their reimbursement covered by a therapeutic developing partner, meaning that their price comes under increased scrutiny from payers. As the prices of stand-alone tests are significantly higher than traditional *in vitro* diagnostics, in the absence of standardised clinical utility evidence, payers are sceptical about the cost effectiveness of such diagnostics and are creating their own evidence requirements. One example is the establishment of the UK-based Diagnostic Assessment Programme within the National Institute for Health and Care Excellence (NICE). The body carries out cost-effectiveness assessments of selected diagnostics and the evidence requirements for such an assessment are typically greater than those required by Notified Bodies for conformity assessments.[5,34]

With the exception of NICE, most payer requirements are not well defined and there are discrepancies depending on the country, region and hospital. Furthermore, they are influenced by short-term incentive barriers in which some payers (or procurement entities in hospitals) are incentivised to make decisions on short-term gain, for example, pay for cheaper tests, or no test, based on immediate budgetary pressures.

The business model for diagnostics is too tightly linked to companion therapeutics

In stratified medicine, the business models for therapeutics and diagnostics come together. Marketing approval, reimbursement,

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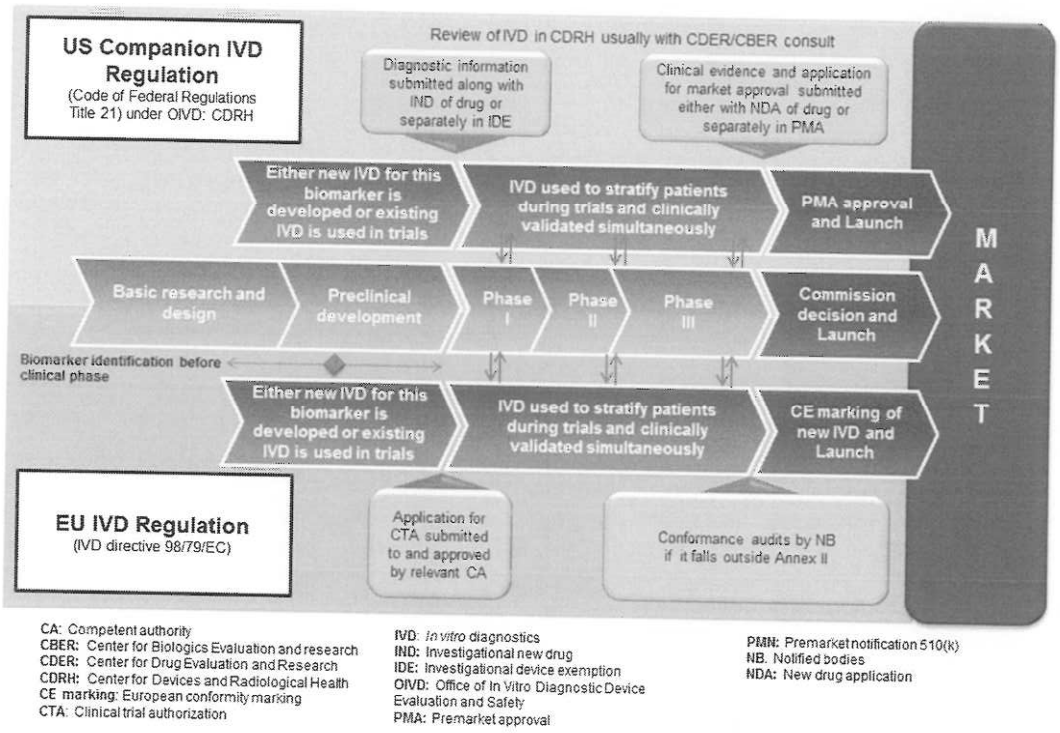

Figure 1. Comparison of US and EU regulatory pathways for *in vitro* diagnostics.

physician prescription and in some cases pathologist choice are tied to the availability of a diagnostic; without the therapeutic, the diagnostic has little relevance in the health-care system. However, when they are employed together, a hybrid-service model arises, thus introducing increased uncertainties and/or risk(s) in the value chain for stakeholders.[35]

The cases of Vectibix and Zelboraf highlight a codependency that exists between diagnostic manufacturers and pharmaceutical companies. Prescription and, increasingly, reimbursement of the therapeutic is dependent upon diagnosing the right subset of patients. Therefore, it is essential to have a companion diagnostic ready for market, and in many cases approved by a regulatory body when the therapeutic launches.[35]

There is a strong rationale for codevelopment of the medicine and diagnostics at an early stage; however, the opportunity cost for diagnostic companies is such that they may be reluctant to commit funds at an early stage. Diagnostic development is typically more rapid than for therapeutics, although with significantly lower returns. Consequently, many diagnostic companies are unwilling to support development costs when the therapeutic product has a high(er) probability of failing. Therapeutic companies often support the diagnostic development through access to patients in a clinical setting and most importantly fully funded reimbursement once the therapeutic is launched.

As few therapeutics serve to benefit from stand-alone diagnostics, such as Oncotype Dx, development is funded privately without the aid of major biopharmaceutical sponsors. Despite the clinical data demonstrating Oncotype Dx's potential to restrict health-care costs,[36] their success suffers from insufficient evidence generation requirements, leading to a lack of predictability at the payer and prescriber level. Until reimbursement and prescriber practices begin to fairly reward the clinical and financial advantages of stand-alone diagnostics, enthusiasm for investment in these technologies will be limited.[37]

Substitution with LDTs undermines commercial exclusivity of regulated diagnostic tests

The Vectibix case highlights an increasingly important commercial issue, the proliferation of LDTs. LDTs are those tests that are performed within a single laboratory and/or hospital. These tests are not placed on the market and are often developed for the diagnosis of rare diseases or to customise already available tests to a subset of certain diseases (for example breast cancer). They do not require a full development and regulatory review. However, they do have a lower direct cost and thus many hospitals opt to perform these 'in house' assays in place of commercially available tests.

In the Vectibix case study we saw that KRAS confirming LDTs are readily available and compete for market share with Qiagen's (Venlo, The Netherlands) therascreen kit. Essentially, Qiagen faces competition from unregulated tests that have no development costs.[38] Competition from an unregulated product with little to no development costs undermines the commercial attractiveness of the diagnostics space.[33]

The exemption of LDTs from FDA or Notified Body review enables the diagnosis of many rare diseases that would otherwise never have a commercially available test, and is encouraged. However, their misuse or inappropriate application can also be life threatening to patients. Variations in test quality and scope can threaten clinical utility and accurate decision making when directing treatment. Recent studies demonstrate significant variation in the standardisation and quality of assays used for HER2 and oestrogen receptor assays,[39,40] and as such the College of American Pathologists and the American Society of Clinical Oncology have established quality assurance systems. The United Kingdom Accreditation Service and the UK National External Quality Assessment Service are excellent examples of quality assurance systems in Europe. In the United States, all clinical laboratories must be certified by CLIA in order to receive funding from Medicare or Medicaid.

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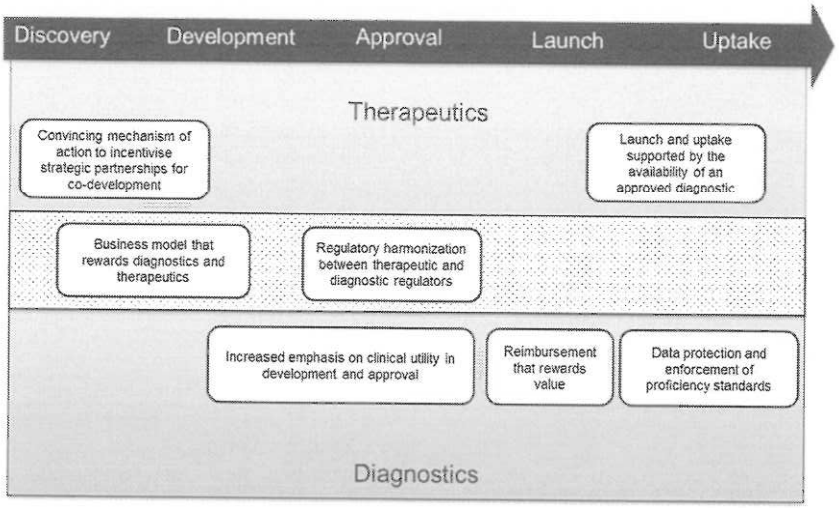

Figure 2. Success factors for therapeutics and diagnostics in stratified medicine.

It is vital that laboratories take part in these proficiency-testing programs. Furthermore, we believe it will be important in the case of complex genomic tests that standards for their conduct and interpretation are established to ensure that development of genomic medicine is not endangered by inaccurate or poor-quality practices.

CONCLUSION

This article highlights a number of significant problems that will inhibit the development of stratified medicine if not urgently addressed. Lack of regulatory harmonisation, poor reimbursement incentives and a proliferation of unregulated diagnostics all present barriers to development and adoption of stratified medicines. Furthermore, the development of stratified medicines is dependent upon a business model that allows both therapeutic and diagnostics companies to thrive (Figure 2).

The historic light touch regulatory emphasis on clinical validity has generated a great deal of uncertainty at the payer and provider levels because of the lack of clinical utility data. Thus, we see a cycle of low investment in evidence generation, increased clinical uncertainty, reduced recommendations for use and poor reimbursement prospects. This challenging economic cycle has been well described in recent publications by Trusheim *et al.*[33] and Hayes *et al*,[37] and the solutions point to an increase in evidence requirements supported by a proportionate rise in reward through adequate reimbursement. More innovative solutions have also been proposed including longer exclusivity periods for diagnostics and advanced purchase commitments.

The 2012 amendments to the European IVD Directive 98/79/EC emphasise safety through the proposed adoption of a risk-based classification system and bring Europe more in line with the US approach to the regulation of diagnostics. This may trigger additional evidence requirements that would also support claims on clinical utility.

New regulation must be forward looking and prepared for the introduction of new technologies that enable identification of multiple biomarkers that can guide treatment to a number of therapeutics. These tests will likely be the future of stratified medicines and regulatory policy must facilitate their uptake in an appropriate manner. Importantly, we recommend that future regulation places a greater emphasis on clinical utility to create more certainty at the payer and provider levels. Raising the evidence barrier through rigorous evaluation of clinical utility may increase certainty, but it will place greater pressure on the business model of diagnostics faced with greater development costs. Payers will need to reward diagnostics that demonstrate cost savings through better management of effective therapies, thus enabling developers to recoup their initial research and development costs while reinvesting in new and better technology at the same time. Those companies that do generate sufficient evidence will need assurance that they receive commercial protection from the proliferation LDTs or other 'me too' commercial tests that may be leveraging the newly available clinical utility data.

In the meantime, progress in stratified medicine will be dependent on translational research initiatives that aim to systematically reveal the molecular landscape of disease and link results to clinical outcomes in large databases. One example of such Big Data initiatives is the National Institute for Health Research (NIHR, UK) Genomics England Programme that aims to perform genome-wide sequencing of 100K genomes from patients with rare diseases and cancers. Results will be correlated to treatment outcome and will allow the identification of novel biomarkers of response or nonresponse.

For these large-scale genome-wide analyses to translate into meaningful outputs for patients, it will be critical to develop Good Genomic Practice,[41] clinical data standardisation and data quality assurance schemes. It will also be important to develop business models that allow controlled access to the database by therapeutic and diagnostic companies and thereby not only facilitate targeted drug development but also guarantee long-term financial sustainability of database generation.

Efforts to overcome the challenges outlined represent an opportunity for industry, patient groups, clinicians and regulators to collaborate synergistically to enhance patient outcomes. Ultimately, although companion diagnostics may decrease clinical uncertainty, they often act to increase commercial and regulatory uncertainty during development. Therefore, it is essential that stratification is applied to reduce the risk/benefit of the entire healthcare translation ecosystem, and not simply provide a means to systematically redistribute risk among stakeholders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ACKNOWLEDGMENTS

We thank members of the research subgroup for the regulatory environment of stratified medicines who provided key inputs and expert opinion to the paper: Dr Ian Hudson (Medicines and Healthcare products Regulatory Agency, UK), Mr Kent Kost (Roche Diagnostics), Dr Thomas Lönngren (NDA Advisory Service Ltd), Dr Marisa Papaluca Amati (European Medicines Agency) and Dr Stephen Spielberg (Food and Drug Administration). This work was supported by the Oxford Partnership Comprehensive Biomedical Research Centre with funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. DAB gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA, USA). The views expressed herein represent those of the authors and do not necessarily represent the views or practices of the authors' employers or any other party. DAB is subject to the CFA Institute and CAIA Association's Codes, Standards, and Guidelines, and as such must stress that this article is provided for academic interest only and must not be construed in any way as an investment recommendation.

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Establish good genomic practice to guide medicine forward

Richard W Barker[1], David A Brindley[1–3] & Anna Schuh[4]

Genomic advances, including next-generation sequencing, offer substantial opportunities and challenges for stratified and personalized medicines. However, the lack of standardization in genomic diagnostics translates into a major risk of error introduction. To ensure the integrity of such data—and their application—we suggest the development of 'good genomic practice' standards to guide the field.

Genomic analysis, which plays an increasing part in patient stratification and prediction of treatment outcomes, follows a multistep and multidisciplinary process spanning the initial sample collection to the ultimate clinical decision. However, a risk of error introduction exists at all stages, from preanalytical steps to laboratory analysis to clinical interpretation and long-term data storage. At present, good laboratory practice (GLP) and good manufacturing practice (GMP) guidelines ensure the quality of tests and therapeutic agents, thus bolstering the reproducibility and consistency of medical research and practice. But the emergence of clinical genomics poses new and specific challenges, and, as such, we believe that good genomic practice (GGP) standards would represent a similarly vital step in the field's development.

Before a genomic analysis even begins, the clinical and ethical implications of genomic testing, such as the possibility of incidental findings revealing the presence of heritable diseases, should be assessed as part of GGP (*Nature* **429**, 478–481, 2004). Clinical genomics training must be considered, as well as, where necessary, clinical service reconfigurations—for example, between genetic counseling and disease-specific clinical specialties (*Nature* **470**, 204–213, 2011).

Maximizing tissue sample quality and minimizing intrasample heterogeneity is crucial. For example, biopsies containing mixtures of normal and tumor cells require review and macrodissection by skilled staff. These considerations are all the more important today given the progressive size reductions in biopsies taken from patients. At the same time, for diseases such as cancer, longitudinal studies and sampling of metastatic material may need to become routine. Given the importance of such sampling, a reliable chain of custody from tissue acquisition to initial analytical processes is crucial. For example, centralized specimen handling accommodating paired tumor and germline samples, barcoding and radio-frequency identification tracking systems to ensure sample security, traceability and information technology connectivity from the patient to the final diagnostic report are all essential.

At the analytical stage, DNA and RNA library preparation methods should be optimized as well as standardized to accommodate the quality of input material and ultimate results. Standard operating procedures should define correct positive and negative controls. These procedures should also minimize contamination risks and interrun and interlaboratory variability. Quality measures must define process failures and duplicate testing. Additionally, labs should use fully validated GMP-grade reagents when available.

The wide range in bioinformatics tools is a major source of the discrepancies in genomics results when it comes to determining the frequency and significance of a particular sequence variation. Validation and standardization of version-controlled alignment tools, variant calling and tumor-normal subtraction algorithms will be required to achieve consistency in reporting relevant mutations.

It is necessary to rigorously curate publicly available databases of sequence variations to determine the presence of clinically relevant variants. Importantly, the final step of any bioinformatics pipeline that aims to produce 'medical-grade genomes' should be the visual inspection of sequencing data by skilled staff.

Assessing the clinical significance of variants remains a key component, including how to manage their medical impact. The level of evidence regarding a variant's clinical significance can range from prospective randomized, controlled multicenter trials to retrospective analyses of single-center cohorts to pedigree studies to functional *in vitro* data. And the clinical bearings of variants can be diverse: they can change a diagnosis, predict prognosis without changing clinical management or serve as strong predictors of treatment response. Thus, stakeholders should work toward consensus guidelines on how to categorize pathogenic variants according to their clinical significance.

Over time, the scope of best practices, including GLP and GMP, has extended beyond the doors of processing suites, for example including sample shipping conditions or posting of clinical reports. Similarly, GGP will have to extend to long-term storage and use of patient genomic data in phenotype and genotype databases. And it should stipulate secure data storage standards, encryption and anonymization to preserve patient confidentiality, where appropriate. GGP should also define the type of genomic information that has to be stored and for how long. Additionally, it should encourage the development of internationally accepted and standardized data storage formats, enabling the secure transfer of data from different laboratories and thus reducing the likelihood of research duplication and supporting validation.

To implement the GGP concept, we suggest the creation of a checklist by an international genomics leadership group that highlights any extant standards that should be used and any gaps in the process that require a concerted standardization effort. Thereafter, pursuing further development through engagement with a wider stakeholder group, a GGP accreditation pathway should be proposed. This accreditation might be used, for example, to help ensure the reproducibility of exome sequencing studies and to support regulatory interactions and submissions.

Genomic medicine is a young discipline with boundless potential to improve human health. We strongly believe that it is timely and crucial for the genomics community to define essential attributes of GGP and the 'medical-grade genome', thus ensuring the field realizes this great potential.

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Keep Australia's carbon pricing

Australia's new government may ditch the nation's pioneering carbon-pricing scheme in a move that would send a negative signal to other countries with plans for carbon trading or taxation (see E. Diringer *Nature* **501,** 307–309; 2013). Researchers and policy-makers need to be more effective in communicating such schemes to the public, to help guard against adversarial politics leading to inferior policy outcomes.

In Australia's present carbon-pricing system, emitters buy government permits for a fixed price of Aus$24 (US$22) per tonne of carbon dioxide produced. Under current law, this scheme is due to become a market-based emissions-trading scheme in 2015 and will allow trading with the cheaper emissions permits from the European Union.

The latest proposals retain Australia's target for lower emissions, but aim to replace the carbon-pricing scheme with government payments to companies that reduce emissions below a specified baseline. Critics include environmentalists, who fear that such a scheme would fail to meet Australia's emissions-reductions target, and economists, who say that it would compromise efficiency.

Although most experts regard a carbon price as the most efficient way of cutting emissions, it has been discredited in the popular discourse by opponents branding it as a punitive tax. In my view, inadequate communication with the public is partly to blame: Australia's former government failed to explain that carbon-pricing revenue is returned to low- and middle-income earners (under the new scheme, the taxpayer would pay to reduce emissions). Moreover, economists should have proclaimed their almost unanimous support for putting a price on carbon emissions.

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Learn from China's local pilot schemes

I agree that international road maps for reducing carbon emissions will ultimately depend on stitching together inspired local initiatives (E. Diringer *Nature* **501,** 307–309; 2013). Good examples are the local pilot schemes set up nationwide in China (see, for example, *Nature* **498,** 145–146; 2013).

The National Development and Reform Commission of China selected five provinces and eight cities in 2010 for the first round of low-carbon pilots, and has now included another province and 28 more cities in the second round. The scheme encourages policy innovation by local governments for low-carbon development and includes timetables for reducing greenhouse-gas emissions.

