



**BALLIOL**  
**COLLEGE**  
UNIVERSITY OF OXFORD

**DEVELOPING EVIDENCE-BASED  
PLASTIC SURGERY:  
THE ROLE OF RESEARCH  
REGISTRATION, PROTOCOLS AND  
REPORTING QUALITY**

**Thesis submitted for the degree of Doctor of Philosophy**

**UNIVERSITY OF OXFORD**

**Michaelmas Term 2017**

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## ABSTRACT

# Developing Evidence-Based Plastic Surgery: The Role of Research Registration, Protocols and Reporting Quality

*Thesis submitted for the degree of Doctor of Philosophy, University of Oxford*

**BACKGROUND:** Evidence-based medicine has had a profound impact on healthcare. In the field of Plastic surgery, powerful examples include; less radical skin cancer excision margins and skin-sparing or even nipple-sparing mastectomies and microsurgical reconstruction. Sustained progression of the field, relies on the development of a high-quality evidence base, with strong use of peer-reviewed research protocols, which are publicly registered and completed studies transparently reported. The extent of compliance with these principles is currently unknown and the author hypothesised that it would be low. The author further hypothesised that registration could be improved by the development of a new global research registry and reporting quality can be improved by the mandatory implementation of reporting guidelines in a journal.

**METHODS:** This thesis incorporated 11 studies. The first two studies used a literature review to determine; the levels of evidence, rates of study registration and protocol publication in the recent Plastic Surgery literature. Thirdly, the design, build and launch of a new global research registry to boost compliance with registration and to determine barriers to it using a survey amongst users. This would be followed by systematic reviews to determine compliance with the STROBE and PRISMA guidelines respectively. An analysis of each guide for authors (GFA) of the surgical journals listed in the Thomson Reuters journal citation report for surgery to determine support for reporting guidelines. The impact of the mandatory implementation of reporting guidelines in a surgical journal would be assessed using a before and after design. Finally, to develop a reporting guideline for surgical case reports (SCARE) and surgical case series (PROCESS) using a DELPHI consensus exercise amongst an expert panel.

**RESULTS:** Protocols were registered in 4% of 595 recent research studies and 0.5% were published. There was a mean compliance of 12/22 for the STROBE guideline (n=94) and 16/27 for the PRISMA guideline (n=79). The *Research Registry*® was launched in February 2015. Analysis of the first 500 previously unregistered studies, showed they came from 57 countries and included 1.77 million patients. Key barriers to registration were a lack of awareness of the need to register and lack of time (n=149). In addition, 45% registered their study at the time of journal submission. The GFA analysis showed 62% didn't mention reporting guidelines at all (n=193). Subsequent mandatory implementation in a single surgical journal, increased compliance with STROBE by 12% (n=152), with CONSORT by 40% (n=13) and with PRISMA by 58% (n=28). The SCARE and PROCESS reporting guidelines were developed and published in late 2016. According to Google Scholar, they have accumulated over 200 citations at the time of writing.

**CONCLUSION:** Study registration, protocol use and reporting quality are poor in plastic surgery. Potential solutions to these long-standing problems have been developed and explored within this thesis. These include the development and use of the *Research Registry*® and the mandatory implementation of reporting guidelines, with both measures front-loaded within a gatekeeper framework for journals. It is now for Plastic Surgeons and the wider surgical community to pick up the gauntlet and drive forward high-quality research, evidence-based surgical practice and better outcomes for their patients and society at large.

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## ACRONYMS

APS	Annals of Plastic Surgery
ASPS	American Society of Plastic Surgery
CONSORT	Consolidated Standards of Reporting Trials
DoH	Declaration of Helsinki
EBM	Evidence Based Medicine
EJPS	European Journal of Plastic Surgery
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
GFA	Guide for Authors
GMC	General Medical Council
ICMJE	International Committee of Medical Journal Editors
IDEAL	Idea, Development, Exploration, Assessment and Long term follow-up
IF	Impact Factor
IRB	Institutional Review Board
JPRAS	Journal of Plastic, Reconstructive and Aesthetic Surgery
LoE	Levels of Evidence
PRISMA	Preferred Reporting items for systematic reviews and meta-analyses
PRS	Plastic and Reconstructive Surgery
RCT	Randomised controlled trial
STARD	Standards for Reporting Diagnostic Accuracy
STROBE	Strengthening the reporting of observational studies in epidemiology
UIN	Unique Identifying Number
WHO	World Health Organisation

## ACKNOWLEDGEMENTS

I would like to thank and acknowledge the contributions of the following people to this thesis. Firstly, my supervisors, Professor Peter McCulloch, Professor of Surgery at the Nuffield Department of Surgical Sciences, University of Oxford and Professor Dennis Orgill, Professor of Plastic Surgery at Brigham and Women's Hospital and Harvard Medical School, Boston, USA. It was a privilege to work with two such well respected authorities in this field and to learn from and be inspired by them. I would also like to thank Professor Doug Altman, Director of the Centre for Statistics in Medicine and Cancer Research UK Medical Statistics Group, University of Oxford for his help on the work on reporting guidelines in chapters 9-12.

I would also like to thank the medical students and junior doctors who participated in these projects as part of the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)) who assisted in data acquisition for the various studies (ensuring independence and thereby minimising bias by involvement of the author) and critical revision of the work and in the case of TEP and SYL helped co-write the individual paper for publication in a journal (chapters 4, 7 and 8 respectively); Alex J. Fowler (AF), Tom E. Pidgeon (TEP), Chris Limb (CL), Buket Gundogan (BG), Rob Coe (RC), Georgie Wellstead (GW), Katie Whitehurst (KW), Hakiran Sagoo (HS), Shiv Rajmohan (SR), Mariana Devesa (MD), Seon-Young Lee (SYL), Charmilie Chandrakumar (CC), Yasser Al Omran (YA), Kiron Koshy (KK), Daniyal J. Jafree (DJ), Mohammed Anwar (MA), Ishani Barai (IB), Kyung Jeong (KJLJ), Martinique Vella-Baldacchino (MVB), Ter-Er Kusu-Orkar (TKO), Mirabel C Millip (MCM) and Alexandra Saetta (AS). They ensured we had two independent teams of data collectors and that bias would be minimised from my direct involvement and hence the quality of this thesis is enhanced.