A survey by my team has revealed that several of these pilots are using innovative measures to upgrade conventional manufacturing and agriculture, to ensure that new industries, buildings and transportation conform with these plans, and to improve energy efficiency and carbon-sink capacity through ecological programmes.

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Better drug access for terminal patients

The distinguished statistician Les Halpin died last month from motor neuron disease, aged 56. He was the founder of the Empower: Access to Medicine campaign to improve the availability of experimental therapies and to accelerate drug approval and licensing for people with life-threatening illnesses (see go.nature.com/v2nr3y).

After his diagnosis in May 2011, Halpin was surprised by the lack of treatments for people with his disease. This led him to ponder, from a statistical viewpoint, the regulatory systems that we apply to biomedical innovation, noting that they are much more risk-averse than the patients they are intended to serve. He believed that as a result, new medicines take longer to develop and are more costly than necessary.

His campaign has enabled drugs to get to market faster and more cheaply (see, for example, go.nature.com/gmgcyu). With support from academics, politicians and industrial scientists, he developed the Halpin Protocol (see go.nature.com/3z2wkd), which has sparked debate in the UK Parliament.

Halpin's campaign to overcome barriers to health-care translation will continue, aiming to lower them objectively and safely through increased flexibility in drug development and regulation.

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Big data for a sustainable future

As discussions on Sustainable Development Goals end this week at the United Nations General Assembly in New York, I call for more 'big data' to help secure a sustainable future (see also D. Griggs *et al. Nature* **495,** 305–307; 2013). We should be collecting big data that can be used to model and test an array of different scenarios for sustainably transforming the production and consumption of energy, improving food and water security, and eradicating poverty.

Managing these issues will also help to rebalance important biogeochemical cycles (especially the carbon, nitrogen and phosphorus cycles), mitigate climate change, reverse ocean acidification and reduce the loss of biodiversity. Big data will help to illuminate the origins, nature and scale of these challenges, and how they relate to one another.

National databases and research centres can be linked to create huge databases. Initiatives similar to those of the Intergovernmental Panel on Climate Change and the Global Ocean Observing System could fill the gaps in scientific, technical and socio-economic data. New initiatives such as Global Pulse (www.unglobalpulse.org) could help in mining and mobilizing big data, which are available in real time as a result of the explosive growth in new media.

The collection and use of big data sets needs to be coordinated globally, between regions and countries, as well as between relevant agencies and institutions. The United Nations and the International Council for Science could help to forge these collaborative initiatives and networks.

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Great scientists and society

Robert White and colleagues point out that most scientific luminaries from centuries past were religious (*Nature* **501,** 33; 2013). This says a great deal about the societies that these scientists lived and worked in, but little about the value or truth of a theistic world view, as can be seen by considering what else these great names have in common: they were all men.

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Journal of Tissue Engineering
Volume 5: 1–8
© The Author(s) 2014
DOI: 10.1177/2041731414551764
tej.sagepub.com
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Quantitative assessment of barriers to the clinical development and adoption of cellular therapies: A pilot study

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Abstract

There has been a large increase in basic science activity in cell therapy and a growing portfolio of cell therapy trials. However, the number of industry products available for widespread clinical use does not match this magnitude of activity. We hypothesize that the paucity of engagement with the clinical community is a key contributor to the lack of commercially successful cell therapy products. To investigate this, we launched a pilot study to survey clinicians from five specialities and to determine what they believe to be the most significant barriers to cellular therapy clinical development and adoption. Our study shows that the main concerns among this group are cost-effectiveness, efficacy, reimbursement, and regulation. Addressing these concerns can best be achieved by ensuring that future clinical trials are conducted to adequately answer the questions of both regulators and the broader clinical community.

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Keywords
Cell- and tissue-based therapy, translational medical research, regenerative medicine, tissue engineering, stem cells

Received: 28 May 2014; accepted: 20 July 2014

Introduction

Cellular therapies offer significant potential to treat multiple diseases and injuries, many of which are poorly addressed by the current standards of care. These groundbreaking therapies have grown out of, and to some extent encompass, concepts from both tissue engineering (TE) and regenerative medicine (RM), first described in the 1980s[1] and 1990s,[2] respectively (see Table 1 for definitions). Despite significant developments in these areas, there are still relatively few commercially available products in widespread use that utilize the principles of these two fields, as seen in Table 2 (adapted from French et al.[3]).

The most widely used products have been in the TE and bone marrow transplant areas, yet as outlined by Jaklenec et al.,[4] the TE space has experienced a fitful tenure over the last 25 years. The failure of products to live up to the promise held during development has negatively impacted upon the willingness of clinicians to embrace these technologies, consequently resulting in a lack of long-term efficacy data.[5] More recently though the sector has overcome some of these early disappointments facilitated by early evidence of clinical success, investor appetite, and expanded research funding.[6–8]

It is important to recognize that there is a lack of consistency in the use of terms such as "cell-based therapies," "regenerative medicine," "tissue engineering," and "stem cell therapy," with some treating the terms as distinct entities, while others use them synonymously.[4] Within this article, the term "cellular" or "cell-based therapy" encompasses any treatment that involves the use of exogenous cells (autologous or allogenic) in an attempt to repair diseased or damaged tissue.

Cell-based therapy progress

The rapid growth of this sector is clearly demonstrated by the soaring number of clinical trials that seek to use cell-based therapies.[9,10] Despite this, the number of cell-based therapies available in the marketplace has remained fairly stagnant.[3]

To better understand this disparity, we have sought to investigate the potential barriers to the clinical development and adoption of this class of novel therapeutics as perceived by the end users of such therapies, clinicians, via an initial pilot study. It is hoped that by successfully identifying these root causes, it will be possible to streamline and accelerate the process by which potentially useful cell-based therapies are developed and then brought into mainstream use. We therefore conducted a pilot study at a leading hospital in the United Kingdom as a necessary and informative basis for future investigations.

Materials and methods

To identify the main barriers to adoption from the point of view of clinicians, 50 specialists were approached at a leading academic teaching hospital group in the United Kingdom, evenly split into the following areas:

- Cardiology
- Neurology
- Ophthalmology
- Orthopedic Surgery
- Plastic and Reconstructive Surgery

These specialities were carefully chosen as areas in which there has been research and development of cellular therapies or in which there is significant contemporary interest in basic stem cell science. Historically, Orthopedic Surgery has been the trailblazer since autologous chondrocyte implantation was first described 20 years ago.[11] The other clinical specialities have been the focus of cell-based therapies in recent years with treatments designed for myocardial infarction,[12] multiple sclerosis,[13] and retinal photoreceptor loss.[14]

Participants were surveyed between July and August of 2013. Participants were asked about their experience using cellular therapeutics and then required to assess whether 12 areas were seen as a barrier to cellular treatment use. A copy of the questionnaire is provided in the Supplementary Material and the areas covered were as follows:

- Safety
- Efficacy
- Clinical trial methodologies
- Cost-effectiveness
- Usability
- Visibility
- Patient characteristics
- Patient attitudes and preferences
- Infrastructure
- Reimbursement
- Community
- Regulation

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A Likert-style scale was used to assess responses. Each question was scored on a scale of 1 (No Barrier) to 5 (Significant Barrier). Responses from the questionnaire were averaged across all respondents and within each speciality and then ranked in order from the smallest perceived barrier to the largest.

The results were analyzed separately by speciality and also as a whole for the complete group. Analysis was carried out using Prism 6 (GraphPad Software Inc., San Diego, CA, USA).

Results

Responses were obtained from 50 individuals in total with 10 in each speciality group. The participants had a range of knowledge and experience with cell-based therapies as shown in Figure 1.

There was no significant difference in the experience spread within the individual specialities (Kruskal–Wallis=7.7; $p=0.17$). The majority of participants had some knowledge of the field of cellular therapies although very few had actually used them in a clinical setting.

Table 1. Definition of key terms.

Term	Definition
Tissue engineering	"An interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function."[38]
Regenerative medicine	A technique that "replaces or regenerates human cells, tissue or organs, to restore or establish normal function."[39]

Figure 2 shows the mean level for perceived barrier for all respondents and the variation in the mean response for each speciality from the group mean. Higher numbers represent a larger perceived barrier to adoption. The data show that the most concerning barriers to clinicians were cost-effectiveness and efficacy, followed by regulation, reimbursement, and safety. Infrastructure also frequently occurred in the top three responses.

Figure 3 shows the average score for each question in each group. A heat map has been constructed with green being the smallest barrier and red the largest barrier to adoption to help visualize the spread of opinion across specialities. Interestingly, a number of notable concerns were identified in relation to clinical speciality, although due to the sample size of this pilot study, further investigation is required. Neurologists identified *patient characteristics* as a major barrier to cell therapy utilization in comparison to the other four clinical specialities (Figure 3). Ophthalmologists were concerned by *usability*; orthopedic surgeons identified *clinical trial methods* and plastic surgeons *efficacy* and *patient preference*.

Discussion

The results from our pilot study show that across multiple specialities, there is a degree of consistency for which barriers to development and adoption are perceived as the largest for cell-based therapies, namely, efficacy and cost-effectiveness. The remaining barriers perceived to be significant do vary between groups with reimbursement, safety, regulations, and infrastructure all identified consistently within the highest ranking barriers, as shown in Figure 4.

Table 2. Cellular therapy products in use.

Medical speciality	Company	Product	Condition
Cardiology	FCB Pharmicell	Heartcelligram	Acute myocardial infarction
Diabetes	Organogenesis	Dermagraft	Diabetic foot ulcers
Diabetes/Vascular Disease	Organogenesis	Apligraf	Venous leg and diabetic foot ulcers
Gastroenterology	Anterogen	Cupistem	Crohn's disease
Maxillofacial Surgery	Organogenesis	Gintuit	Gingival repair
Orthopedics	Genzyme	Carticel	Articular cartilage repair
Orthopedics	Medipost	Cartistem	Articular cartilage repair
Orthopedics	NuVasive	Osteocel Plus	Skeletal defects
Orthopedics	Orthofix	Trinity Evolution	Musculoskeletal defects
Orthopedics	TiGenix	ChondroCelect	Articular cartilage repair
Plastics	Avita Medical	ReCell	Burns/scars
Plastics, Orthopedics, Ophthalmology	Japan Tissue Engineering	J-TEC Epidermis/Cartilage/ Corneal Epithelium	Burns, cartilage repair, ocular repair
Urology	Dendreon	Provenge	Prostate cancer
	Osiris	Prochymal	Graft-vs-host disease
	Genzyme	Epicel	Severe burns

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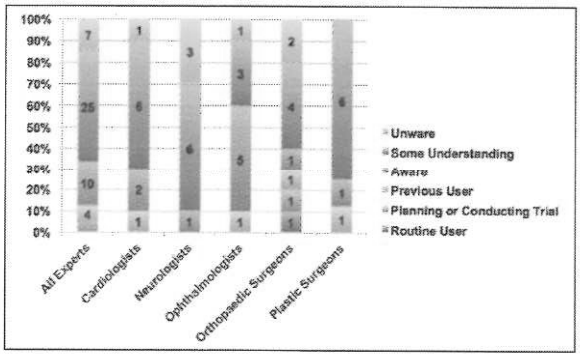

Figure 1. Survey participant knowledge and extent of familiarity with cell therapy products.

It is no surprise that *efficacy* poses a considerable barrier in the opinion of those asked, followed closely by *safety*, as the primary aim of the clinician is to treat and hopefully cure the patient. Deficiencies in safety and efficacy results can to some extent be explained by the often limited understanding of the underlying mechanism of action.[15] Additionally, heterogeneity in clinical trial structures, treatment protocols, and results presentation, combined with the limited body of historic patient outcome data, further impede clinical decision-making for when these treatments may be beneficial.[16–19] Data limitations are also challenging from a health economics perspective.

In most cases, cellular therapies are significantly more expensive than the treatment that they seek to replace.[20] They can, however, potentially offer a longer lasting solution and the opportunity to regenerate tissue, unlike traditional treatments.[21] It is therefore vital, in both private and public provider systems, to ensure that adequate product *cost-effectiveness* is demonstrated to justify appropriate *reimbursement* codes for the entire treatment pathway, which in the case of autologous products includes medical procedures relating to tissue acquisition.[22] As such, it is evident that many cell-based therapeutics are likely to exhibit different direct and indirect cost structures to established non-cell-based products and services,[23] in part, due to the unique infrastructural demands concerning their delivery.

For all healthcare innovations, the requisite delivery *infrastructure* and appropriate *regulation(s)* are intimately linked;[24] principally, due to the need to maintain product critical quality attributes (CQAs) throughout the entire biomanufacturing process from tissue acquisition to administration.[25–27] Given the interdependence of cellular therapies on their bioprocessing environment,[28] they are highly reliant upon the availability and compliance of Current Good Manufacturing Practices (cGMP) laboratories, internal and external to hospital settings, that must adhere to strict workflows for provision and manipulation of cells and tissues for the safe re-implantation to the patient.[29] The lack of supporting data for point-of-care (POC) processing technologies which avoid the need for cGMP laboratories explains, to some extent, the lack of clinical confidence in these systems.[30,31] Moving forward, these systems must therefore be designed such that ease of use and safety of the cellular material is paramount and the path to approval is clear.[32]

More generally, *clinical trial methodologies* were not felt to be a large barrier to adoption within our pilot study, which may be due to a perception of the rigor with which trials are conducted or a lack of concern regarding the methodology of clinical trials, yet recent late-stage failures intimate that greater caution may be required.[33,34] Interestingly, orthopedics, a speciality in which cell therapies have been more frequently utilized, identified clinical trial methodologies as a barrier in comparison to the other clinical groups. *Usability* was of moderate concern to most groups which further emphasizes the need to develop technologies that are easily adopted for a wide variety of clinical settings, ideally with minimal training for support staff, such as operating department assistants. Finally, *patient attitudes and preferences* were frequently listed in the three smallest barriers to adoption, possibly due to a lack of patient awareness as to the available options and/or a clinician belief that it may not be worth discussing options with patients for which they have limited confidence or that are not readily available. It should be noted, however, that as this pilot study was performed in the United Kingdom, an emphasis with regard to patient attitudes and preferences in private payer systems, such as the United States, maybe expected to yield different results.

Additionally, the ranking distribution for different issues may be due to the variation in previous exposure to these treatments. Although there was no significant difference in the self-reported level of experience of cellular therapies between the groups, there is a great deal of variation in the extent to which trials of cell therapy treatments have penetrated the various specialities.[35] Simply by examining the currently available cellular therapies as shown by the review undertaken by French et al.,[3] very few of these treatments are available within normal clinical practice.

Limitations

The main limitation affecting this study comes from the use of a questionnaire and from the sample size of the pilot study. It is not possible with this design to ensure that there is exactly the same level of understanding of the issues being asked about between specialists. This variation in understanding will, however, better reflect the understanding of all clinicians rather than use subject experts only. It is also not possible to determine the exact nature of the reason for which experts attribute a particular score, so underlying motivations may be better elicited in future studies with the opportunity for qualitative responses. The restriction of this pilot study to a single hospital group will also skew the conclusions that we have attempted to draw

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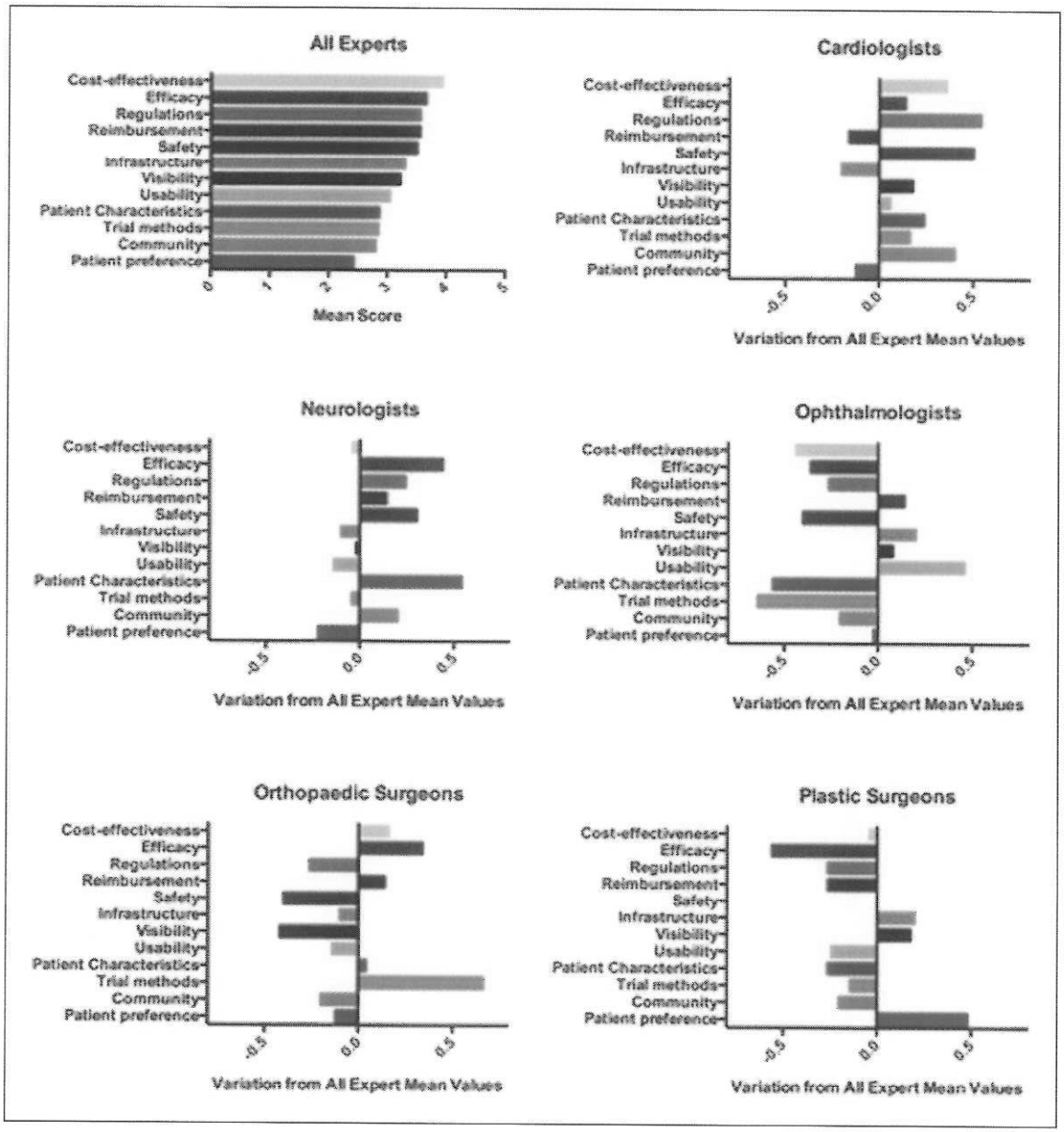

Figure 2. Perceived barriers to clinical development and adoption as identified through pilot questionnaire. Responses are presented as the mean for the whole group and then variation in each speciality's mean response from the group mean. A higher score represents a greater perceived barrier.

from the results. Nonetheless, scores obtained were wide-ranging both between groups and individuals, hence the risk of having surveyed a biased subset of specialists was likely minimal.

The route ahead

While immense investment into the cell-based therapy market has occurred over the last decade,[36,37] this increase has sadly not been matched by the widespread availability of treatments to patients. It is clear that while the scientific barriers to the creation and development of effective cellular therapies are gradually being overcome, another sizable potential barrier to broad adoption lies in the attitudes and decision-making processes of the clinical community to prescribe and recommend such innovative approaches.

Despite the diverse availability of cell-based therapies in different clinical specialities, it is clear from this pilot study that similar barriers to clinical development and adoption are common among all. The majority of these barriers related to clinician concern (cost-effectiveness, efficacy, and safety) can only be successfully tackled by

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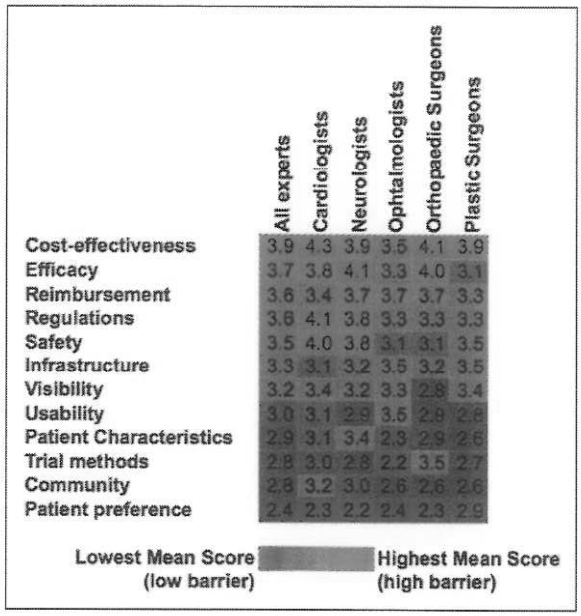

Figure 3. Heat map of mean response data to perceived barriers by clinical speciality. Data are presented as the mean response from the polled clinicians.

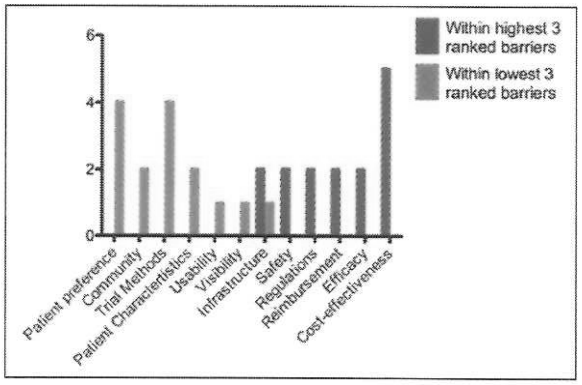

Figure 4. Frequency with which each barrier appears in highest or lowest three perceived barriers (ordered as per "All Experts" mean ranking).

conducting well-designed clinical trials that effectively address the following areas:

- Appropriate length of follow-up to ensure that clinical benefits are maintained over a period that is clinically relevant. Significant benefits would also be gained from identifying short-term indicators correlated with long-term outcomes for the indication in question.
- Use of a variety of clinical- and laboratory-based outcome measures to allow comparison between different trials.
- Current standard of care, where possible, is included within the trials as a control arm.
- Design therapies and trials to enable the regulatory issues of different markets to be addressed in an efficient manner.

Thoughtful clinical trial design, focused on the above criteria and involving the clinicians at an early stage, should allow not only effectiveness of a treatment to be confirmed but also safety and cost-effectiveness with relative ease. It should then be possible to address regulatory issues in such a way as to minimize delays in bringing these innovative treatments to market, and therein reaching the end goal of treating patients suffering with unmet medical needs.

It is our intention to progress the findings identified in this pilot study by carrying out a further round of questioning covering an international set of locations and widening the specialities to include others such as Ear, Nose, and Throat Surgery and Urology. The sample number of the clinicians surveyed will be significantly extended. This will, hopefully, allow us to capture a broader, and more representative view of the barriers that clinicians perceive to be preventing cellular therapy use. Findings will then be reviewed by an international expert panel to maximize the value of conclusions drawn from the data obtained.

Centre for the Advancement of Sustainable Medical Innovation Translational Stem Cell Consortium

Clinical perspective questionnaire

The Centre for the Advancement of Sustainable Medical Innovation (CASMI) Translational Stem Cell Consortium (CTSCC) is an international, multi-stakeholder collaboration aiming to provide a global nexus for the efficient and sustainable translation of fundamental stem cell science into tangible products and services. Due to the novel nature of cellular therapies, it is evident that the clinical community will play a critical role in their successful adoption. As such, it is imperative that we poll the opinions of surgical clinicians like yourself in order to best address the potential barriers that currently or may in the future be impediments to these therapies from your perspective.

Section 1: Respondent Background Information

Clinical Specialty: _____

Job Title or Position: _____

Extent of Experience with Cellular Therapeutics: (Please indicate all that apply)

Please state the reasons that stopped you from using cellular therapy (if any):

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Routine user of cellular therapies	Aware of available cellular therapies in your field; however, specific reason(s) unwilling to use them. (please state why below)
Currently holding or planning a cell therapy clinical trial	Some understanding the fundamental science underpinning cellular therapeutics
A previous user of cellular therapies; however, for any reason(s) have ceased using them	Unaware of landscape and possible cellular therapy options

Section 2: Assessment of Barriers to Clinical Adoption

Following an industry review, the following factors have been suggested as barriers to the adoption of cellular therapeutics. Below please indicate the extent to which you believe each case is a potential impediment to their clinical success, where 1 = No Barrier(s) and 5 = Significant Barrier(s)

1. *Safety*: Extent of available data concerning product safety including the stage of development of underlying science and/or characteristics of biomaterials utilized in tissue engineering.
2. *Efficacy*: Extent to which available data concerning product efficacy profiles, including the extent to which mechanisms of action, have been proposed and identified.
3. *Clinical Trial Methodologies*: Quality and rigor of clinical trial designs implemented.
4. *Cost-Effectiveness*: Availability of data to inform evaluations of the benefits of cellular therapeutics versus standard(s) of care.
5. *Usability*: Limitations in ease of use.
6. *Visibility*: Level of awareness of cellular therapeutics and their applications within the clinical community.
7. *Patient Characteristics*: Limitations in the number of patients with suitable prognosis to facilitate the administration of a cellular therapeutic:
8. *Patient Attitudes & Preferences*: Level of patient familiarity, resistance, or concern around cell therapies, such as concerns regarding "stem cell stigma."
9. *Infrastructure*: Uncertainties in clinical delivery including available expertise, equipment, "chain(s) of custody" control, or others.
10. *Reimbursement*: Relative provision and/or knowledge of reimbursement pathways compared to routine therapies.
11. *Community*: Impact of peer opinion(s) on clinical decision-making.
12. *Regulation*: Level of certainty or ambiguity in the regulatory pathway including the regulatory classification of cellular therapeutics and/or responsibilities of clinical practitioners and fear of malpractice.

Acknowledgements

This work was carried out by the Centre for the Advancement of Sustainable Medical Innovation (CASMI) and we wish to express our sincere thanks to the following organizations that have contributed to the consortium as funding and event partners—without whom the consortium and the benefits it will bring to stem cell translation would be unacceptably constrained: GE Healthcare, CCRM, TAP Biosystems, Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, and NIH Centre for Regenerative Medicine. We would also like to thank Mr Prasanna Sooriakumaran for his assistance with this study. Andrew Carr and David A Brindley are joint senior authors.

Declaration of conflicting interests

We would like to make the following declarations regarding conflicts of interest:

B.R. is a stockholder in Pathfinder Cell Therapy (MA, USA). R.W.B. is an independent director and/or stockholder in Celgene (NJ, USA). K.B. is an employee and/or stockholder in Sartorius Stedim (Göttingen, Germany). J.M.K. was supported by National Institutes of Health grant HL095722, Department of Defense grant W81XWH-13-1-0305, and by a Movember-Prostate Cancer Foundation Challenge. The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B. gratefully acknowledges the support from the SENS Research Foundation (Mountain View, CA, USA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that among other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. D.A.B. is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such, this author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. Additionally, at the time of publication, D.A.B. and the organizations with which he is affiliated may or may not have agreed and/or pending funding commitments from the organizations named herein. D.A.B. has also conducted paid consultancy for Lonza Group and Sartorius Stedim within the past 7 years with a cumulative value of greater than US$10,000. All the other authors do not declare any additional conflicts of interest, as defined by the journal. However, the authors are happy to respond to direct requests for confirmation and stress that affiliations stated may or may not constitute a disclosure of employment and/or ownership of financial instruments in the named entity.

Funding

This work was supported by National Institutes of Health grant HL095722, Department of Defense grant W81XWH-13-1-0305, and by a Movember-Prostate Cancer Foundation Challenge Award to J.M.K.

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BMJ

BMJ 2014;348:g3253 doi: 10.1136/bmj.g3253 (Published 21 May 2014)

RESEARCH

Use of placebo controls in the evaluation of surgery: systematic review

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Abstract

Objective To investigate whether placebo controls should be used in the evaluation of surgical interventions.

Design Systematic review.

Data sources We searched Medline, Embase, and the Cochrane Controlled Trials Register from their inception to November 2013.

Study selection Randomised clinical trials comparing any surgical intervention with placebo. Surgery was defined as any procedure that both changes the anatomy and requires a skin incision or use of endoscopic techniques.

Data extraction Three reviewers (KW, BJFD, IR) independently identified the relevant trials and extracted data on study details, outcomes, and harms from included studies.

Results In 39 out of 53 (74%) trials there was improvement in the placebo arm and in 27 (51%) trials the effect of placebo did not differ from that of surgery. In 26 (49%) trials, surgery was superior to placebo but the magnitude of the effect of the surgical intervention over that of the placebo was generally small. Serious adverse events were reported in the placebo arm in 18 trials (34%) and in the surgical arm in 22 trials (41.5%); in four trials authors did not specify in which arm the events occurred. However, in many studies adverse events were unrelated to the intervention or associated with the severity of the condition. The existing placebo controlled trials investigated only less invasive procedures that did not involve laparotomy, thoracotomy, craniotomy, or extensive tissue dissection.

Conclusions Placebo controlled trial is a powerful, feasible way of showing the efficacy of surgical procedures. The risks of adverse effects associated with the placebo are small. In half of the studies, the results provide evidence against continued use of the investigated surgical procedures. Without well designed placebo controlled trials of surgery, ineffective treatment may continue unchallenged.

Introduction

Modern surgery is changing rapidly. Surgical interventions can now be offered to improve function and quality of life not just to save life. The improvement in the safety of surgical procedures and anaesthesia has facilitated this change.[1] The mortality associated with anaesthesia has decreased from between 64 and 100 in 100 000 in the 1940s to between 0.4 and 1 in 100 000 at present.[1 2] The prevalence of serious adverse events related to surgical interventions has remained relatively constant over the past 10 years, despite an increase in the number of surgical procedures performed each year.[3 4] The postoperative death rate is between 1.9% and 4% and in most cases is due to the primary disease.[3 5]

The increase in the applications for surgical procedures has been driven by a greater involvement of technology in surgical procedures. Such technological advances have made many

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Terms used to search databases
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interventions less invasive, more likely to be endoscopic, and less resembling typical open surgery, such as laparotomy. However, these new procedures are often introduced into surgical practice without any formal evaluation of safety and efficacy, such as using randomised clinical trials. This is because, unlike drug products, such verification is currently not mandated by regulatory authorities.[6] Furthermore, there is generally a scarcity of information reported on the surgical learning curves or the iterative development of a new technique. Both existing and innovative surgical practice clearly needs to be evaluated, and any evaluative method should take account of the unique idiosyncrasies and challenges presented by surgical interventions.

In considering any scientific evaluation, it is important to remember that an outcome of a surgical treatment is a cumulative effect of the three main elements: critical surgical element, placebo effects, and non-specific effects.[7] The critical or crucial surgical element is the component of the surgical procedure that is believed to provide the therapeutic effect and is distinct from aspects of the procedures that are diagnostic or required to access the disease being treated.[8] The placebo effects are related to the patients' expectation and the "meaning of surgery," whereas the non-specific effects are caused by fluctuations in symptoms, the clinical course of the disease, regression to the mean, report bias, and consequences of taking part in the trial, including interaction with the surgeons, nurses, and medical staff.[7 9 10] It is reasonable to assume that surgery is associated with a placebo effect.[11-13] Firstly, because invasive procedures have a stronger placebo effect than non-invasive ones[12] and, secondly, because a confident diagnosis and a decisive approach to treatment, typical for surgery, usually results in a strong placebo effect.[14]

Placebo controlled randomised clinical trials of surgical interventions are relatively uncommon.[15-17] Studies published so far have often led to fierce debates on the ethics, feasibility, and role of placebo in surgery.[18-21] One reason for the poor uptake is that many surgeons, as well as ethicists, have voiced concerns about the safety of patients in the placebo group. Many of the concerns are based on personal opinion, with little supporting evidence.[18-21] In the absence of any comprehensive information on the use of placebo controls in surgery, and the lack of evidence for harm or benefit of incorporating a placebo intervention, a systematic review of placebo use in surgical trials is warranted.

We assessed whether placebo controls should be used in the evaluation of surgical interventions by systematically reviewing all clinical trials in which the efficacy of surgery was compared with a placebo control.

Methods

Selection criteria

We performed a systematic review adhering to published guidance from the Cochrane Collaboration.[22] Studies were eligible if they were randomised clinical trials in which the efficacy of surgery was compared with placebo. We defined surgery as any interventional procedure that changes the anatomy and requires a skin incision or the use of endoscopic techniques; dental studies were excluded. We used the term placebo to refer to a surgical placebo, a sham surgery, or an imitation procedure intended to mimic the active intervention; including the scenario when a scope was inserted and nothing was done but patients were sedated or under general anaesthesia and could not distinguish whether or not they underwent the actual surgery. We did not limit the inclusion criteria to any particular condition, patient group, intervention, or type of outcome. We excluded studies investigating anaesthesia or other drug substances used perioperatively.

Search strategy

We developed search strategies for three electronic databases: Medline (Ovid), Embase (Ovid), and the Cochrane Central Register of Controlled Trials. We searched the databases from the date of their inception to 14 November 2013, with no restriction on language. (See supplementary appendix 1 for details of the search terms.) We did not systematically search for studies reported only as conference abstracts.

Three reviewers (KW, IR, BJFD) independently screened the initial set of records identified from the search and then screened the full text of any potentially relevant articles. Each reviewer independently assessed the eligibility of each study, and the final list of included studies was agreed by consensus.

We also screened the references of the relevant articles. Furthermore, we searched ClinicalTrials.gov (on 14 November 2013), a database of registered randomised clinical trials, to identify any recently completed or ongoing studies.

Dealing with duplicate publications

If several articles reported outcomes from a single trial (that is, with the same authors, location, patient population, and recruitment dates), we only included the article reporting the main outcome for the trial.

Data extraction

We used a standardised data extraction form to collect information about the characteristics of each study as well as the clinical improvement and superiority of the surgical intervention compared with the placebo for the main study outcome, as reported by the authors in the published article. For each study we extracted the year of publication; study population; condition; intervention; outcomes; sample size; number of participants; number of events, as well as mean and standard deviation for continuous outcomes; and serious adverse events and whether they were related to the procedure. To reduce the chance of errors, the three review authors extracted data separately, checked the entries for consistency, and agreed on a single set of data.

Risk of bias assessment

The three review authors also independently assessed the risk of bias in the included studies using the risk of bias tool criteria recommended by the Cochrane guidelines.[22 23] In particular we assessed the method of random sequence generation; concealment of treatment; blinding of participants, care providers, and assessors; success of blinding; and use of intention to treat analysis.

Data synthesis

We assessed the beneficial effect of the surgical intervention on the basis of the original conclusions as any improvement in the main outcome of the trial and as superiority of the surgical treatment over the placebo—that is, the additional benefits of the critical surgical element. Moreover, we calculated statistically significant difference between the surgical intervention and placebo using the information reported in the results section of each study. We calculated the odds ratio for binary outcomes and the effect size for continuous outcomes using the effect estimate from analysis of covariance, the

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difference in change score, or the difference in postoperative score, depending on the method of analysis and data reported within each individual study. We included only the primary outcome measure, whenever it was explicitly specified. If two primary outcomes were reported, we used both; however, when there were several main outcome measures, we chose those reported in the abstract or those used in other studies, so that the forest plots present similar outcomes. Where necessary, we changed the direction of effect so that the improvement was consistently presented in the same way in the forest plots.

As a measure of harms, we examined serious adverse events and whether they were attributable to the surgical or the placebo intervention. An optimal strategy to identify reports of adverse events does not exist.[24] We defined serious adverse events as harmful events that occurred during the trial, such as prolonged hospital stay, and events that required admission to hospital or resulted in death. We summarised the serious adverse events data using a grading system according to their severity, as definitely, likely or unlikely to be serious, and a grading system according to relation between the event and the procedure as definitely, likely, unlikely to be related to the procedure. Wherever possible, we used the results from the intention to treat analysis. Most studies did not provide sufficient information about harms to enable a formal statistical analysis.

Owing to the considerable heterogeneity of conditions, interventions, and outcomes it was not feasible to combine the results of individual studies in a meta-analysis. We present a descriptive analysis of the results of each individual study and present data in tables and figures. All analyses were carried out in Stata (version 12.1).

Results

Study selection

The search of Medline, Embase, and Cochrane databases identified a total of 4543 records. We found an additional 23 articles using a hand search of relevant literature and the references of the articles identified using the database search. Out of these 4566 records, 1597 duplicates were discarded, leaving 2969 records; of these, 2860 did not meet inclusion criteria, and a further 56 studies were excluded after reviewing the full text of the article. Among them were 12 articles reporting additional outcomes of a trial, seven follow-up papers, and seven studies that reported results in a way that made the comparison between the surgical and placebo arm impossible. This resulted in 53 full text articles that met the inclusion criteria and were included in this review. Figure 1⇓ details the study identification and reasons for exclusion.

A keyword search of the ClinicalTrials.gov database identified 14 relevant trials, including two studies already found using the electronic search[25 26] and 12 studies that were not yet available as full text articles in November 2013.