I would like to thank Donald M Mackay, Head of Health Care Libraries and Nia Roberts, Outreach Librarian, both from The Bodleian Health Care Libraries in Oxford and Paula Sands, Academic Liaison Librarian, University of Southampton for their help with developing and performing the electronic searches. Last but not least, I would like to thank my wife Maliha and my two children Amelia and Harris together with my parents Rafique and Rehana and my three sisters Robina, Sophia and Shimona as a source of motivation, inspiration and encouragement throughout the course of this D.Phil.

## STATEMENT OF CONTRIBUTION

The research concepts, study designs, data analyses and interpretation are the original work of the author. The work was completed under the supervision of Professor Peter McCulloch from Nuffield Department of Surgical Sciences, University of Oxford and Professor Dennis P. Orgill, Department of Plastic Surgery, Brigham and Women’s Hospital in Boston and Harvard Medical School.

All tables and figures contained within this thesis are the author’s own creation except where stated otherwise. All chapters have been written and edited by the author and each has been further enhanced and developed when compared to any chapter summary that may have been published in a peer-reviewed journal during the course of the D.Phil. It should be noted that the concept, design, build and launch of the *Research Registry*® was entirely the work of the author. In accordance with the International Committee of Medical Journal Editors (ICMJE) authorship criteria<sup>1</sup>, contributions are shown in the table below.

Contribution	Riaz Agha	Medical Students/ Junior Doctors	Supervisors (PM and DO)
Concept/Design	✓	✗	✓
Data Acquisition	✓	✓	✗
Data Analysis	✓	✗	✗
Data Interpretation	✓	✗	✗
Thesis Drafting	✓	✗	✗
Thesis Critical Revision	✓	✗*	✓
Final approval of the version to be published	✓	✗	✗
Agreement to be accountable for all the work	✓	✗	✗

<sup>1</sup> International Committee of Medical Journal Editors. Defining the Role of Authors and Contributors [online]. Available at: <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html> (accessed 5 August 2016). \*Medical students/junior doctors were involved in revising individual papers on which they were co-authors.

## DISSERTATION AUTHENTICITY STATEMENT

I hereby declare that no part of this thesis has been submitted for any other degree at this or any other university. I confirm that I have read the Department of Continuing Education's rules relating to plagiarism as found in the Student Handbook.

I confirm that the work presented here is my own except where otherwise indicated.

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Signed.....

Date.....12 January 2018.....

Approximate number of words: \_\_\_\_\_49,997\_\_\_\_\_

## **ETHICAL APPROVAL, CONFLICTS OF INTEREST AND FUNDING**

### **Ethical Approval**

In accordance with the policy of the Central University Research Ethics Committee (CUREC), this work will not require ethical approval as there are no human participants.<sup>1</sup>

### **Conflicts of Interest**

The author is the founder of IJS Publishing Group Ltd and the Managing and Executive Editor for the International Journal of Surgery and International Journal of Surgery Case Reports, which had a prominent role in chapters 5, 6, 10 and 13.

### **Funding**

The author is grateful for the following sources of funding towards the D.Phil in general and the research in chapter 13 respectively.

- Clarendon Fund Scholarship covering all university and college fees as well as a maintenance grant (Approx. £34,000).
- Balliol Interdisciplinary Institute, Balliol College, University of Oxford (£3,000) – towards work in chapter 13.
- Paton-Masser Memorial Fund, British Association of Plastic, Reconstructive and Aesthetic Surgeons (£2,500) - towards work in chapter 13.

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<sup>1</sup> University of Oxford. Policy Statement: Policy on the Ethical Conduct of Research Involving Human Participants and Personal Data [online]. Available at: <http://www.admin.ox.ac.uk/curec/policystatement/> (accessed 29 June 2014).

# CHAPTER 1

## INTRODUCTION TO THE THESIS

## 1.1 OVERVIEW

*“Most Published Research Findings Are False”<sup>1</sup>*

John Ioannidis 2005

Scientific research is a booming industry. Increasing scientific knowledge over the decades has had a profound impact on healthcare and wider society. From organ transplantation to stem cell therapies and from placing a man on the moon to the advent of driverless cars, the impact is clear and present. In the period 1996-2011, 15 million people authored 25 million scientific papers.<sup>2</sup> True and readily applicable major contributions are rare. Many new associations and treatment effects are inflated or exaggerated.<sup>3</sup> Apparently promising therapies are stopped after further evidence comes to light.<sup>4</sup> Indeed, the same can happen to established therapies, after larger more well powered studies are performed. For example, the Million Women study showing that women taking hormone replacement therapy (HRT) had double the risk of developing breast cancer compared to non-users.<sup>5</sup> Other findings have been surprising, such as evidence that oxygen administration in acute uncomplicated myocardial infarction may actually increase mortality, contrary to traditional teaching.<sup>6</sup>

Greater still is the number of poorly designed, conducted and reported studies which suffer from being underpowered and deploying inappropriate statistical methods.<sup>7,8,9,10</sup> John Ioannidis' indictment above of the scientific literature is a reflection of these issues. Indeed, concerns have been raised about the prevalence of methodological errors in medical research for nearly a century.<sup>11</sup> Recent reports have highlighted how crucial

aspects of study methodology are often missing.<sup>12,13</sup> This lack of transparency makes reproducibility difficult and ‘short-circuits’ critical appraisal.

The whole situation is compounded by a lack of protocol usage, poor rates of study registration and negative publication bias through misreporting and non-reporting. The corollary is poor reproducibility and external validity with an estimated 85% of research resources wasted.<sup>14</sup>

## **1.2 HYPOTHESES**

1. Study registration, use of protocols and reporting quality is poor in the Plastic Surgery literature.
2. Study registration can be improved by the creation of a new global research registry.
3. Reporting quality can be improved by the mandatory implementation of reporting guidelines in a journal.