Risk of bias assessment

All included studies were assessed for risk of bias (see supplementary appendix 2). The risk of bias related to sequence generation, concealment of treatment allocation, and blinding during the procedures was generally low. In some trials the measures undertaken to maintain blinding were not explicitly described; however, these trials used endoscopic techniques in patients under general anaesthesia or sedation. Patients and assessors were blinded in almost all trials; in the trials in which assessors were not blinded, the outcomes were objective. Only 12/53 (23%) trials assessed whether the blinding was successful, including one in which the patients were likely to guess the correct allocation.[60]

Characteristics of the reviewed trials

Overall, 39 of the 53 (74%) included studies were published after 2000. Most of the trials investigated minor and not directly life threatening conditions, such as severe obesity (n=7; 13%) or gastro-oesophageal reflux (n=6; 11%). The most common type of intervention was endoscopy, with 23 trials (43%) using this technique as a part of the investigated procedure. Thirteen trials (25%) used some exogenous material, implant, or tissue, and a further six used balloons. Most studies reported subjective outcomes such as pain (n=13; 25%), improvement in symptoms or function (n=17; 32%), or quality of life (n=8; 15%). Less than half of the trials (n=22; 42%) reported an objective primary outcome—that is, measures that did not depend on judgment of patients or assessors. The majority of trials were small; the number of randomised participants ranged between 10 and 298, with a median of 60. No placebo controlled surgical trials investigating more invasive surgical procedures such as laparotomy, thoracotomy, craniotomy, or extensive tissue dissection were identified. Tables 1⇓ and 2⇓ list the characteristics of each trial.

Clinical benefit of improvement as reported by the trials' authors

In around three quarters (n=38; 72%) of the studies the authors reported an improvement in both the surgical group and the placebo group (table 3⇓). In a further seven trials,[30-36] the clinical improvement was observed in the surgical group but not in the placebo group; however, in five of these studies,[30-33 36] the outcome measures were objective and did not depend on patients' ratings. Finally, in six studies no improvement was reported in either group,[37-42] and one study could not be interpreted in terms of improvement as the main outcome was failure of treatment defined as new or continued bleeding.[43]

Superiority of surgery over placebo as reported by the trials' authors

In half of the included studies (n=26; 49%) the authors reported superiority of the surgical procedure over the placebo intervention, and in the remaining trials (n=27; 51%) the active surgical procedure was not statistically different from that of the placebo intervention (table 3).

Statistically estimated clinical benefit of critical surgical element in comparison to placebo

Overall, the magnitude of the treatment effect when the active surgical intervention group was compared with the placebo group was small but generally favoured the surgical treatment. The forest plots in figures 2⇓ and 3⇓ present the effect sizes and odds ratios for individual trials.

In 12 studies, the surgical intervention was significantly superior to placebo (tables 1 and 2 and figs 2 and 3).[28-30 33 34 36 44-49] In 11 studies, the effect of the surgical intervention was significantly better for only some of the reported primary outcome measures.[31 32 50-58] In 24 studies (45%), there was no statistically significant benefit of the active surgical intervention over the placebo (tables 1 and 2 and figs 2 and 3). In six studies we could not calculate the statistical estimated clinical benefit because the results were reported as median values and could not be used to calculate an effect size.[27 35 42 59-61]

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Harms

In just under half of the trials (n=23/53; 43%) the authors stated that there were no serious adverse events, although sometimes they reported minor adverse events (table 2). Three out of 53 studies (6%) did not report any information about adverse events. In the remaining 27 studies (51%), serious adverse events occurred in at least one of the study arms (table 1). In 17 of these 27 studies, serious adverse events were observed in both the surgical and the placebo arms, in five studies serious adverse events were only present in the active group, whereas in four studies the authors did not specify in which group the serious adverse events occurred. Not all serious adverse events were related to the procedure. For example, in six trials on gastrointestinal bleeding, deaths, rebleeds, or continuous bleeding were the main outcome of the study and were a result of the investigated condition and of the procedure being ineffective rather than it being harmful. In only two of these trials, adverse events, such as a perforation, were directly related to the intervention. In several trials, adverse events were rare (<5% of patients) or were unrelated to the procedure—for example, death from other causes. In general, the placebo arm was reported to be safer and adverse events were more serious and more common in the active group.

The interventions in the placebo arm were overall associated with less serious adverse events compared with the active arm, as the main surgical element was omitted and the authors made an effort to minimise risks by withholding part of the intervention—for example, partial burr holes rather than full trepanation[40] or not administering heparin.[39] Often the type of serious adverse events in the placebo group depended on the severity of the investigated condition and the invasiveness of the chosen procedure. Moreover, the serious adverse events in the placebo group were more likely if the procedures involved exogenous material; out of 13 trials using implanted exogenous substances, materials, or tissue, eight reported serious adverse events.[28 37-40 62-64]

Of the 27 trials in which serious adverse events occurred, 17 trials reported events that were related or likely to be related to the procedure in the surgical group (table 1). Most of the studies did not specify whether the serious adverse events were directly or potentially associated with critical surgical element or other elements of surgical interventions. Complications in the placebo group related or likely to be related to some element of the procedure were reported in nine studies. Harms definitely directly related to the surgical placebo were reported in two studies, and included infections[64] as well as complications related to the device and the investigated condition itself[37]; both trials were stopped early because of concerns about safety. In one of the trials on gastrointestinal bleeding, aspiration occurred in two patients in the placebo group that could have been related to the procedure as well as to the condition.[31]

The only adverse event reported as related to anaesthesia was in a trial by Schwartz and colleagues,[56] in which one patient in the placebo group had a bruise as result of a misplaced intravenous line during sedation.

Discussion

Surgical randomised clinical trials incorporating a placebo arm are rare but this review shows that the results of many of the trials provide clear evidence against continued use of the investigated surgical procedures and in well designed studies the risks of adverse effects are small and the placebo arm is safer than surgery. The identified surgical randomised clinical trials were heterogeneous. The existing placebo controlled trials investigated only less invasive procedures that did not involve laparotomy, thoracotomy, craniotomy, or extensive tissue dissection. About a half of the reviewed trials showed superiority of the surgical procedure over placebo intervention, but the magnitude of the effect directly related to the crucial surgical element was generally small. The majority of the trials showed an improvement in the surgical group as well as in the placebo group, which would suggest that some surgical procedures may have a placebo effect and that some of the benefits of surgery are related to factors other than the crucial surgical element.

Serious adverse events were reported in half of the reviewed trials, and the severity of possible serious adverse events was often related to the seriousness of the investigated condition and the invasiveness of the chosen procedure. Generally, the incidence of complications in the placebo group was lower than that in the surgical arm.

Strengths and weaknesses of this study

Modern surgery involves not only open surgery but also minimally invasive procedures, implants, and transplants; therefore, the boundary between surgery and other medical procedures was not always clear. In addition, identifying unique studies was not always straightforward—that is, differentiating between papers reporting two similar trials or different outcomes of the same trial.

Many trials reported several outcomes, often without identifying the primary measure. As a consequence we had to report only the outcomes for which the study had been powered, those reported in the abstract, or those used in other similar studies. The lack of a clear primary outcome also meant that we could not report a single primary outcome per study.

The available data only allowed comparison of effects in the surgical arm versus the placebo arm and did not allow for any estimation of the magnitude of the placebo effect. Interestingly, the effects for surgery versus placebo were smaller than expected. Only one study included an observational group.[56] We specifically chose not to include surgical trials with waiting list controls. Analysis of the placebo effect without controlling for non-specific effects of being in the trial would be flawed, as was pointed out in the comments[66 67] in the original paper on placebo effects in surgery by Beecher.[68]

The quality of the included studies varied. Many studies were small and used several primary outcome measures or cumulative measures or used a subgroup analysis without comparisons between groups. Reporting of adverse events was poor and many authors did not specify the primary cause of the complications or in which group they occurred. In the recent trials, the adverse events were described in more detail, but further improvement is required.[69] The standardised way of reporting harms was published only in 2004.[70]

Possible benefits and harms and implications for clinicians and policy makers

The main benefit and value of placebo controlled randomised clinical trials is their ability to show the real efficacy of a surgical intervention. If a procedure is effective and superior over the placebo, the case is strong for it to be commissioned and funded. The opposite is also true; if a surgical procedure has no benefit over placebo the argument is strong for stopping its use. The well designed placebo controlled trial of surgery is a useful tool to challenge the continued commissioning and use of ineffective treatments.

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The trial participants usually gain direct benefits, the main one being the perceived improvement attributable to the intervention. Whether this is acceptable by doctors and patients is the subject of an ongoing debate.[71 72] Indirect benefits may include confirming or disproving the primary diagnosis thereby allowing patients to be referred for a more appropriate treatment. A reduced waiting time or receiving treatment free of charge (for treatment that is ordinarily paid for by patients) is a further potential advantage of taking part in a trial.

In the modern clinical setting the distinction between the research and treatment is less clear and these two are often integrated. The balance between benefits and overall risk to a patient in a trial and in standard clinical care are usually not much different, as both the clinical outcomes and the additional risks and inconveniences caused by additional assessments are not great.[73 74]

The negative consequences for the trial patients may be considered mainly in terms of harms. In most of the trials, the investigated conditions were non-life threatening and the main aim of surgery was to improve function, symptoms, and quality of life, to reduce pain, or to remove the need for drug use. In these trials the harms were either lack of improvement or complications arising from the procedure, such as perforation after endoscopy. In the trials on gastrointestinal bleeding, the investigated condition was potentially life threatening and the procedure was not elective. In these six trials the negative events, such as bleeding and deaths, were the primary outcome and an indicator that the intervention was ineffective.

Placebo controlled surgical trials raise important ethical concerns[18-20] but are justified when there is a genuine equipoise[19]; that is, a disagreement in the medical community about whether one treatment is superior to another, because standard treatment does not exist or its efficacy is questioned.

Such trials conform to the ethical principles of non-maleficence—that is, the duty not to inflict expected harm, and justice.[21] Surgical intervention may be associated with greater risk than drug intervention; therefore, to be justified it must be associated with greater "pure" benefit to outweigh such risks. Surgical trials are justified by equipoise not only when there is uncertainty about pure benefit, but also when there is uncertainty about whether benefit outweighs harms.

If a standard medical treatment is available, it may be offered as a part of the study, as in the trials on tissue transplantation in Parkinson's disease, in which the participants continued their L-dopa drug. In addition to that, if one of the treatments in the trial becomes recognised as effective or a new treatment becomes available during the conduct of the trial, equipoise is disturbed and ethically the study should be stopped, as was the case in one trial[61] where the intervention was accepted by the insurer as a standard procedure and the trial was terminated early, before it could show the superiority of the active procedure.

Another ethical concern is deception and risk to the trust between patients and surgeons. In the majority of studies and always in the recent trials, patients were informed about taking part in a placebo controlled trial, and informed consent was obtained. In the study by Moseley and colleagues, participants were also asked to write a clause in their notes acknowledging the fact that they might receive placebo intervention and that placebo might not be effective.[75] If patients are fully informed and give proper consent, then from the ethical point of view the conditions of free consent and autonomy are fulfilled.

Surgery of any form, including placebo surgery, is associated with some level of risk, whereas a placebo tablet or drug is not. Therefore the balance between risks and benefits in surgical placebo controlled randomised clinical trials is different from that in drug trials. In most of the studies that reported serious adverse events, such complications were expected in the investigated conditions; even in the study on Alzheimer's disease, mortality was comparable with other trials.[37] What matters most is that risk is minimised and that actual harm is as small as possible.[76-78] In the reviewed trials, the placebo arm was usually designed to pose as little risk to the participants as possible and to be significantly less risky than the active surgical procedure.

In a situation where there is no certainty that the surgery is effective, the balance between risks and benefits within a study actually may be better in the placebo arm. For example, in the trials on fetal nigral tissue transplantation for Parkinson's disease, the active treatment was no better than placebo in terms of outcome and resulted in more severe side effects, such as dystonias and dyskinesias. Moreover, the risk of infection and other complications associated with the actual tissue implantation was much higher than the risk in the placebo group. Interestingly, in the study by Freed and colleagues,[38] patients who had been in the placebo group still opted for the surgical procedure after the trial, despite the fact that no clear benefit of fetal nigral tissue transplantation had been shown. This may be because patients believe that invasive,[12] new,[79] and expensive[80] procedures are actually more effective.

Effects of existing trials on change in practice

The results of the placebo controlled surgical trials performed so far have had a varied impact on clinical care. With the exception of the trials on debridement for osteoarthritis[75] or internal mammary artery ligation for angina,[81] most of the trials did not result in a major change in practice. Moseley's study on debridement for knee osteoarthritis was well received and resulted in limiting the recommendations for debridement and lavage for osteoarthritis of the knee to patients only with clear mechanical symptoms such as locking.[82] The reaction of the medical community to the trials on tissue transplantation to treat Parkinson's disease was also favourable. Although this treatment is not currently recommended,[40] the need for more studies on mechanisms of disease and on tissue transplantation is recognised.[83 84] These studies also provoked a discussion about ethical aspects of randomised clinical trials and placebo.[18 19 21 85]

In contrast, the results of the trials on the efficacy of vertebroplasty[62 64] were challenged and their authors were criticised for undermining the evidence supporting this commonly used procedure. The critics acknowledged that the injection of cement might be associated with many side effects, some of them potentially dangerous, but they argued that the treatment was justified because earlier unblinded trials had shown superiority of vertebroplasty over medical treatment.[62 64 86] This argument against the validity of placebo controlled trials neglected any potential placebo effect of vertebroplasty.

Unanswered questions and future research

The placebo component of surgery has to be explored and better understood. Future surgical trials need to be better designed and to include the observational control arm to allow the estimation of the magnitude of the placebo effect while controlling for non-specific factors such as spontaneous improvement or regression to the mean. We need to know the size of these effects and factors that influence their magnitude in order to properly interpret results of clinical trials in general, especially as many

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surgical trials nowadays use an observational design or case registers.

Placebo controlled trials in surgery are as important as they are in medicine, and they are justified in the same way. They are powerful, feasible way of showing the efficacy of surgical procedures. They are necessary to protect the welfare of present and future patients as well as to conduct proper cost effectiveness analyses. Only then may publicly funded surgical interventions be distributed fairly and justly. Without such studies ineffective treatment may continue unchallenged.

As surgery is inherently associated with some risk, it is important that the surgical treatment is truly effective and that the benefits outweigh the risks. Placebo controlled surgical trials are not free from adverse events but risks are generally minimal in well designed trials and the control arm is much safer than the active treatment. However, this review highlighted the need for better reporting of trials, including serious adverse events and their relation to a particular element of surgical procedure.

A need exists to "demystify" and extend the use of the surgical placebo in clinical trials. These should result in a greater acceptance of this type of trial by the surgical community, ethics committees, funding bodies, and patients. In turn, this would lead to more studies, better guidelines on the design and reporting of studies, and a larger body of evidence about efficacy and the risks of surgical interventions. Placebo controlled surgical trials are highly informative and should be considered for selected procedures.

Contributors: KW, AJC, and DJB conceived and designed the study. KW, AJ, SH, and GSC designed the search strategy and statistical analysis. KW, IR, and BJFD collected and managed the data. KW drafted the manuscript and is the guarantor of the study. KW, AJC, DJB, IR, BJFD, DB, JS, SH, and GSC critically revised the manuscript for important intellectual content. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis, and revised and approved the final version of the article.

Funding: This study was funded by the NIHR Oxford Musculoskeletal Biomedical Research Unit. The funding source had no role in the design and conduct of the study, in the collection, analysis and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: the authors are involved in a placebo controlled surgical trial on shoulder pain (NCT01623011); no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

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What is already known on this topic

Placebo controlled randomised clinical trials on efficacy of surgical procedures are rare and the main concerns are related to the benefits and harms related to such trials

What this study adds

In many of the reviewed trials improvement was present in both arms suggesting that the clinical effect may not be a result of the surgery; moreover, statistical superiority of the surgical procedure over the placebo was small

The absence of an observational or non-treatment control group in most studies precludes any evaluation of the magnitude of the placebo effect

Placebo controlled surgical trials are not free from adverse events, but the harms can be minimised and the placebo arm is generally much safer than the surgery arm

Placebo controlled trials of surgery are a powerful, feasible way of showing the efficacy of surgical procedures and without them ineffective treatment may continue unchallenged

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Accepted: 5 May 2014

Cite this as: *BMJ* 2014;348:g3253

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Tables

Table 1| **Characteristics of reviewed trials reporting serious adverse events**

									Serious adverse event††			
									Surgery		Placebo	
Reference	Condition	Intervention	Ex	Primary outcomes	No	Improvement	Superior	Significant*	Ser	Rel	Ser	Rel
Silverberg et al 2008	Alzheimer's disease	Ventriculoperitoneal shunt	Y	Clinical assessment	230	N	ND	N	Y	Y	Y	Y
Kallmes et al 2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Y	Pain, function	131	Both study arms	ND	N	Y	Y‡	Y	L‡
Castro et al 2010	Severe asthma	Radiofrequency bronchial thermoplasty	N	Quality of life	297	Both study arms	Surgical	Y/N	Y	Y‡	Y	L‡
Gross et al 2011	Parkinson's disease	Human cells transplantation	Y	Clinical assessment	71	Both study arms	ND	N	Y	Y	Y	U
Freed et al 2001	Parkinson's disease	Dopamine neurons transplantation	Y	Perception of change	40	N	ND	N	Y	L	Y	U‡
Stone et al 2002	Coronary disease	PMLR	N	Function	141	Both study arms	ND	Y	Y	L	Y	L‡
Salem et al 2004	Coronary disease	PMLR	N	Clinical assessment	82	Both study arms	Surgical	Y	Y	L	Y	L
Abbott et al 2004	Endometriosis	Laparoscopy+excision	N	Pain, quality of life	39	Both study arms	Surgical	Y/N	Y	L	Y	U‡
Lee et al 2001	Urinary stress incontinence	Autologous fat injection	N	Symptoms, function, objective test	68	Both study arms	ND	N	Y	Y	L	Y
Dowson et al 2008	Migraine	Patent foramen ovale closure	Y	Pain	147	N	ND	N	Y	Y	L	L
Hartigan et al 1994	Oesophageal varices§	Endoscopy+sclerotherapy	N	Bleeding, death	253	NR	Surgical	N	Y	†	Y	†
Fleischer et al 1985	Bleeding esophageal varices§	Endoscopy+laser	N	Bleeding	20	Surgical	Surgical	Y/N	Y	Y†	Y	Y†
Fullarton et al 1989	Bleeding peptic ulcers§	Endoscopy+heater probe	N	Bleeding	43	Surgical	Surgical	Y/N	Y	Y†	Y	†
Freitas et al 1985	Bleeding peptic ulcers§	Endoscopy+electrocoagulation	N	Bleeding, death	78	Both study arms	Surgical	N	Y	†	Y	†
MacLeod et al 1983	Bleeding peptic ulcers§	Endoscopy+laser	N	Bleeding, death	45	Both study arms	Surgical	N	Y	†	Y	†
Laine et al 1987	Upper gastrointestinal tract bleeding§	Endoscopy+electrocoagulation	N	Bleeding, death	44	Both study arms	Surgical	Y/N	Y	†	Y	†
Leon et al 2005	Coronary disease	PMLR	N	Function	298	Both study arms	ND	N	Y	L‡	Y	L‡
Corley et al 2003	GERD	Radiofrequency surgery	N	Symptoms, quality of life	64	Both study arms	Surgical	N	U	L	Y	L‡
Geenen et al 1989	Sphincter of Oddi dysfunction	Endoscopic sphincterotomy+ERCP	N	Symptoms, objective test	47	Both study arms	Surgical	Y	‡	Y	‡	Y
Buchbinder et al 2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Y	Pain	78	Both study arms	ND	N	‡	L	‡	L
Thompson et al 2013	Obesity	Transoral outlet reduction	N	Objective test	77	Surgical	Surgical	Y	‡	U	‡	U
Pauza et al 2004	Discogenic low back pain	Intradiscal electrothermal therapy	N	Pain, function, quality of life	64	Both study arms	Surgical	Y/N	‡	U	‡	U
Swank et al 2003	Chronic abdominal pain	Laparoscopy+adhesiolysis	N	Pain, quality of life, drugs	100	Both study arms	ND	Y/N	Y	Y	N	N

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Table 1 (continued)

Reference	Condition	Intervention	Ex	Primary outcomes	No	Improvement	Superior	Significant*	Serious adverse event††			
									Surgery		Placebo	
									Ser	Rel	Ser	Rel
Deviere et al 2005	GERD	Endoscopy+copolymer	Y	Drugs	64	Both study arms	Surgical	Y	Y	Y‡	N	N
Rothstein et al 2007	GERD	Endoscopy+plication	N	Quality of life	159	Both study arms	Surgical	Y	Y	L	N	N
Shaheen et al 2009	Barrett's oesophagus	Radiofrequency ablation	N	Clinical assessment	127	Both study arms	Surgical	Y	Y	L‡	N	N
Olanow et al 2003	Parkinson's disease	Fetal tissue transplantation	Y	Clinical assessment	34	N	ND	N	Y	U	N	N

Ex=exogenous material used; Imp=improvement as originally reported by the trial's authors, Sup=superiority of one arm over other as originally reported by trials' authors; No=number of patients randomised into trial; Sig=statistical significance of one arm over the other as calculated by us; Ser=whether adverse events were serious; Rel=whether serious adverse events were relevant to the procedure; ND=no difference; Y=yes; N= no; Y/N=yes or no depending on outcome; L=likely to be serious or related to the procedure; U=unlikely to be serious or related to procedure; PMLR=percutaneous myocardial laser revascularisation; NR=not reported; GERD=gastro-oesophageal reflux disease; ERCP=endoscopic retrograde cholangiopancreatography.

*Statistical significance of effect as calculated by us using reported values.

†Serious adverse events were direct consequence of investigated conditions not interventions.

††Graded according to severity: definitely serious (Y), that is, reported as serious adverse events by trial authors; likely to be serious (L), that is, not specifically reported as serious but resulting in death or admission to hospital; and unlikely (U) to be serious or reported as minor adverse events. Adverse events were also graded according to causality as definitely related to the procedure (Y), that is, reported by trials' authors as such; likely to be related to the procedure (L) as classified by us on basis of details reported by trials' authors; and unlikely to be related to the procedure or reported by trials' authors as unrelated to the procedure (U).

‡Trials' authors did not specify arm in which adverse events occurred.

§Trials on upper gastrointestinal ulcers or varices in which bleeding or death were the primary outcome.

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Table 2| **Characteristics of reviewed trials not reporting serious adverse events**

									Serious adverse event			
									Surgery		Placebo	
Reference	Condition	Intervention	Ex	Primary outcomes	No	Impr	Sup	Significant*	Ser	Rel	Ser	Rel
Guyron et al 2009	Migraine	"Deactivation" of trigger points	N	Pain	76	Both study arms	Surgical	Y/N	N	N	N	N
Scolapio et al 2001	Dysphagia	Endoscopy+B dilation	N	Function	86	Both study arms	ND	N	N	N	N	N
Bajbouj et al 2009	Globus sensation	Endoscopy+ablation of inlet patches	N	Symptoms	21	Surgical	Surgical	Y	N	N	N	N
Arts et al 2012	GERD	Radiofrequency surgery	N	Objective test	22	Surgical	Surgical	Y	N	N	N	N
Montgomery et al 2006	GERD	Endoscopic gastroplasty	N	Objective test, quality of life, drugs	46	Both study arms	ND	NR	N	N	N	N
Schwartz et al 2007	GERD	Endoscopic gastroplasty	N	Symptoms, drugs	60	Both study arms	Surgical	Y/N	N	N	N	N
Geliebter et al 1990	Obesity	Endoscopy+B	B	Objective test	10	Both study arms	ND	N	N	N	N	N
Hogan et al 1989	Obesity	Endoscopy+B	B	Objective test	59	Both study arms	ND	NR	N	N	N	N
Lindor et al 1987	Obesity	Endoscopy+B	B	Objective test	22	Both study arms	ND	N	N	N	N	N
Mathus-Vliegen et al 1990	Obesity	Endoscopy+B	B	Objective test	28	Both study arms	ND	N	N	N	N	N
Meshkinpour et al 1988	Obesity	Endoscopy+B	B	Objective test	23	Both study arms	ND	N	N	N	N	N
Genco et al 2006	Obesity	Endoscopy+B	B	Objective test, death	32	Both study arms	Surgical	Y	N	N	N	N
Bradley et al 2002	Osteoarthritis	Tidal irrigation	N	Pain, function	180	Both study arms	ND	Y/N	N	N	N	N
Moseley et al 2002	Osteoarthritis	Arthroscopic debridement or lavage	N	Pain	180	Both study arms	ND	N	N	N	N	N
Freeman et al 2005	Discogenic low back pain	Intradiscal electrothermal therapy	N	Pain, quality of life, clinical assessment	57	N	ND	N	N	N	N	N
Baeck et al 2009	Sleep apnoea	Radiofrequency surgery	N	Objective test, symptoms, quality of life	32	N	ND	NR	N	N	N	N
Gillespie et al 2011	Sleep apnoea	Palatal implants	Y	Objective test	51	Placebo	ND	N	N	N	N	N
Maurer et al 2012	Sleep apnoea	Palatal implants	Y	Objective test	22	Both study arms	ND	N	N	N	N	N
Friedman et al 2008	Sleep apnoea	Palatal implants	Y	Objective test	62	Surgical	Surgical	Y	N	N	N	N
Steward et al 2008	Sleep apnoea	Palatal implants	Y	Objective test, function	100	Both study arms	Surgical	N	N	N	N	N
van Schie et al 2000	Diabetic foot	Silicone injection	Y	Clinical assessment	28	Surgical	Surgical	NR	N	N	N	N
Davys et al 2005	Plantar callosities in RA	Debridement of callosity	N	Pain	38	Both study arms	ND	NR	N	N	N	N
Sutton et al 1994	Endometriosis	Laparoscopy+laser	N	Pain, symptoms	74	Both study arms	Surgical	Y	N	N	N	N
Jarrell et al 2005	Endometriosis	Laparoscopy+excision	N	Pain	29	Both study arms	ND	NR	NR	NR	NR	NR
Thomsen et al 1981	Meniere's disease	Decompression	N	Symptoms, clinical assessment	30	Both study arms	ND	N	NR	NR	NR	NR

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Table 2 (continued)

									Serious adverse event			
									Surgery		Placebo	
Reference	Condition	Intervention	Ex	Primary outcomes	No	Impr	Sup	Significant*	Ser	Rel	Ser	Rel
Stuck et al 2005	Snoring	Radiofrequency surgery of soft palate	N	Symptoms	26	Both study arms	Surgical	Y/N	NR	NR	NR	NR

Ex=exogenous material used; Imp=improvement as originally reported by the trial's authors, Sup=superiority of one arm over other as originally reported by trials' authors; No=number of patients randomised into trial; Sig=statistical significance of one arm the over other as calculated by us; Ser=whether adverse events were serious; Rel=whether serious adverse events were related to the procedure; ND=no difference; Y=yes; N= no; Y/N=yes or no depending on outcome; L=likely to be serious or related to the procedure; B=balloon; U=unlikely to be serious or related to the procedure; GERD=gastro-oesophageal reflux disease; NR=not reported; RA=rheumatoid arthritis.

*Statistical significance of effect as calculated by us using reported values.

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Table 3| **Outcomes as reported by trials' authors**

	Superiority		
Intervention	No difference	Surgery	Total
Surgery and placebo	20	18	38
Surgery only	0	7	7
Placebo only	1	0	1
Neither surgery nor placebo	6	0	6
NA	0	1	1
Total	27	26	53

NA=outcome was prevention of death so trial cannot be interpreted in terms of improvement.

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Figures

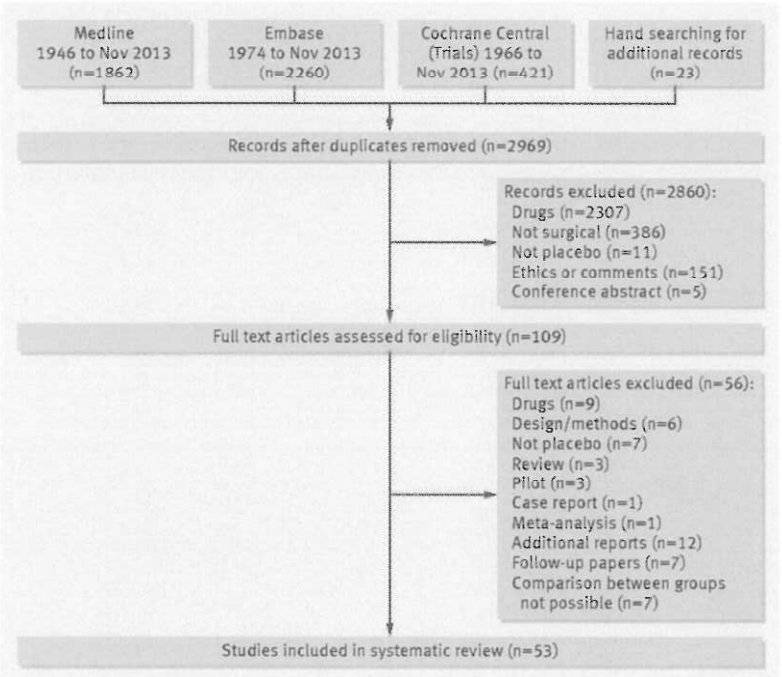

Fig 1 Flow chart of study identification, listing first reason for exclusion during review process

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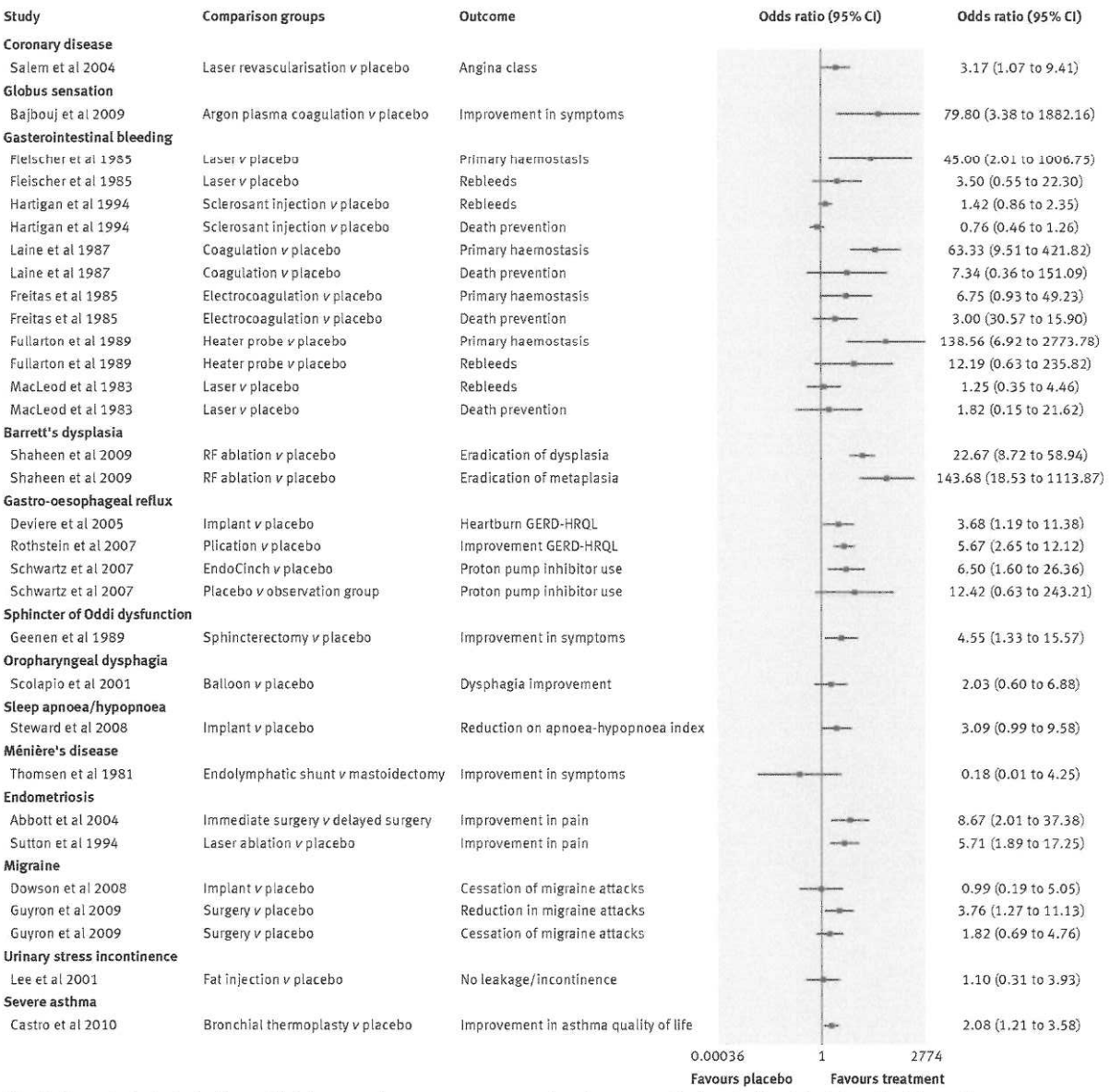

Fig 2 Forest plot of studies with binary outcome measures showing magnitude of effect (odds ratios) in active group compared with placebo group. GERD-HRQL=gastro-oesophageal reflux disease health related quality of life

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Study	Comparison groups	Outcome	Effect size (95% CI)
Osteoarthritis			
Bradley et al 2002	Tidal irrigation *v* placebo	WOMAC pain	0.35 (0.05 to 0.65)
Bradley et al 2002	Tidal irrigation *v* placebo	WOMAC function	0.28 (-0.01 to 0.58)
Moseley et al 2002	Lavage *v* placebo	KSPS pain	0.09 (-0.4 to 0.29)
Moseley et al 2002	Debridement *v* placebo	KSPS pain	0.01 (-0.37 to 0.39)
Severe asthma			
Castro et al 2010	Bronchial thermoplasty *v* placebo	Asthma quality of life	0.16 (-0.08 to 0.41)
Coronary disease			
Leon et al 2005	Laser (high dose) *v* placebo	Exercise tolerance	0.15 (-0.13 to 0.43)
Leon et al 2005	Laser (low dose) *v* placebo	Exercise tolerance	0.22 (-0.06 to 0.49)
Stone et al 2002	Laser *v* placebo	Exercise tolerance	0.50 (0.17 to 0.84)
Obesity			
Mathus-Vliegen et al 1990	Balloon *v* placebo	Weight loss (kg)	-0.25 (-1.01 to 0.50)
Mathus-Vliegen et al 1990	Balloon *v* placebo	Weight loss (BMI)	-0.23 (-0.99 to 0.52)
Geliebter et al 1990	Balloon *v* placebo	Weight loss (kg)	0.38 (-0.50 to 1.27)
Lindor et al 1987	Balloon *v* placebo	Weight loss (kg)	0.61 (-0.27 to 1.48)
Meshkinpour et al 1988	Balloon *v* placebo	Weight loss (kg)	0.14 (-0.55 to 0.84)
Genco et al 2006	Balloon *v* placebo	Weight loss (kg)	2.79 (1.80 to 3.78)
Genco et al 2006	Balloon *v* placebo	Weight loss (BMI)	1.89 (1.05 to 2.73)
Thompson et al 2013	Outlet reduction *v* placebo	Weight loss (%)	0.50 (0.02 to 0.97)
Gastro-oesophageal reflux			
Arts et al 2010	Stretta procedure RF *v* placebo	Gastrointestinal distensibility	1.55 (0.50 to 2.60)
Corley et al 2003	RF *v* placebo	Heartburn symptoms	0.40 (-0.16 to 0.96)
Corley et al 2003	RF *v* placebo	GERD-HRQL	0.43 (-0.13 to 1.00)
Schwartz et al 2007	EndoCinch *v* placebo	Heartburn score	1.09 (0.43 to 1.76)
Schwartz et al 2007	EndoCinch *v* placebo	Regurgitation score	0.62 (-0.01 to 1.26)
Schwartz et al 2007	Placebo *v* observation group	Heartburn score	-0.48 (-1.14 to 0.18)
Schwartz et al 2007	Placebo *v* observation group	Regurgitation score	0.14 (-0.50 to 0.79)
Sleep apnoea/hypopnoea			
Friedman et al 2008	Implant *v* placebo	Apnoea-hypopnoea index	1.39 (0.80 to 1.98)
Gillespie et al 2011	Implant *v* placebo	Change in CPAP pressure	-0.18 (-0.74 to 0.37)
Maurer et al 2012	Implant *v* placebo	Apnoea-hypopnoea index	0.78 (-0.14 to 1.69)
Steward et al 2008	Implant *v* placebo	Apnoea-hypopnoea index	0.34 (-0.06 to 0.75)
Steward et al 2008	Implant *v* placebo	ESS	0.05 (-0.35 to 0.45)
Snoring			
Stuck et al 2005	RF *v* placebo	Visual analogue scale snoring	1.19 (0.30 to 2.08)
Stuck et al 2005	RF *v* placebo	ESS	0.13 (-0.69 to 0.95)
Endometriosis			
Abbott et al 2004	Immediate surgery *v* delayed surgery	Visual analogue scale pain	-0.28 (-0.91 to 0.35)
Abbott et al 2004	Immediate surgery *v* delayed surgery	EQ5D	0.12 (-0.50 to 0.75)
Chronic abdominal pain			
Swank et al 2003	Adhesiolysis *v* placebo	Visual analogue scale pain	0.45 (0.05 to 0.85)
Swank et al 2003	Adhesiolysis *v* placebo	SF-36 pain	0.40 (-0.00 to 0.80)
Alzheimer's disease			
Silverberg et al 2008	CSF drainage *v* placebo	MDRS	0.19 (-0.12 to 0.50)
Parkinson's disease			
Gross et al 2011	Transplantation *v* placebo	UPDRS during off state	0.04 (-0.44 to 0.52)
Freed et al 2001	Transplantation *v* placebo	Rating of parkinsonism	0.21 (-0.42 to 0.84)
Olanow et al 2003	Transplantation 4 donors *v* placebo	UPDRS during off state	-0.30 (-1.12 to 0.52)
Olanow et al 2003	Transplantation 1 donor *v* placebo	UPDRS during off state	0.42 (-0.43 to 1.27)
Chronic discogenic pain			
Freeman et al 2005	Electrothermal therapy *v* placebo	SF-36 physical	0.36 (-0.20 to 0.92)
Pauza et al 2004	Electrothermal therapy *v* placebo	Visual analogue pain	0.45 (-0.08 to 0.99)
Pauza et al 2004	Electrothermal therapy *v* placebo	ODI	0.69 (0.15 to 1.24)
Osteoporotic vertebral fracture			
Kallmes et al 2009	Vertebroplasty *v* placebo	RMS	0.16 (-0.19 to 0.50)
Kallmes et al 2009	Vertebroplasty *v* placebo	NRS pain	0.24 (-0.11 to 0.59)
Buchbinder et al 2009	Vertebroplasty *v* placebo	NRS pain	0.23 (-0.24 to 0.69)