## **1.3 RESEARCH QUESTIONS AND OBJECTIVES FOR THIS THESIS**

To investigate and test these hypotheses as well as advance the field, the following research questions and objectives were set:

1. To determine the levels of evidence in the recent Plastic Surgery literature, to compare with other surgical specialties and assess trends over time.
2. To determine the rates of study registration and protocol publication in the Plastic Surgery literature.
3. To build and implement a new global research registry to boost research registration.

4. To determine the barriers to research registration.
5. To determine the reporting quality of observational studies in Plastic Surgery.
6. To determine the reporting quality of systematic reviews in Plastic Surgery.<sup>1</sup>
7. To determine the existing support for reporting guidelines within surgical journals.
8. Assess the impact of the mandatory implementation of reporting guidelines in a surgical journal.
9. To develop a reporting guideline for surgical case reports.
10. To develop a reporting guideline for surgical case series.

## **1.4 STRUCTURE OF THE THESIS**

### **Chapter 2: Background and literature review**

This chapter outlines the problems with medical research and the findings of recent research in this area. The chapter concludes by laying out the rationale for the thesis.

### **Chapter 3: Levels of evidence in plastic surgery – bibliometric trends and comparison with five other surgical specialties**

Chapter 3 reports on the levels of evidence published in the top three plastic surgery journals in 2003 and 2013 and compares this with five other surgical specialties, allowing both a cross-sectional and longitudinal analysis. The chapter sets out the methods and results of this work and concludes with a summary of the main findings and their implications for future research.

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1. The reporting quality of randomised controlled trials (RCTs) has been determined already by the author in prior work (and shown to be poor – see appendix I and II).<sup>13</sup>

**Chapter 4: The Use of Study Registration and Protocols in Plastic Surgery Research: A Systematic Review**

Chapter 4 is a systematic review on the prevalence of study registration and protocol publication in the recent plastic surgery literature.

**Chapter 5: Development of a global research registry and evaluation of the first 500 registrations**

Chapter 5 describes the development of a new global research registry and the nature and quality of the first 500 registrations.

**Chapter 6: An analysis of barriers to research registration – a survey of 1,000 registered studies**

Chapter 6 describes the methodology, results and discussion of a survey of the first 1,000 authors to register their study on the Research Registry.

**Chapter 7: The reporting quality of observational studies in Plastic Surgery needs improvement: a systematic review**

Chapter 7 describes a systematic review of the compliance of observational studies in Plastic Surgery with the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

**Chapter 8: The reporting quality of systematic reviews in Plastic Surgery needs improvement: a systematic review**

Chapter 8 describes a systematic review of the compliance of systematic reviews in Plastic Surgery with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

**Chapter 9: Support for reporting guidelines in surgical journals needs improvement: a systematic review**

Chapter 9 is a systematic review of the recommendation of reporting guidelines within the guide for authors (GFA) of surgical journals. It builds on chapters 7 and 8 by looking at the extent to which reporting guidelines are endorsed within journals.

**Chapter 10: Impact of the Mandatory Implementation of Reporting Guidelines on Reporting Quality in a Surgical Journal: A Before and After Study**

Chapter 10 describes the change in compliance with the STROBE, CONSORT and PRISMA guidelines before and after a policy of mandatory enforcement at a surgical journal came into effect.

**Chapter 11: Development of the SCARE Guideline for Reporting Surgical Case Reports**

Chapter 11 describes the development of the surgical case reports (SCARE) reporting guideline including the methodology and results of the DELPHI consensus exercise.

## **Chapter 12: The Methodological and Reporting Quality of Case Series in Surgery needs improvement: A Systematic Review**

Chapter 12 is a systematic review focusing on the methodological and reporting quality of recent case series in surgery. The aim being to determine the elements that are commonly missing and could be used to inform the development of a reporting guideline on case series.

## **Chapter 13: Development of Preferred Reporting of Case Series in Surgery: The PROCESS Guideline**

Chapter 13 describes the development of the PROCESS Statement for surgical case series including the methodology and results of the DELPHI consensus exercise.

## **Chapter 14: Discussion and conclusions**

Chapter 14 summarises the findings of the components that make up this thesis. How the thesis fits into the context of the existing literature and how it addresses knowledge gaps is discussed. The collective implications for policy directions and how future research can build on these findings are explored. Finally, the conclusions that can be drawn from this thesis are described.

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# CHAPTER 2

## **BACKGROUND, LITERATURE REVIEW AND RATIONALE FOR THE THESIS**



**BALLIOL**  
**COLLEGE**  
UNIVERSITY OF OXFORD

Significant portions of this chapter have been summarised and published in the *Aesthetic Surgery Journal*<sup>1</sup> and the *International Journal of Surgery*.<sup>2</sup>

## 2.1 THE PERFECT STORM OF 21<sup>ST</sup> CENTURY HEALTHCARE

The state of 21<sup>st</sup> century healthcare is a perfect storm, with unprecedented demands being placed on healthcare systems globally. In the developed world, there are soaring rates of obesity, diabetes and chronic disease in the context of an ageing society, so patients are becoming increasingly complex.<sup>1,2</sup> In the developing world, there are high rates of trauma and tobacco use, infant and maternal mortality, infectious diseases and malnutrition.<sup>3,4</sup> Such trends are occurring within the context of rising; global demand for surgery/interventions,<sup>5</sup> use of costly technology and drugs, costs of healthcare,<sup>6</sup> and geopolitical instability against the backdrop of tight fiscal restraint resulting from a global financial crisis.<sup>7</sup>

There has also been a concomitant surge in public and patient expectations, as well regulatory demands.<sup>8</sup> Juxtaposed to this, is the growing realisation and demand for patient choice, with patient-centered care that respects patient autonomy, that is high quality, safe, timely, efficient and equitable; combined with less variation and greater reliability.<sup>9</sup> Indeed, this "perfect storm" extends to aesthetic surgery too as demonstrated in part by poor evidence of new technologies and the significant involvement of industry.<sup>10,11</sup>

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<sup>1</sup> Agha RA and Orgill DP. *Evidence-Based Plastic Surgery: Its Rise, Importance, and a Practical Guide*. *Aesthetic Surgery Journal* 2016;36(3):366-71.