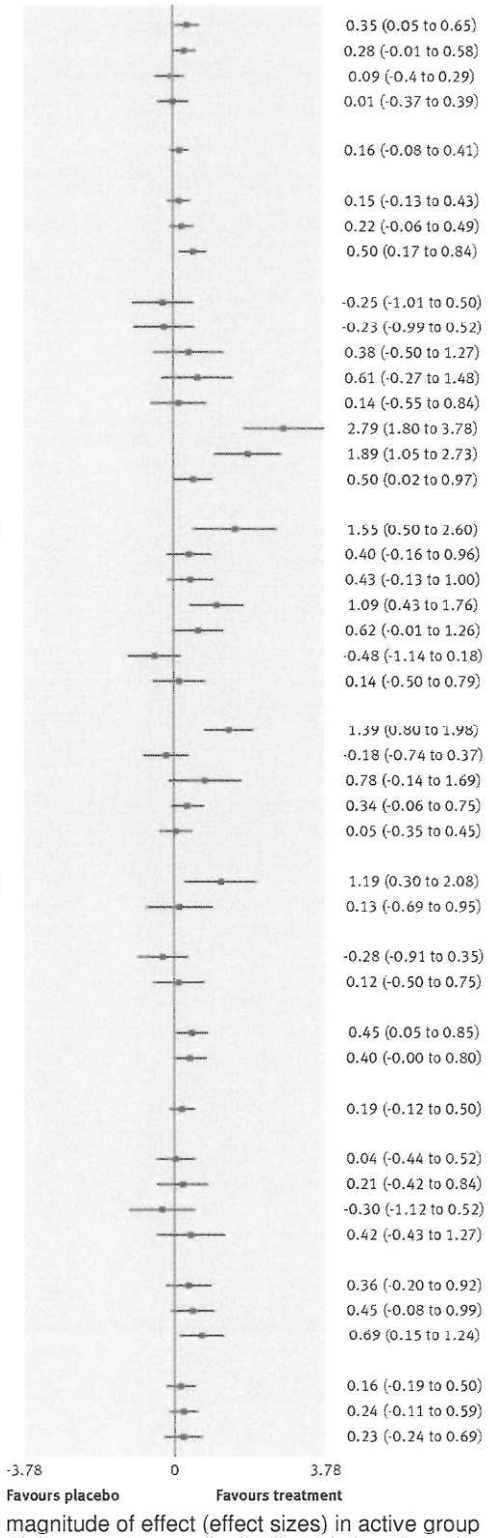

Fig 3 Forest plot of studies with continuous outcome measures showing magnitude of effect (effect sizes) in active group compared with placebo group. Outcome values in Stone and colleagues trial were not normally distributed; therefore, the effect size does not represent the true difference. WOMAC=Western Ontario and McMaster Universities arthritis index; KSPS=knee specific pain scale; QoL=quality of life; BMI=body mass index; GERD-HRQL=gastro-oesophageal reflux disease health related quality of life; NRS=numerical rating scale; RF=radiofrequency; SF-36=short form (36) health survey; CSF=cerebrospinal fluid; UPDRS=unified Parkinson's disease rating scale; EQ5D=EuroQol Group health questionnaire; RMS=modified Roland-Morris scale; ODI=Oswestry disability index; ESS=Epworth sleepiness scale; MDRS=Mattis dementia rating scale

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REJUVENATION RESEARCH
Volume 17, Number 1, 2014
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2014.1545

CASMI TSCC Launch Event, Paris, France, July 2013: An Assessment of the Key Barriers to the Commercialization and Clinical Adoption of Pluripotent Stem Cell Therapies*

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Abstract

The high incidence of unmet medical needs in combination with the rising burden of chronic diseases, linked to an increasingly aging population, necessitates new approaches to therapeutic intervention. One potential class of health care innovation that may offer an alternative approach to addressing current shortfalls is stem cell therapies. The CASMI Translational Stem Cell Consortium (CTSCC) was formed to elucidate the key hurdles to the commercialization and clinical adoption of stem cell technologies, with a particular focus on pluripotent stem cell (PSC) technologies. As a global pre-competitive academic–industry consortium, the CTSCC unites thought leaders from a range of sectors and technical specialties in defining and discovering solutions to roadblocks that will impede the field. Targeted toward stakeholder requirements at the delivery end of the translational spectrum, the CTSCC aims to provide mechanisms for multidirectional dialogue and to produce academically rigorous and commercially practicable research outputs to accelerate industry progress. On the 30th and 31st of July, 2013, the CASMI Translational Stem Cell Consortium (CTSCC) held a launch event at the Saint James Club, Paris, France.

Introduction

On the 30th and 31st of July, 2013, the CASMI Translational Stem Cell Consortium (CTSCC) held a launch event at the Saint James Club, Paris, France. A number of roundtable and panel discussions directed and engaged debate around select focus areas for pluripotent stem cells (PSCs)—standards, biomanufacturing, regulation and intellectual property (IP), strategic partnerships, and clinical adoption. The main purpose of the event was to determine the critical factors within each area on the basis of the viewpoints of opinion leaders and senior managers across industry, academia, and translation centers to establish where the CTSCC might best complement ongoing activities and bridge existing gaps to aid in the advancement of the field. Following these discussions, a questionnaire was circulated to the group and several factors were identified as crucial in hindering the progress into the clinic of either PSC-derived therapies themselves or stem cell therapies more broadly. Despite a relatively small sample size, given the high quality of respondents and depth of analysis produced, it was deemed critical to share the resulting findings with the community in hopes of promoting further development of the field as a whole.

The compiled questionnaire data presented herein has significant limitations in that the sample size of questionnaire responders (20 in total) was low. However, the inherent value of the data is rooted in the deep discussion from a preceding event that educated the focus, in addition to the prominent influence of questionnaire responders, all leaders within their respective areas, spanning multiple specialties and sectors. A potential confounding issue is that responders might have identified focus areas with a view to the perceived capabilities of the CTSCC team and not solely on the basis of sector need.

Three overarching directives can be identified from the responses provided:

1. A fundamental requirement to advance the basic scientific understanding of the underlying biology is focused around product attributes that are linked to clinical safety and efficacy.
2. Measures should be enabled to encourage widespread utilization of stem cell banking resources and to foster open global exchange.

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Based on the findings of the CASMI TSCC launch event, Paris, France, July, 2013.

3. Mechanisms should be created to more effectively align the demands and expectations of industry and academia.

Key Findings

The questions posed in the survey were based around input from the CTSCC's funding and research partners and the Consortium's research findings to date.[1] The resulting questionnaire was completed by 20 opinion leaders and senior managers, importantly with balanced representation from industry, academia, and translation center/other (Fig. S1) (Supplementary Data are available at www.liebertonline.com/rej/).

To compare prioritization of components within a question group, a "score" was assigned based on the following computation. A cumulative count of total responses for each component was calculated, and the mean value for the total count was calculated. The mean count for the question group was then subtracted from the cumulative counts for each component to define the score. This reflected the distance from the group mean of the total count for a component within a question group.

Standards

The delineation of standards for stem cells and stem cell–derived therapies offers numerous productive functions, such as enabling efficient dialogue between disparate stakeholder groups, expediting regulatory approval, and facilitating transfer and applications of cell lines. Standards also play an essential role in the effective evaluation and assessment of significance in clinical outcomes. Defining standards for stem cell therapies, and PSC-derived therapies in particular, is challenging due to the inherent plasticity of living cells.

Standards focus areas were ranked with principal topics of interest identified as "Standardizing characterization methodologies, technologies and instrumentation to create reference standards including appropriate tolerances" and "Global harmonization of standards for stem cell bank creation" (Fig. 1A). While PSCs in their undifferentiated state are unlikely to be a therapeutic product, the need for standards in stem cell line selection and bank creation, especially those intended as current Good Manufacturing

A

Rank	Standards Focus Area	Score
1	Standardizing characterization methodologies, technologies and instrumentation to create reference standards including appropriate tolerances	12.3
2	Global harmonization of standards for stem cell bank creation	9.29
3	Impact of existing standardization efforts on market hindrance and/or success	2.29
4	Defining the differences and benefits of standards vs 'considerations'	-4.71
5	Indication specific standardization guidance	-5.71
6	Creation of a Pluripotent Stem Cell Standardization Initiative	-5.71
7	Standardization framework for tool providers	-7.71

B

Rank	Regulation Focus Area	Score
1	Engagement of FDA/MHRA/EMA/PDMA to define a harmonized framework for convergence of regulatory principles and clinical trials	9.8
2	Regulation of combinational products (cells + biomaterial)	7.8
3	Guidelines for cell efficacy measures, particularly indication specific	2.8
4	Risk:benefit analysis techniques both for cell therapy specific and non cell therapy specific	2.8
5	Improvements in understanding of regulatory education among academics	-1.2
6	Expediting combination products (e.g. by using 'existing/pre-approved' biomaterials and simultaneous assessment of cell and biomaterial)	-2.2
7	Importance of Japanese iPS trial approval and its implications for other markets	-2.2
8	Risk:benefit analysis techniques specifically for combinational products	-2.2
9	Role of mechanism of action in regulatory decision-making	-5.2
10	FDA breakthrough status designation	-10.2

C

Rank	IP Focus Area	Score
1	Academia's increasing desire to operate as "businesses", owning IP rather than doing open access research, and impact on innovation	6.0
2	Challenges and potential of patent pooling (including investigation into current cross-licensing approaches)	1.0
3	Impact of cell generation protocol patents on industry development	-7.0

D

Rank	Biomanufacturing Focus Area	Score
1	Review the challenges associated with the affordable distribution of PSC therapeutics after manufacture	3.8
2	Uniting academic cGMP product development strategies with expectations of early stage CMOs and potential industry partners	2.8
3	Building on and adapting the deskilled, large-scale production approaches that have been developed to enable cost-effective and reproducible manufacture in the field of biopharma drugs	2.8
4	Investigate COGS reduction methodologies through QbD and DOE, particularly for CTs requiring significant cell numbers where reagent cost will be problematic	-4.2
5	Discerning potential impact of introduction of process analytical technologies (PAT) for real-time culture monitoring	-5.2

E

Rank	Strategic Partnerships Focus Area	Score
1	Growth and impact of translational centers such as HSCI, CCRM, I-Stem, Cell Therapy Catapult.	6.0
2	Need for public funding for strategic partnerships at early stages of industry development	4.0
3	Aspects and commonalities of successful partnerships, including benefits of shared common interests/vision and ability to formulate a mutual 'win'	-2.0
4	Need to define the concept of a 'translation centre'	-3.0
5	Defining academic vs company rights in partnerships and need for better communication of industry's expectations	-5.0

F

Rank	Clinical adoption Focus Area	Score
1	Elucidation of optimal indications based on existing market products, technological modalities, standard of care, infrastructure, clinician training, direct vs indirect costs for state.	4.25
2	Selection of high priority indications via clinician/researcher workshops	2.25
3	Development of methods to determine value versus cost and hence viability of pricing	-1.75
4	Joint design of clinical trials between innovators and health systems	-4.75

FIG. 1. Prioritization of key challenges within focus areas: "Score" was assigned based on distance of the cumulative count for a question group component from the mean cumulative count within the question group. (**A**) Standards, (**B**) Regulation, (**C**) Intellectual Property (IP), (**D**) Biomanufacturing, (**E**) Strategic Partnerships (HSCI, Harvard Stem Cell Institute, US; CCRM, Centre for Commercialization of Regenerative Medicine, Canada; I-Stem, France; Cell Therapy Catapult, UK), and (**F**) Clinical Adoption. FDA, Food and Drug Administration; MHRA, Medicines and Healthcare Products Regulatory Agency; EMA, European Medicines Agency; PMDA, Pharmaceutical and Medical Devices Agency; iPS, induced pluripotent stem cells; IP, intellectual property; PSC, pluripotent stem cells; cGMP, current Good Manufacturing Practices; CMO, Contract Manufacturing Organization; COGs, Cost of Good; QbD, Quality by Design; DOE, design of experiments; CTs, cell therapies.

Practices (cGMP) materials, was highlighted: "Sorting out if the line will be acceptable for use at the end of a multi-year effort is critical. Finding a line that was developed under appropriate conditions that also efficiently performs in the differentiation protocol is not trivial." This is of particular relevance due to the reported variation in differentiation abilities and efficiencies of various PSC lines.[2–4]

The relative importance of a range of *in vitro* and *in vivo* assessments within the context of a cell standardization framework was investigated. Of the *in vivo* assessments, "tumorgenicity" (score 9.5) and "immune response" (score 5.5) were rated as the most important parameters (Fig. S2Aii). Highlighted within the *in vitro* assessment question group were "identity" (score 9.0), "expression of phenotypic markers" (score 3.0), and "genomic stability" (score 2.0) (Fig. S2Ai). As identity is frequently assigned based on the expression of a limited number of cell-surface markers, it was stressed that "this is dependent on phenotypic and gene expression profiles." It was, however, noted that the "development of informative functional/potency assays with associated release criteria are critical—more relevant than marker expression," a common view shared in academic and industry literature.[5–7]

Regulation

Productive communication with international regulators is critical to clinical trial initiation, reporting, and product approval. There have been efforts by regulators in the United States, European Community (EC), and Japan to revise and devise a regulatory system more suitable for cell-based therapies due to the numerous unique and inherent challenges not historically encountered with traditional pharmaceutical.[8–11]

The "Engagement of Food and Drug Administration (FDA)/Medicines and Healthcare Products Regulatory Agency (MHRA)/European Medicines Agency (EMA)/Pharmaceuticals and Medical Devices Agency (PMDA) to define a harmonized framework for the convergence of regulatory principles and clinical trials" and the "Regulation of combinational products (cells + biomaterial)" were highlighted as key focus areas for the CTSCC (Fig. 1B). It was noted that the engagement of the FDA/MHRA/EMA/PDMA is already happening, led in part by the The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (www.ich.org). When the relative importance of factors in regulatory safety submissions was assessed, respondents identified "immunogenicity" (score 4.0), "cell overgrowth" (score 4.0), and "residual pluripotent stem cell level" (score 3.0) as important criteria (Fig. S2B).

Biomanufacturing

A prerequisite to the widespread commercialization and clinical adoption of PSC-derived therapies and stem cell therapies is the transition to cGMP manufacturing-scale processes that reduce and/or eliminate the variability introduced by manual approaches. Concurrently, in addition to regulatory compliance though a Quality by Design (QbD) approach, it is essential that any biomanufacturing strategy also supports Cost of Goods (CoGs), which is a profitable business model.

Of the specific focus areas within the biomanufacturing theme, the areas outlined for investigation by the CTSCC were "Review the challenges associated with the affordable distribution of PSC therapeutics after manufacture," "Uniting academic cGMP product development strategies with expectations of early stage CMOs and potential industry partners," and "Building on and adapting the deskilled, large-scale production approaches that have been developed to enable cost-effective and reproducible manufacture in the field of biopharma drugs" (Fig.1D). "Key process scale-up challenges," such as suspension cell culture technologies and automated systems (score 9.89), was rated as the most significant hurdle, followed by "communication of industry process expectations to innovators" (score 4.89) and "inadequate process development strategies" (score 3.89) (Fig. S3C).

Strategic Partnerships

Partnerships within and across sectors have become increasingly prevalent throughout biomedical sciences.[12] This collaborative approach has been embraced significantly within the cell therapy field, as a risk-sharing strategy between academia/Small and Medium Enterprises (SMEs) and the traditional trailblazers, "big pharma," and as a result of the early stage of the field.[13] A number of "translation centers" have also been formed with a view to empower the clinical and commercial potential of the field. Therefore, the CTSCC looked to understand the various partnerships that have been formed to date and to assess potential implications for the future stem cell therapy industry.

As specific focus areas for the CTSCC, "Growth and impact of translational centers such as Harvard Stem Cell Institute (HSCI), Centre for Commercialization of Regenerative Medicine (CCRM), I-Stem, Cell Therapy Catapult" (score 6.0), and "Need for public funding for strategic partnerships at early stages of industry development" (score 4.0) were rated as the most important areas for investigation (Fig. 1E). Cell banking has taken on a leading role in the stem cell field,[14,15] the important banking initiative features were identified as "access" (score 8.4) and "comparability of cell lines offered" (score 5.4) (Fig. S3A).

Intellectual property

Intellectual property rights are central to the existing model of protecting revenues from market-leading innovations in drug development, while at the same time encouraging innovation through the sharing of information. The ill fit of the current IP process/approach for the cell therapy field has frequently been discussed.[16–19]

"Academia's increasing desire to operate as 'businesses', owning IP rather than doing open access research, and its impact on innovation" was identified as a primary focus area for the CTSCC within IP (Fig. 1D). The most significant IP challenges were identified as the "(Mis)alignment of aims of public and private partners in collaborations" (score 6.86), the "optimal stage of technological development at which to patent" (score 5.86), and a "lack of rigorous publicly available IP landscapes for cell based technologies" (score 5.86) (Fig. S2C).

Clinical

Despite the fact that highly skilled clinicians will typically make the decision of which therapeutic option is best suited for a particular patient, this important stakeholder group has been poorly integrated into the early product development of stem cell therapies. An improved understanding of the decision-making process, practicalities, and preferences of clinicians that can be directly used to shape product development should facilitate improved uptake following market approval.

Of the focus areas for specific investigation, the requirement for the "Elucidation of optimal indications based on existing market products, technological modalities, standard of care, infrastructure, clinician training, direct vs. indirect costs for state" was highlighted (Fig. 1F). This multifactorial approach to identifying possible areas in which stem cell therapies might be most effective was supported by a respondent outlining the need to match the technology to a disease rather than going after a specific indication to improve the likelihood of positive outcomes. The "Provision of relevant and/or indication specific end points" (score 9.55), "examination of reimbursement assessment models, *e.g.*, Quality-adjusted life years (QALYs)" (score 5.55), and the "optimization of clinical trial design" (score 4.55) were all identified as key aspects of clinical engagement (Fig. SB).

Conclusion

The translational pathway for pluripotent stem cell–derived products and other stem cell therapies is impeded by a range of deficiencies in scientific knowledge, technological capabilities, and regulatory uncertainties.[20,21] The CTSCC was formed to unify international and multidisciplinary luminaries from major stakeholder groups to break down translational barriers.[1,22] Through disseminating timely and clear findings reflecting contemporary opinions of sector leaders, the aim of this effort will make a practicable contribution to stem cell translation.

The data described herein, albeit with a limited sample size, begins to form a picture of the prevailing critical limiting factors in the stem cell translation pathway. Across respondent groups and questionnaire responses, there was a prevailing requirement for a heightened emphasis on research into the fundamental principles and basic biology as related to key requirements, both safety and efficacy, of the potential cell product. Additionally, the increased support and use of stem cell banks, with concepts surrounding harmonization of standards, comparability of cell lines offered, and open access privileges, were tantamount for their success. Finally, the further alignment between sectors, predominantly industry and academia and particularly in the current financial climate, stands to benefit all involved, as would a route to improved comparability of clinical end points.

In closing, pre-competitive collaborative consortia, such as the CTSCC, have a critical role to play in co-ordinating at times disparate expert stakeholders in the rapidly developing stem cell technology field.[1,23] And in so doing, de-risking and maximizing the overall research and development product of the field ultimately benefits patients suffering with debilitating diseases.

Acknowledgments

The authors wish to express their gratitude to the following for their support and insight during the preparation of this manuscript: Research and funding partners of the CTSCC; in particular to questionnaire responders and attendees of the CTSCC's July 2013 meeting, upon which the findings of this manuscript are based; Richard Barker (CASMI), Andrew Carr (Oxford), Zhanfeng Cui (Oxford), Megan Morys (CASMI), David Newble (TAP Biosystems), Brock Reeve (HSCI), Sven Wagner (Sartorius Stedim), and Ivan Wall (UCL). We wish to express our sincere thanks to the following organizations that have contributed to the consortium as funding and events partners, without whom the consortium and the benefits it will bring to stem cell translation would be unacceptably constrained: GE Healthcare, CCRM, TAP Biosystems, Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, and NIH Centre for Regenerative Medicine.

Author Disclosure Statement

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers.

D.A.B. gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that amongst other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. D.A.B. has conducted paid consultancy for the Technology Strategy Board (funder of UK CT Catapult) (Swindon, UK), Lonza (Basel, Switzerland), and CCRM (Toronto, Canada) within the past 7 years with a cumulative value of greater than $10,000. D.A.B. has also received hospitality from TAP Biosystems within the past 7 years with a cumulative value of less than $10,000. Additionally, at the time of writing, D.A.B. may have pending private and/or academic funding pending with other organizations named. D.A.B. is subject to the CFA Institute and CAIA Association's Codes, Standards, and Guidelines, and as such this author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation.

K.E.B's employer, TAP Biosystems, is currently in late-stage, publicly disclosed negotiations with Sartorius Stedim concerning a potential acquisition. Please contact K.E.B for further information.

A.F. declares no competing financial interests.

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REJUVENATION RESEARCH
Volume 16, Number 2, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2013.1423

Commercialization of Regenerative Medicine: Learning from Spin-Outs

Anna French,[1–3] R. Lee Buckler,[4,5] and David A. Brindley[6–8]

Abstract

The meeting "Commercialization of Your Regenerative Medicine Research: Lessons from Spin Out Successes" was hosted by the Oxbridge Biotech Roundtable (OBR) (Oxford, UK) at the University of Oxford in February, 2013, and attracted a multi-stakeholder audience spanning academia and industry. The event featured case studies from Gregg Sando, CEO, Cell Medica (London, UK), John Sinden, CSO, Reneuron (Guilford, UK), and Paul Kemp, CEO and CSO, Intercytex (Manchester, UK). OBR is a student-led initiative with over 7000 members across eight different UK and US locations with a mission to foster a conversation about the healthcare and life sciences industry. Here we review the main themes of the meeting and the major questions facing the regenerative medicine industry and its rapidly emerging subsets of cellular and gene therapies. Notably, we discuss the compatibility of regenerative therapies to the existing healthcare infrastructure, biomanufacturing challenges (including scalability and comparability), and the amenability of regenerative therapies to existing reimbursement and investment models. Furthermore, we reiterate key words of advice from seasoned industry leaders intended to accelerate the translation path from lab bench to the marketplace.

Introduction

An aging worldwide population and declining research and development (R&D) productivity in the pharmaceutical industry have created a perfect storm places both patients and industry in a position amenable to the adoption of safe and efficacious novel therapeutics, including regenerative medicines. Herein, we apply an inclusive definition of regenerative medicines, encompassing tissue engineering, cellular therapies, gene therapies, some aspects of transplantation and a small subset of "conventional" therapeutics—including small molecules and monoclonal antibodies—whose primary modality is to stimulate the restoration of normal *in vivo* function.

While regenerative therapies may be subject to significant technological heterogeneity, their core purposes are aligned—to provide novel therapies that address unmet medical needs and/or offer superior interventions to current standards of care in a safe and efficacious manner and at a cost that individual patients, and society as a whole, can bear. The increasing burden of chronic disease and extending global life expectancies increases the desirability, and perhaps necessity, of regenerative medicines. Indeed, the replacement or supplementation of non-functional tissues with living cells or tissues may be the only possible treatment option in some instances. However, the translation path for regenerative therapies from lab bench to the marketplace has historically been a source of uncertainty for product developers and investors.

"Conventional" therapeutics have a defined and well-trodden path to market; however, the translation pathway for regenerative therapies is perceived to contain a range of uncertainties spanning regulation, reimbursement, biomanufacturing, immunogenicity, and investment models. This is in spite of an increasing number of regenerative, and particularly cellular, therapies entering clinical trials, contributing to an increasing portfolio of approved products (Table 1). However, it has often been overlooked that despite some unique inherent challenges, the application of cellular

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TABLE 1. SUMMARY OF SELECT REVENUE-GENERATING CELL THERAPY AND REGENERATIVE MEDICINE PRODUCTS IN 2012, A MARKET PROJECTED TO BE GENERATING $900 MILLION[a]

Company	*Lead product(s)*	*Indication*	*Market launch*	*Allogeneic/ autologous*	*Estimated revenue (million $/year)*	*Current markets*
Advanced Biohealing, a Shire company (Dublin, Ireland)	Dermagraft	Diabetic foot ulcers	2001	Allo	>100	US, Canada
Dendreon (Seattle, WA)	Provenge	Prostate cancer	2010	Auto	>100	US
Organogenesis (Canton, MA)	Apligraf	Venous leg ulcers/ diabetic foot ulcers	1998/2000	Allo	>100	US, Saudi Arabia
NuVasive (San Diego, CA)	Osteocel Plus	Skeletal defects	2005	Allo	>50	US
Orthofix (Curaçao, Netherlands Antilles)	Trinity Evolution	Musculoskeletal defects	2009	Allo	>50	US
Genzyme, a Sanofi Company (Boston, MA)	Carticel	Articular cartilage repair	2007	Auto	>10	US, EU
Anterogen (Seoul, South Korea)	Cupistem	Crohn disease	2012	Auto	<10	S. Korea
Avita Medical (Perth, Australia)	ReCell	Burns, scars	2007	Auto	<10	EU,UK, Australia, Canada
FCB Pharmicell (Seoul, South Korea)	Heartcelligram	Acute myocardial infarction	2011	Auto	<10	S. Korea
Genzyme, a Sanofi company (Boston, MA)	Epicel	Severe burns	2007	Allo	<10	US, EU
Japan Tissue Engineering (Gamagori, Japan)	J-TEC Epidermis / Cartilage/ Corneal Epithelium	Burns, cartilage repair, ocular repair	2012	Auto	<10	Japan
Medipost (Seoul, South Korea)	Caristem	Articular cartilage repair	2012	Allo	<10	S. Korea
TiGenix (Leuven, Belgium)	ChondroCelect	Articular cartilage repair	2009	Auto	<10	EU

[a]Overall there were 36 commercial cell products in 2012 (including 15 from the US, 14 from Europe, 3 from South Korea, and 3 from Japan). All of the market leaders are for use in skin, bone, or cartilage repair, excluding Provenge which is, approved for the treatment of late-stage prostate cancer.

therapies in a clinical setting offers a number of built-in simplicities.

The very basis of cells as a therapy, whether allogeneic or autologous, is that they are part of the everyday building blocks of the human body, not a foreign modality such as is the case for many drugs. Second, in relation to diseases, such as diabetes, where the patient is diagnosed due to clinical symptoms and signs, the variability in biochemical pathway perturbation may be vast, meaning that many traditional drugs will only work on particular patient subgroups. Within obvious limitations, cell therapies can bypass this complexity and simply provide the required cell or tissue functionality. Finally, in relation to manufacturing procedures, a number of financially burdensome and energy-requiring conditions, such as high processing pressures and temperatures that are required for the industrial manufacturing of traditional pharmaceuticals, are not required or are simply inappropriate.

With this in mind, what can we learn from the early ventures in the regenerative medicine and cell therapy sectors and what are the key outstanding components of the translatory ecosystem required to facilitate the rapid and reliable translation of such products into routine medical practice?

"The Protagonists"

The discussion was led by senior leaders from three UK-based cell therapy companies: Cell Medica, Reneuron, and Intercytex (Table 2). The contributing companies span a range of therapeutic technologies, indications, and stages of development.

Cell Medica specializes in antigen-specific T cells. Their lead product launch, Cytovir CMV, is a T cell infusion of cells that have been exposed to cytomegalovirus (CMV) and are infused following chemotherapy and subsequent bone marrow transplant. This product is expected to be launched toward the end of 2013. Cell Medica currently has two randomized controlled studies currently being rolled out across the major transplant centers in the United Kingdom, funded

TABLE 2. SUMMARY OF COMPANIES PRESENTING AT "COMMERCIALISATION OF YOUR REGENERATIVE MEDICINE RESEARCH: LESSONS FROM SPIN OUT SUCCESSES" MEETING (FEBRUARY 2013, OXFORD, UK)

Company (location)	*Founded*	*Lead product(s)*	*Indication*	*Stage of development*	*Allogeneic/ autologous*
Cell Medica (London, UK)	2006	Cytovir CMV	Anti-viral post-chemotherapy	Phase III	Allo
ReNeuron (Guildford, UK)	2005	ReN001	Symptoms of stroke	Phase II application	Allo
Intercytex (Manchester, UK)	2010	VAVELTA	Acne scarring	Phase II completed	Allo

by a Translation award from the Wellcome Trust (London, UK). The potential for anti-viral T cell therapies is extensive, as over 20% of cancers are associated with viral infection.[1,2] Other T cell–based cell infusions currently in clinical trials include chimeric antigen receptor (CAR) T cells engineered to express a receptor that will directly interact with an antigen on the surface of a tumor cell and therefore promote cell-mediated killing of cancerous cells.[3]

Intercytex began back in 2000 and, following financial difficulties, was relaunched in 2010. Boasting both a product and services portfolio, Intercytex is focused on the application of a human dermal fibroblast infusion, ICX-RHY (also marketed as VAVELTA) to treat epidermolysis bullosa or to improve scarring. Phase II clinical trials for the use of VAVELTA in nasolabial folds and for acne scarring have been completed. Intercytex's services expertise is also available via a contract translation service, Cell2Therapy, which includes good manufacturing practice (GMP) manufacturing facilities, based in Manchester, United Kingdom.

Reneuron started in 1997. Their lead offering, ReN001, a stem cell therapy to alleviate the acute symptoms of stroke, has completed a Phase I trial. Reneuron's product portfolio is aimed more widely than at just neurological diseases, encompassing peripheral vascular disease and retinal degeneration. Although the likelihood of success for any drug at Phase II is extremely unfavorable, that of therapeutics for central nervous system (CNS) disorders makes for even more bleak reading. Here stem cells present a real opportunity for commercial entities and patients alike.[4]

Tissue-Engineered Wound Care: A Key Passage in the Evolution of Regenerative Medicine

Aside from perhaps transplantation, no field has made a greater contribution to the development of today's regenerative medicine sector than early tissue engineering companies, including Organogenesis (Waltham, MA) and Advanced Tissue Sciences, later renamed Advanced Bio-healing (La Jolla, CA) (New York, NY). Together these two stalwarts of tissue engineering have shared a journey that has included being featured on the cover of *Time* magazine,[5] bankruptcy,[6] and more recently a successful $750m acquisition by a major pharmaceutical company (Shire's $750m acquisition of ABH in July, 2012).

In the 1990s, both US-based companies were establishing themselves with human fibroblast products designed for the treatment of diabetic ulcers (as well as venous leg ulcers in the case of Organogenesis). Organogenesis' product Apligraft gained Food and Drug Administration (FDA) approval in 1998, with Advanced Tissue Sciences' Dermagraft (Silver Springs, MD) coming in 2001. Paul Kemp, former Organogenesis executive, described the early strategic partnership with Eli Lilly (Indianapolis, IN) and licensing of marketing rights to Novartis (Basel, Switzerland), both global pharma giants. By 2002, both companies had filed for Chapter 11 bankruptcy. Encouragingly, the core technologies of both companies re-emerged and have found a profitable position. Such tales of success bring into question the differing bankruptcy laws between the United Kingdom and United States, with the latter being more accommodating for biotech small- or medium-sized enterprises (SMEs), whose short-term cash flows are unpredictable and can often render companies temporarily insolvent.

Conversely, other companies, including Reneuron, have emerged as "pure" cell therapy companies after experiences, some successful and others not, with a number of other technologies. For example, Reneuron in-licensed a number of non–stem cell products in the 2000s, broadening the company portfolio. One such product, ReN1869, an antagonist to the histamine receptor H1 and used as an analgesic, was initially in-licensed from Novo Nordisk (Bagsværd, Denmark) but failed Phase II clinical trials in 2003.

However, irrespective of the routes by which a number of the successful cell therapy companies of today were formed, what were the common pitfalls that they had to overcome to secure their success?

Square Peg–Round Hole: Examples of Fundamental Differences Between the Regulation of Conventional Pharmaceuticals and Cellular Therapies

Some of the guiding strategies emanating from the industry's leaders and those imposed by regulatory authorities were established in relation to fundamentally different conventional (bio)pharmaceuticals, such as small molecules and biologics. This forced structure therefore impacts on product development of cellular therapies at all stages of development from academia to industry.

Patient recruitment

In clinical trials for conventional pharmaceuticals, healthy volunteers are recruited in Phase I trials, with the primary end point being product safety—usually at a reduced dose. However, in cell therapy clinical trials, healthy volunteers are not used, principally due to ethical restrictions around administering a potentially permanent therapy to a healthy volunteer. Therefore, Phase I trials for cellular therapeutics use patients from the target population(s) and may demonstrate some limited proof of efficacy.

Categorization heterogeneity

Historically, pharmaceutical products, including monoclonal antibodies, have been regulated as medicinal products, with a clear distinction between medicinal products and

medical devices. However, although the situation is improving as the industry develops, this has not always been the case for cellular products. For example, cellular therapeutics may be regulated as a transplant, medicinal product, advanced therapy medicinal product (ATMP), point-of-care devices, or indeed in some cases deemed a component of the "practice of medicine." Therefore, today a number of established cellular therapies, such as VAVELTA, have been required to undergo a "grandfathering" process to apply contemporary regulatory standards retrospectively. Furthermore, the effective management of this heterogeneous challenge is hampered by limited access to specialist regulatory expertise and robust technologies to support regulatory submissions, including cellular characterization assays.[7]

Cell Therapy Manufacturing: The Pursuit of Scalability and Profitability

Manufacturing is a frequently overlooked topic in cell therapy development, frequently (and unfairly) perceived to be lacking the novelty of basic science and the near-term commercial and societal impact(s) of late-stage clinical development. However, biomanufacturing is a mission critical step in the translation pathway for cellular therapeutics, particularly given the interdependency of cellular critical quality attributes and their bioprocessing environment.[8–10]

Manufacturing is a key element of scalability, although the fit in relation to autologous or allogeneic therapies clearly differs. For example, allogeneic products, such as Reneuron's neuronal stem cell lines and Intercytex's fibroblasts, do not require re-derivation and are amenable to scale-up. In comparison, Cell Medica's autologous T cell therapy cannot be scaled, although potentials for cost and time savings maybe found from different spheres, including automation.[8] This difference also implies consequences in production safety testing where, for allogeneic cells, one test will cover multiple product units, whereas testing at the per-unit level is required for autologous therapies.[11] Recent progress has been made with large-scale stem cell cultures and bioreactors, including through the use of micro-carriers to facilitate the three-dimensional culture of adherent cell lines.[12,13] Overall, it is clear that the cost drivers for cell therapy bioprocessing, particularly for autologous products are quality assurance (QA)/quality control (QC) testing, with a less significant contribution from downstream processing costs that dominate cost of goods (COGs) for conventional (bio)pharmaceuticals.

Funding and return on investment for cellular therapies

Traditionally, fledgling companies have had to solicit large-scale investor funding to enable them to transit through the "valley of death" and progress to late-stage clinical trials, positioning themselves for an acquisition by big-pharma or initial public offerings (IPOs). However, given the challenges experienced by vanguard gene therapy and tissue engineering companies, such exit routes for investors (in particular IPOs) have been difficult to access.[14]

The principal sources of investor wariness toward regenerative therapies, aside from a challenging economic environment, are uncertainties surrounding the type and concentration of risks, in particular, technology development and technology adoption risks. To date the typical 5- to 10-year investment window of a venture investor has been broadly insufficient to satisfactorily mitigate these risks.[14] One force in place to enact a change is Syncona, a Wellcome Trust (London, UK) internal venture capital division, which has a longer investment horizon, seeking to address the imbalance between realistic innovation time scales and those of the conventional venture model. Furthermore, international organizations, including the California Institute for Regenerative Medicine (CIRM; San Francisco, CA), are relaxing their funding requirements, encouraging engagement with industry and international academic partners and accelerating the development path toward reimbursement.

One of the key issues in the reimbursement question is that of novel licensing strategies, for example, adaptive licensing, which to date has been poorly discussed in the context of regenerative medicine(s). Adaptive licensing involves the flexible and iterative use of data as the therapy, is introduced to an increasing number of patients. Indeed, the discussion of conditional approval, which precedes licensing, is an interesting one that would permit earlier reimbursement. Cell therapy could be an ideal setting for a new reimbursement model, because precise tracking is more achievable than with traditional drugs and therefore patient-by-patient reimbursement is more appropriate. Overall, such proposed adaptations of licensing systems are suggested to both increase accessibility of treatment to patients and to help reduce investment risk. Educating politicians about pricing issues is a key priority of leaders from within the life sciences and health care industries, as highlighted by the recent House of Lords inquiry into regenerative medicine commercialization.