<sup>2</sup> Agha R and Rosin D. *The Research Registry – Answering the Call to Register Every Research Study Involving Human Participants*. *International Journal of Surgery* 2015;16:113-115.

## **2.2 THE SPECIALTY OF PLASTIC SURGERY**

The specialty is incredibly broad, encompassing the following areas:

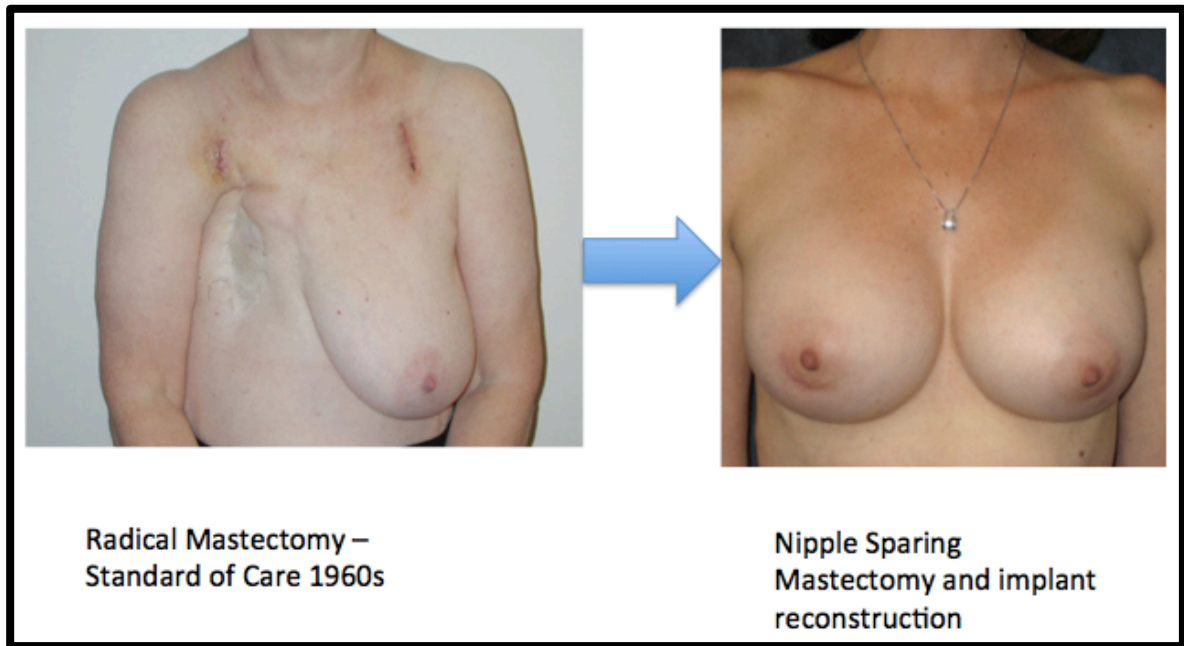
- Head and neck surgery
- Craniofacial surgery
- Breast reconstruction
- Skin cancer/Sarcoma
- Hand, wrist and upper limb surgery
- Lower limb reconstruction
- Complex wound and scar management
- Burns – acute management and reconstruction
- Microsurgery – reconstruction of composite tissue defects following trauma or cancer resection
- Aesthetic surgery

It also includes several super-specialist areas such as the repair/reconstruction of congenital abnormalities including; limb deformity, hypospadias and cleft palate as well as hand and face transplantation and gender reassignment. Plastic surgeons also operate across a wide range of patients (male, female, children, elderly) and deal with defects or the functional/aesthetic impacts of cancer, trauma, infection, inflammatory or congenital conditions. The specialty is not limited to a particular anatomical region and is more technique-based than other surgical specialties, who often consult Plastic Surgeons for complex or chronic wound and scar management on their own patients.

## **2.3 THE EVIDENCE-BASED MEDICINE REVOLUTION AND ITS IMPORTANCE IN PLASTIC SURGERY**

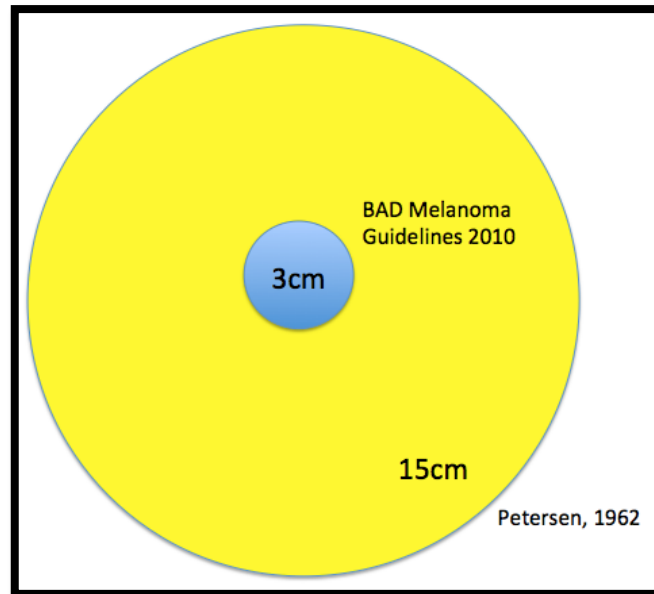
Over the last 20 years a quiet revolution has taken place, which might just have presented us with our most powerful weapon against these trends – evidence-based medicine (EBM).<sup>12,13,14</sup> The beauty of EBM is that ultimately, we get closer to the ‘truth’, the right answer or the correct management plan for a patient than we otherwise would have done.

In 1984, Haagensen and Bodian wrote in support of Halsted’s radical mastectomy.<sup>15</sup> Defending it against less radical techniques and the criticism that is “cripples the arm and shoulder”, they stated: “*My patients swim and play golf and tennis very well*” and that “Detailed and very long-term results with these newer methods are not yet available and may never be because of the great expense and effort required.” Indeed, it did, Veronesi’s seminal randomized controlled trial (RCT) with 20-year follow-up, found that wide local excision had comparable outcomes to mastectomy for breast tumours less than 2cm in diameter.<sup>16</sup> The significance of this is that Halsted radical mastectomy was the standard of care in the 1960s, now the majority of breast cancer patients would have a wide local excision and those needing a mastectomy would have a skin or even nipple sparing one (figure 2.1).



**Figure 2.1:** How the standard of care and outcomes for breast cancer patients have changed from the 1960s till the present time, driven by good research, patients and clinicians. Photos from the Breast Preservation Foundation.

Another powerful example is melanoma excision margins. In 1962, Petersen was advocating 15cm margins, today the largest is 3cm from the British Association of Dermatology Guidelines which are endorsed by the British Association of Plastic, Reconstructive and Aesthetic Surgeons (figure 2.1).<sup>17,18</sup>



**Figure 2.2:** Relative 3cm and 15cm excision margins for melanoma.

Donald Lalonde has eloquently discussed how he changed his own practice in light of the evidence across a range of areas.<sup>19</sup> EBM is a logical approach to patient management that integrates a step, which ensures we can learn from others and their collective experiences of treating hundreds and thousands of patients and integrate that with our own. Clinical judgment is therefore based on a larger sample, has greater validity and has more statistical power.

Sackett has defined EBM as the integration of clinical expertise and patient preferences with the best available research evidence to make decisions about the care of patients.<sup>20</sup> This logical ‘triple-lock’ is both a movement, a philosophy and something that can be utilised in individual doctor-patient consultations when reviewing treatment options. EBM cannot therefore be done well; simply by reviewing the evidence, it takes time for clinicians to build ‘muscles’ around judgment and to develop their expertise. The “*this*

*works well in my hands*” argument is still valid within an EBM framework. For instance, a Cochrane systematic review analysing three RCTs found that drains had no benefit in reduction mammoplasty, but some surgeons still prefer to use drains for fear of haematoma.<sup>21</sup> Indeed, anecdotally, we understand some surgeons stopped using drains on such evidence and their haematoma rate increased, so reverted to their previous practice.

If a person’s experience is discordant with good evidence, this may represent poor luck, but it should trigger a search for the reasons why? Are patients being correctly selected, is the technique being executed in the same way, is the post-operative setting and support comparable. The same goes for integrating patient preferences and judging the impact of a treatment on a patient. Judging the best available research evidence is a matter of critical appraisal.

So how should one interpret research? How should one decide the ramifications for clinical practice? These are questions that clinicians and policy makers have been grappling with since the dawn of EBM and before.<sup>22</sup> *“Don’t believe everything you read”* is what our parents tell us as children. So, what should we believe and how do we go about it. Indeed, this year is the 350<sup>th</sup> anniversary of the scientific journal – what better time to consider such issues.<sup>23</sup>

Over the last decade there have been increasing calls for the adoption of an evidence-based medicine (EBM) approach within surgery and this trend includes plastic surgery. The evidence base in plastic surgery is still dominated by case series but with higher levels

of evidence and RCTs in particular being encouraged.<sup>24,25,26,27,28,29,30,31</sup> Poor methodology and reporting undermines' proper critical appraisal of research, prevents its inclusion in systematic reviews and meta-analyses and resulting clinical judgments could be misleading and potentially dangerous.

The challenge to integrate EBM into clinical decision making is huge, with 30-40% of patients not receiving care consistent with the available evidence and 20% or more are receiving care that is unnecessary or even harmful.<sup>32</sup> Warnings about such a situation were first aired by Archie Cochrane, who criticised interventions that had little or no evidence of effectiveness.<sup>33</sup>

## **2.4 THE NATURE OF SURGICAL PRACTICE AND INNOVATION**

During the last 60 years we have seen advances of unquestionable importance to patients which have been based on surgical research. Examples include, the development of cardiac and vascular surgery, organ transplantation, joint replacement, minimally invasive surgery and most recently robotic surgery.<sup>34</sup> The development and evaluation of surgical and interventional techniques has a natural history and timeline, proceeding through stages that can be similar to drug development. However, there are some important differences that we shall come on to discuss.

Surgery conventionally, has been defined as a procedure involving an incision with an instrument.<sup>35</sup> Krummel proposed that an operation consists of two components: the first being imaging (e.g. visual or radiological) and the second is a manipulation (e.g. manual or energy based).<sup>36</sup> Surgical advances have usually been related to clear-cut anatomical

and pathophysiological concepts e.g. cessation of bleeding, fixation of bony fracture, excision of an abnormal growth, amputation of a limb or digit affected by severe infection. More rarely the premise may be on less solid ground e.g. total colon resection to treat female autointoxication.<sup>37</sup> The history of surgical innovation includes much trial and error.

Surgical innovation and practice are inherently connected. A bench scientist may be working on a problem in a step-by-step, iterative way, making sequential progress through a problem towards new knowledge and discovery. Whereas surgeons are continually brought into close proximity with patients presenting to them either in an emergency or electively, with their own unique problems or combinations thereof that require a solution. Add to this the patient's unique anatomy, history, ideas, concerns and expectations. Innovative solutions may stem from extensive planning and discussion with colleagues or they may involve spontaneous improvisation during a procedure or serendipity will provide a unique opportunity for the surgeon with the prepared mind to grasp.

At times, a surgeon may be proceeding along the course of an established therapy, which they then modify, given the unique situation they find themselves in during the operation, a small innovative step or series of steps. Indeed, this intrinsically iterative nature of surgical practice may potentiate surgeons to routinely experiment with an established operation to the point that it may change unrecognisably.<sup>38</sup> This process can ultimately make it impossible to decide whether the operation is just an evolutionary variation or the actual first stage of a novel therapy. This can lead to a grey zone where patients may not be robustly protected against the uncertainties posed by the innovation.<sup>39,40</sup>

This is far removed from the framework for the development of a new drug in the pharmaceutical sector, where assessment occurs along its phases of development, is well characterised, regulated and where even small changes in formulation will require retesting at a more basic level<sup>35</sup>:

- ❖ Phase 0 – micro dose pharmacology (focus on toxicity, experimental, animal).
- ❖ Phase 1 - single and multiple-dose safety and tolerability studies in small numbers of healthy volunteers.
- ❖ Phase 2 - studies over the target dose range in the patient population (learning).
- ❖ Phase 3 - large-scale efficacy and safety studies (confirmatory).
- ❖ Phase 4 - Postmarketing interventional studies (e.g. to assess other patient populations, new indications, or new formulations, and to assess adverse effects).