Another issue is that of value-based pricing adoption, which is particularly relevant to cell therapy products that enact a "cure," therefore eliminating the need for subsequent treatment and procedures. How such a value is to be calculated in a way that is satisfactory to both company and customer taking in account the cost vs. benefits of improved quality of life will be thrashed out as products reach the point of sale. Moreover, a curative model is particularly difficult to implement in private payer systems, where insurance holders regularly switch providers. Therefore, it is feasible to foresee situations in which the value of a permanent, curative regenerative therapy is captured by an insurer other than the original payer.

Prominent Words of Advice

One of the reasons that the leaders, such as those assembled at OBR's event, so freely give their time is that they wish to prevent the mistakes of history being repeated. So what were the key messages (Table 3)? The first is that the key to success is having the ability to identify a poor idea as much as a brilliant one. As can be said of any sector, with a newly spun-out company, the team is of utmost importance; you must surround yourself with people that you believe in and that, in turn, believe in you. Clearly on Paul Kemp's mind was the importance of incubating innovation in academia for as long as possible, making the most of available non-dilutive cash such as that provided by Cell Therapy (London, UK), and the Wellcome Trust.

These initial lifelines will enable a company to get closer to the revenue-generating stage before investor capital is required and provide the ever-elusive element of time. Another key is to focus on rare diseases where therapies are

TABLE 3. KEY ADVICE, RATIONAL AND IMPLICATIONS FOR EMERGING CELL THERAPY AND REGENERATIVE MEDICINE COMPANIES FROM "COMMERCIALISATION OF YOUR REGENERATIVE MEDICINE RESEARCH: LESSONS FROM SPIN OUT SUCCESSES' MEETING (FEBRUARY, 2013, OXFORD, UK)

No.	*Key learning/ advice*	*Exemplification*	*Opportunities*	*Challenges*	*Suggested reading*[a]
1	Innovation and resource prioritization.	Importance of prioritizing resources around highest impact projects to identify potential market leaders and eliminate less promising targets.	Increase research and development (R&D) productivity. Decrease product development costs.	Difficult to assess potential risk(s) and benefit(s) for early stage products. Potentially successful products remain undeveloped.	15,16
2	Utilizing non-dilutive funding sources and resources.	Utilize non-dilutive funding sources including Technology Strategy Board (Swindon, UK), Californian Institute for Regenerative Medicine (CIRM, CA) and NIH NCATS.	Low-cost access to capital. Access to physical (shared) resources, including incubator space. More flexible timescales to clinical stage.	Limited incentives for commercial outperformance. Reduced access to commercial strategic advice versus venture capital (VC) funding sources, etc.	17–19
3	Focus on rare and/or orphan indications.	Focus research programs on indications with major unmet medical needs and/or orphan status as efficacy of treatment is compared to best current practice.	Greater support from regulatory agencies. Greater chance of success in later stage clinical trial phases.	Smaller market(s) than major indications. Often technologically high risk due to relative lack of prior research.	20,21
4	Perseverance in an emerging sector.	Short-term technical and/or financial challenges can often lead to rapid and disproportionate changes in stakeholder perception. This is inevitable with sector pioneers. Recent evidence has demonstrated success in both auto and allo business models.	Short-term industry stresses can present opportunities to acquire high-quality intellectual property (IP) and human capital at reduced cost. Opportunity to learn from failure.	Can severely delay industry development even for organizations not directly involved in events.	22–25
5	Knowledge of IP and regulatory setting.	Spin-outs from academia often lack direct regulatory knowledge and support. Seeking this understanding from the outset will support good translational research and avoid unnecessary pitfalls.	Decreased possible loss of momentum at IND (investigational new drug) and clinical stages Ability to predict stumbling blocks.	Time consuming. Regulatory structure may change within R&D period.	26

[a]Number denotes reference listing number.

frequently unavailable. In this scenario, showing efficacy in comparison to the best current treatment is much more attainable. Two other essential elements for success in translating basic research are the "right" clinical target and the all important issue of timing.

The most poignant message arising from the meeting was that even for companies that have encountered issues, maybe as deep and dark as a bankruptcy filing, there is a way back, in the United States at least.

Conclusion

Irrespective of the hurdles that must be overcome and the badly needed infrastructure changes discussed herein, the coming decade heralds an exciting and overwhelmingly positive period for the cell therapy field. Will we see a larger section of "bench-to-bedside" translation occurring within academia? And if so, how can the knowledge, such as that of regulatory affairs found in great strength in industry, but lacking in academia, be brought in for the sector to function efficiently?

From the investors' perspective, what the regenerative medicine and cell therapy fields sorely need is a larger number of success stories to persuade them that vast potential can be realized. We will watch the progress of Cell Medica, Intercytex, and Reneuron's products to licensing with great interest. While the scale of the sector in the United States is undoubted, the rate of growth in UK cell therapy in comparison to the rest of the world is extremely encouraging.

As San Diego, CA, and Boston, MA, have made themselves biotech hubs, for the United Kingdom to be positioned as a leader within the regenerative medicine and cell therapy space, the constituents must act proactively to compete with both the United States and rising stars such as Singapore and South Korea. Globally, if a clear, unmet medical need is present that can be resolved by a cell therapy, then surely businesses, academia, and health care providers such as the National Health Service can find a way to function productively for the benefit of all, and, most importantly, those suffering from debilitating and life-threatening diseases.

Acknowledgments

The authors wish to express their gratitude to the following for their support and insight during the preparation of this manuscript: Alex Pasteur (Fidelity Biosciences), Andy Carr (NDORMS), Brock Reeve (HSCI), Gregg Sando (Cell Medica), John Sinden (ReNeuron), Kim Bure (TAP Biosystems), Paul Kemp (Intercytex), Reni Benjamin (Burrill & Co.), Richard Barker (CASMI), Suzanne Watt (NDCLS), and William Sahlman (HBS).

Author Disclosure Statement

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B. gratefully acknowledges support from the SENS Research Foundation (Mountain View, CA). D.A.B. is a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK), a company that amongst other services provides cell therapy biomanufacturing, regulatory, and financial advice to clients in the cell therapy sector. D.A.B. has conducted a paid consultancy for the Technology Strategy Board (Swindon, UK) within the past 7 years with a cumulative value of greater than $10,000. D.A.B. is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such, this author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation.

Additionally, at press time, D.A.B. and the organizations with which he is affiliated, may or may not have agreed and/or pending funding commitments from the organizations named herein.

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Bench —— to ——→ Bicycle

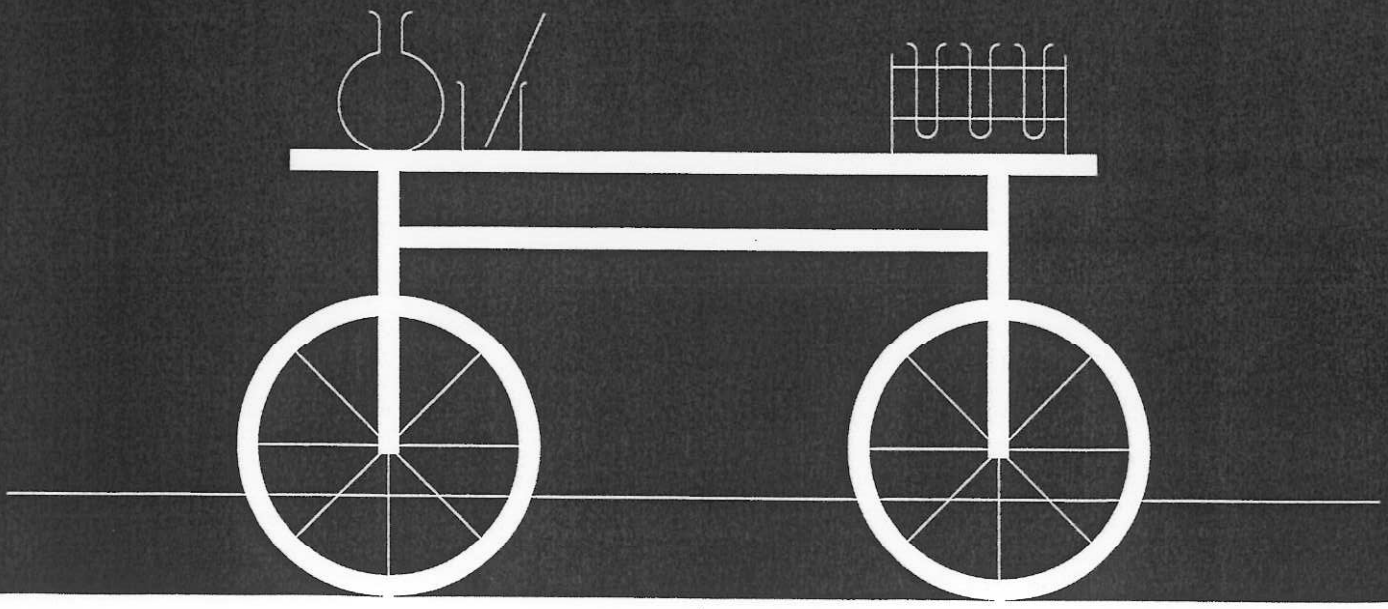
A CLINICAL PERSPECTIVE ON PERSONALISED MEDICINE
BY **DAVID BRINDLEY**

Healthcare in the 20th century was empowered by scientific advancements made by a few for the benefit of many. The 21st century will be characterised by the democratisation of medicine, where patients are active participants in the development and delivery of healthcare innovations through wearable devices, a key component of healthcare in 2030.

Wearables — small personal devices that monitor and transmit high volumes of personal physiological data — are now firmly seeded in the vernacular and promise improved understanding of patient and population disease levels. Blood pressure monitoring can be linked to applications determining optimal daily doses of antihypertensives, reducing unnecessary use of medication and maximising treatment efficacy. Wearables also offer regulators, clinicians and pharmaceutical companies transformative improvements in pharmacovigilence datasets, notably around patient adherence monitoring. This then helps reduce regulatory uncertainty and enables novel regulatory paths, including adaptive licensing and FDA breakthrough status, to become more accessible than ever before. Questions remain however, as to who is the most appropriate custodian of the collected data.

Presently, healthcare providers are the dominant collectors and custodians of patient level healthcare data, together with — to a lesser extent — healthcare insurers. The advent of wearables and virtual medical consultations places patients at the heart of data collection, and critical practical and ethical questions remain concerning the extent to which patients should be able to determine with whom collected data should be shared, and its permitted uses. Two independent groups identified as potential 'data controllers' are patient advocacy and disease-specific organisations. As demonstrated by the recent cases of Glybera[1] and Kalydeco[2], such organisations are evolving rapidly

Wearable technologies offer potentially step-changing improvements in the 'resolution of disease' at an individual and population level.



from being sources of information for patients to becoming active participants in regulatory and product development decision-making.

Wearable technologies offer potentially step-changing improvements in the 'resolution of disease' at an individual and population level. As illustrated by Jawbone users living through the recent northern California earthquake, where records of users awakened at 03:20am by the state's biggest earthquake in 25 years correlated with seismic activity, they offer an opportunity to directly monitor our response to the external environment, and to immediate changes[a].

Genomics

While recording the number of people awakened by an earthquake may seem to be little more than the nucleus of a transient news story, it illustrates the portent of an exciting chapter in modern medicine: epigenetics.

Describing the intricate interaction between an individual's genome and their long-term exposure to environmental factors, epigenetics is simultaneously transforming our understanding of disease aetiology while also informing the most effective ways to treat it. For example, we are now beginning to elucidate the underlying genetic consequences of environmental factors such as smoking on underlying patient genetics through processes such as DNA methylation and histone modification[a]. Consequently, improved knowledge of biomolecular pathways is yielding druggable targets: for example, BRCA1 in breast cancer, the in vivo target for Herceptin (trastuzumab) — a monoclonal antibody for breast cancer — offered with combinational diagnostic Oncotype DX.

The data-rich 2030 healthcare system will also enable patient stratification and data mining at a population level, utilising pharmaceutical authentication tools intended to respond to commercial threats such as parallel importing — where pharmaceuticals purchased in lower price markets are illicitly sold in higher priced markets. Products such as AegateASSURE™ and KODAK TRACELESS Anywhere™ systems may be linked to patient records in order to tightly correlate medication with patient outcomes, thus yielding unforeseen pharmacological trends and applications for repurposing existing drugs. Where existing therapies are insufficiently efficacious, genomics also offers the opportunity for bespoke therapeutic approaches including gene editing techniques such as CRISPR. These are currently applied to add, disrupt or change the sequence of specific genes, in indications such as cystic fibrosis and haematological disorders including blood disorders such as sickle cell anaemia. The technique takes a subpopulation of cells in a bone marrow aspirate, namely mesenchymal stem cells (MSCs), then identifies and corrects errant genes to allow a population of gene corrected cells to be expanded ex vivo and administered back to a patient, permanently correcting the mutation and thus the disease. Therefore, it is apparent that by 2030, healthcare will be characterised by the convergence of e-health, genomics and applications of stem cells in regenerative medicine.

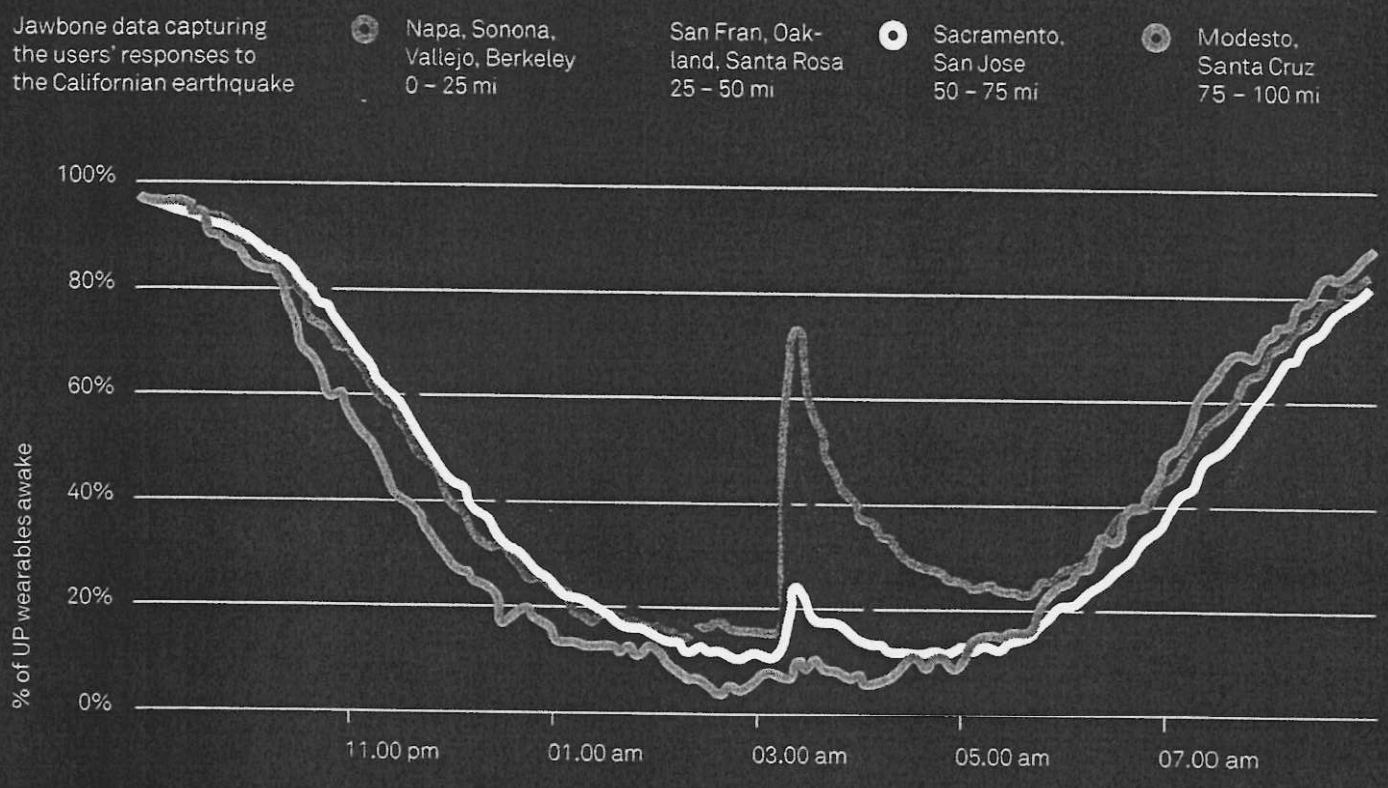
Routine application of regenerative medicines

Few areas of medical research have grasped public attention more than regenerative medicine, sustaining a cocktail of public hype, expectation and — in the case of embryonic stem cells (hESCs) — ethical concerns. However, as our understanding of the underpinning science and proof of efficacious patient outcomes grows[b], the full ambit of regenerative medicine technologies — cell therapy, gene therapy, immunotherapy (iTx) and tissue engineering — is likely to become routine clinical practice in 2030. Perhaps most futuristically, this includes the alluring prospect of replacement engineered tissues and organs to address the shortages currently experienced.

It is apparent that by 2030, healthcare will be characterised by the convergence of e-health, genomics and applications of stem cells in regenerative medicine.

Tissue engineering, and the broader descriptor of regenerative medicine, has its origins in transplantation medicine, pioneered by Christiaan Barnard (first heart transplant) and Donnall Thomas (first bone marrow transplantation). However, today tissue engineering — supported by advancements in transplant immunology and 3D printing — has demonstrated utility in the production of tracheas, bladders, kidneys, skin, vaginas, ears, livers, blood vessels and, somewhat esoterically, hamburgers. Availability of replacement organs to the many rather than the fortunate few will result in higher quality of life and productivity for society as a whole. Additionally, unlike conventional pharmaceuticals, regenerative medicines are likely to require multiple pharma business models, thereby supporting novel structures and growth areas. Current pharmaceuticals are dominated by a universal business model focused on allogeneic (non-patient specific) products — 'pills in a box.' Conversely, due to fundamental immunological challenges, including graft vs host disease (GvHD), regenerative medicines are likely to sustain both allogeneic and autologous (patient specific) products, following a transplant model. Therefore, the 'product-plus' offerings of 2014 are likely to grow in importance and breadth in the healthcare systems of 2030.

Jawbone data capturing the users' responses to the Californian earthquake



Conclusion

Accurately extrapolating the impact of healthcare trends decades into the future is challenging. However, there is little doubt that the technological triumvirate of e-health, genomics and regenerative medicines will have a profound and transformative effect on future patient outcomes, not least through the integration of these technologies into 'product plus' offerings.

In merely the last decade, genomic sequencing has been translated from human curiosity into tractable solutions at a pace that has far outstripped Moore's Law. Concurrently, the expectations of patients and payers have changed, with people now wishing to be active for longer. Therefore, the pre-eminent mantra in healthcare translation — '(lab) bench to bedside' — is under threat as healthcare in 2030 may best be described by the mantra '(lab) bench to bicycle'.

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