This more robust development framework, stemmed from failures of the past e.g. Thalidomide in the 1960s (which led in the UK to the development of the body now known as the Commission on Human Medicines).<sup>35</sup> Despite this, there are still problems illustrated by; the withdrawal of COX2 inhibitors for increasing the risk of myocardial infarction (MI), the Million Women Study showing increased risk of breast cancer in those who take hormone replacement therapy (HRT), the near deaths caused by the monoclonal antibody TGN1412 in 2007 or Flecainide, the post-MI anti-arrhythmic that is now estimated to have led to the premature deaths of more Americans than the Vietnam or Korean Wars.<sup>41,42,43,44</sup>

Most robust regulation and continual improvements have made drug development more challenging and expensive, as evidenced by a recent Food and Drug Administration (FDA) report.<sup>45</sup> New devices that may be used in surgery, also require a premarket

approval level of evidence lower than that for drugs.<sup>35</sup> Furthermore, if a device is similar to already approved devices, then a fast-track system allows its introduction into practice after demonstrating basic efficacy e.g. the introduction of a vacuum assisted closure (VAC) wound management device after a case series and radiofrequency ablation devices for liver tumours after a single group (non-comparative) prospective cohort study.<sup>46,47</sup> No comparisons were made in these studies with the ‘gold’ standards at the time. The VAC went on to confirm its efficacy after its widespread introduction, in RCTs and become a staple in the field of wound management having treated over nine million wounds according to the manufacturer.<sup>48,49</sup> However, in the case of radiofrequency ablation of liver tumours, subsequent evidence on morbidity, mortality and efficacy as well as comparison with surgical resection was mixed.<sup>50,51</sup>

Such introductions of new procedures are not integrated into any regulatory framework unless researchers choose to make them part of a research study. Hence, there is a lack of governance and regulatory oversight. If they chose not to, they can in many instances still publish their results as a case series without the need for ethical committee approval.<sup>35</sup> A clear element of self-regulation exists as the FDA and other regulators focus on drugs and devices, not operative techniques.<sup>35</sup> Therefore, between innovation and harm to the patient lies little more than a surgeon's sense of responsibility, dedication, and fear of medico-legal consequences.

Formal and comparative assessments, long-term monitoring of outcomes, patient-reported outcomes, cost-effectiveness and quality control were not high on the agenda in the past.<sup>52</sup> The assessment of surgical innovation is made complex through a number of factors and idiosyncrasies related to surgical practice; early “tinkering” (small iterative adjustments

that mean the technique is not stable), the complexity of defining the surgical intervention, accommodating surgical learning curves, quality control, the difficulty in developing standard outcome measures and strong preferences from either the surgeon, patient or both resulting in a lack of equipoise.<sup>52</sup> This can make it more difficult for the surgical innovator to build their research in a systematic and structured way. Indeed, this is reflected in the frequency of surgical RCTs, which have remained low at 9% in 1993 and 8% thirteen years later in 2006. Those that are published have been shown to suffer from poor reporting.<sup>53,54</sup>

Historically, a number of factors have caused surgical research to suffer including; a lack of funding, patchy regulation, the absence of an embedded culture of research and a lack of training in research methods. The ramification is an underrepresentation of randomised trials in surgery.<sup>55,56</sup> A framework to help fix many of the problems discussed above, has been put forward – The IDEAL Framework.<sup>57</sup> The author discusses this in greater detail in chapter 14.5.

## **2.5 CRITICISMS AND RESISTANCE TO EBM IN GENERAL AND PLASTIC SURGERY SPECIFICALLY**

Although the logic of EBM is clear, there is dissent among clinicians and policy makers about its implementation in day-to-day practice. These debates have divided surgeons, who have felt that EBM has curtailed their autonomy and has neglected patient individuality.<sup>58,59</sup> There is a misconception that EBM limits autonomy and decision-making with doctors being forced along algorithms in a robotic fashion, so called “cookbook medicine”.<sup>60,61,62,63</sup> A charge that follows from this misconception, is that

variations in management are not only discouraged but punishable and that EBM does not account for variation in disease processes, anatomy, physiology and clinical expertise.<sup>64</sup>

Many aspects of EBM have come under scrutiny, including the way it should be implemented at the bedside and whether EBM simply ends up providing average rather than state-of-the-art treatment.<sup>65</sup> Increased EBM awareness has led to some confusion, controversy and resistance with some misunderstanding of what EBM really is and how it integrates with existing clinical decision making, traditional medical teaching and surgical apprenticeship.<sup>66</sup> Eaves et al, have discussed areas where Plastic Surgeons may feel threatened by EBM.<sup>66</sup> There is felt to be an inherent implication with EBM, that the 'current' situation or utilisation of knowledge or decision making is inadequate.<sup>66</sup>

Evidence-based practices have spread to other fields like public policy, drug policy, marketing and business management. Resistance has been encountered in other areas too.<sup>63</sup> Pfeffer and Sutton described barriers in evidence-based management with businesses dealing with 'evidence overload', too much evidence and people can't find what they need, poor quality evidence and an over-reliance on personal experience and stories which then outweigh evidence which doesn't resonate in the same way.<sup>67</sup> Plastic Surgeons attempting to lead change towards EBM, have commented that this does sound familiar.<sup>66</sup>

Indeed, a reported misconception is that EBM is for the non-surgeons. The research base within surgery is also skewed towards case reports and case series. Offer and Perks reported that 3-9% of studies in the surgical literature are RCTs and there were few applicable to Plastic Surgery.<sup>68</sup> There are of course ethical dilemmas with sham surgery

and the challenges of persuading plastic surgeons to pursue higher quality studies with a lack of research skills and knowledge of EBM tenets.<sup>69,70</sup> Steps are being taken to address these points with the American Academy of Facial Plastic and Reconstructive Surgery having formed a new EBM committee with the charge to infuse, instruct, and integrate the tenets of EBM into its various educational meetings, fellowship curriculum, and research endeavours.<sup>24</sup>

The scientific underpinning of much of clinical care is surprisingly limited and Plastic Surgery as a field, has developed in such a culture, with surgeons relying on techniques or practice traditions they were taught many years ago, but which they feel more comfortable with.<sup>14,66</sup> There are also other powerful forces at play, like defensive medicine and over-prescription, which are estimated to waste \$211 billion annually or nearly 10% of the \$2.2 trillion spent on all healthcare expenditure in the USA.<sup>71</sup>

Potter et al, performed semistructured qualitative interviews with 35 breast reconstruction surgeons (from either a Plastic Surgery or Breast Surgery background), to explore their preferences and beliefs towards randomisation and the feasibility of surgical RCTs.<sup>72</sup> Participants were drawn from 15 centres across the UK and interviews were transcribed verbatim and analysed thematically. They found that surgeons often struggle with the concept of equipoise i.e. where it's not clear whether one reconstruction technique would be better than another.<sup>72</sup> If surgeons didn't feel in equipoise, they wouldn't accept randomisation as a method of treatment allocation. In breast reconstruction, there are often multiple treatment options available and patients and surgeons often exhibit strong preferences. There was limited acknowledgement of the methodological weaknesses of non-randomised studies and a lack of understanding of pragmatic trial design and the

value of RCTs in generating high quality data with less bias.<sup>72</sup> Many surgeons commented that there are simply too many things to control for in an operation and given that this won't happen, bias is introduced and you are now not doing a fair comparison of two different techniques.<sup>72</sup>

They concluded by underscoring the need to help surgeons understand evidence, equipose and bias and stated that investment into education and infrastructure for RCTs from funders like the Medical Research Council (MRC) and the National Institute of Health Research (NIHR) combined with strong leadership may begin to address these gaps.<sup>72</sup> Potter et al's work is particularly poignant, when one considers the history of breast reconstruction RCTs. Since 1995, just 13 have been conducted and only two addressed important questions like the optimal type or timing of surgery.<sup>73,74</sup> Both of these were small, single-centre RCTs that failed to meet their own recruitment targets. Prevailing expert opinion is that RCTs in breast reconstruction would be unethical, impractical and/or inappropriate because of strong surgeon and patient preferences in procedure selection.<sup>75,76,77</sup>

## **2.6 DRIVE FOR EBM WITHIN PLASTIC SURGERY**

The drive for EBM within the specialty has become a priority area. In August 2010, leaders from numerous Plastic Surgery organisations met at the Colorado Springs EBM summit. The resulting consensus statement stated that:

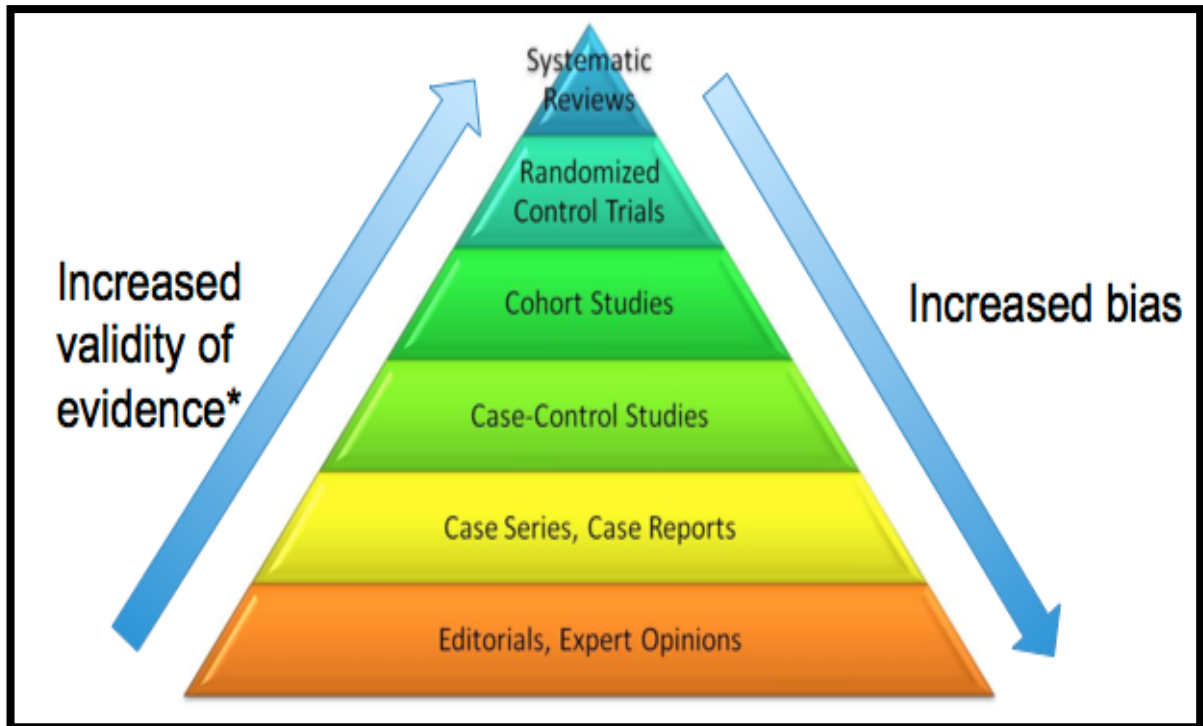
*“Incorporating EBM into all the core specialties of plastic surgery, both aesthetic and reconstructive, is critical to ongoing improvements in patient safety and quality of care*

*and must be a priority of all plastic surgery organizations, leadership, researchers, educators, practicing surgeons, and the public.”*

There is a significant focus now on how EBM can be weaved into clinical decision making more seamlessly at the bedside and in the clinic and how do we best teach EBM to trainees in Plastic Surgery. Furthermore, comparative effectiveness and cost studies are now a high priority research area for the Plastic Surgery Foundation (founded 1948).<sup>78</sup>

## **2.7 DETERMINING THE BEST AVAILABLE EVIDENCE – LEVELS OF EVIDENCE**

Part of determining the ‘best available research evidence’, is to categorise research into the appropriate level of evidence (LOE) as defined by the American Society of Plastic Surgeons (figure 2).<sup>79,80,81</sup> This aids searching and transparency, with higher levels of evidence associated with less bias and greater validity if performed well. The performance and reporting of higher level of evidence plastic surgery clinical research was stressed in an edition of the Clinics in Plastic Surgery in 2008.<sup>82</sup> In January 2011, a specialty wide EBM initiative in Plastic Surgery was launched.<sup>83,84</sup> This included the listing of the LOE on all articles amenable to the LOE grading.<sup>85</sup>



**Figure 2.3:** The Levels of Evidence Pyramid (adapted from Chung et al, 2009)<sup>86</sup>.

## 2.8 RESEARCH QUESTIONS AND OBJECTIVES

*What is current status of the evidence base in plastic surgery, and what are the trends?*

*How does this compare with other surgical specialties?*

This will allow us to see what levels of evidence recent research in Plastic Surgery is being performed at. We can then monitor how the drive for higher levels of evidence is impacting on the research being performed and published. Loiselle et al found that from 1983 to 2003, when ranking 989 articles in a single journal, the level of evidence increased from 4.42 to 4.16, those with control or placebo groups increased from 7.21% to 13.7%, and the number of RCTs increased from 0% to 7%.<sup>87</sup> Sinno et al found that of 726 studies published in four major plastic surgery journals in 2007, the average level of evidence was 3.2 and only 2.2% of articles were level I evidence.<sup>88</sup> Chang et al found that

of 1419 aesthetic surgery studies published in three plastic surgery journals over the decade 1998-2007, 86.3% were level IV or V evidence and only 3.2% were RCTs.<sup>89</sup> Chuback et al found that the mean level of evidence in 126 presentations at North American plastic surgical meetings in 2010-11 was 3.45.<sup>90</sup>

In comparison, Hanzlik et al found over the period 1975 to 2005, the percentage of level I studies in the Journal of Bone and Joint Surgery (American volume) increased from 4% to 21% and the combined percentages of level I-III studies increasing from 17% to 52%.<sup>91</sup>

### **OBJECTIVE ONE**

To determine the levels of evidence in the recent Plastic Surgery literature, to compare with other surgical specialties and assess trends over time.

### ***What is the current nature of study registration and use of protocols in Plastic Surgery?***

Imagine you're a patient signing a consent form for an operation and only knowing about the good outcomes and none of the risks. This is akin to what is happening in much of healthcare research today. Negative studies don't get published and positive studies sometimes get published twice.<sup>92</sup> Such publication bias is skewing the research base to the detriment of scientific progress. There is strong evidence that much research remains unpublished and this is especially true of those studies with 'inconvenient' or negative findings.<sup>93</sup>

### **Publication Bias and Selective Reporting**

In April 2014, we found out that the UK government had wasted £500m on stockpiling Tamiflu – a drug the Cochrane Collaboration determined had little or no impact on the

complications of influenza infection such as pneumonia.<sup>94</sup> This occurred because Roche, the pharmaceutical company behind it withheld crucial information on its clinical trials for half a decade.<sup>94</sup>

We typically associate such publication bias and selective reporting with big pharmaceutical companies but there is increasing evidence that this is occurring in the academic community as well. In a cross-sectional analysis of 677 trials (excluding phase I studies) registered on ClinicalTrials.gov, just 46% of those that had completed by 2005 were published by 2007.<sup>95</sup> In a more recent study, Jones et al assessed 585 clinical trials that had recruited at least 500 participants and were prospectively registered on ClinicalTrials.gov and completed by January 2009. They found that, by November 2012, 29% of these trials remained unpublished.<sup>96</sup> Such evidence points to worrying rates of non-publication in both registered and large trials. This problem is likely to be magnified with smaller studies, especially unregistered ones.

Dwan et al conducted a systematic review of publication and outcome reporting bias.<sup>97</sup> They found direct empirical evidence for the existence of study publication and outcome reporting bias. There was strong evidence that positive or statistically significant results were more likely to be published. In surgery, Chapman et al found that one in five surgical RCTs are discontinued early and one in three remains unpublished two years after their conclusion.<sup>98</sup> They stated that negative findings were a barrier to publication and appealed for journals to publish them. They concluded by stating that public trust in research will be badly damaged if we continue to ‘mothball’ negative studies and recruitment will become an even greater challenge.<sup>98</sup>

Ross et al showed that only 42% of trials that stated they concluded in 2005 were actually published over two years later.<sup>99</sup> They concluded by stating that: “*The scientific community should be prioritizing the timely and accurate publication and dissemination of clinical trial results, regardless of the strength and direction of the trial results.*” This is a challenge to the human behavior clinicians and researchers exhibit when editors express their bias through their decisions – favoring positive studies. Indeed, whilst Negative studies don’t get published and positive studies sometimes get published twice.<sup>100</sup> Research registration is one of the ways to tackle this.

In this context, it is important to discuss what these terms negative and positive studies mean. Negative studies have been defined as showing a result that goes against the investigated hypothesis.<sup>101,102</sup> For example, if treatment A and treatment B are under investigation, with the hypothesis being that treat A is better, yet the results showed no difference or that treatment A was worse, than that would be a negative study. If treat A was found to be better, in line with the hypothesis, than that would be a positive study.

## The Benefits of Registering Research

The benefits of research registries have been argued previously.<sup>103,104</sup> For the sake of brevity we have summarised these in the table below:

<b>TABLE 2.1 BENEFITS OF RESEARCH REGISTRATION</b>	
<b>STAKEHOLDER</b>	<b>BENEFIT</b>
Research and clinical community	<ul style="list-style-type: none"> <li>❖ Reduce publication and reporting bias (not all studies performed are published – especially negative studies).</li> <li>❖ Increase transparency.</li> <li>❖ Identify on-going studies in their field – the cutting edge and gaps.</li> <li>❖ Aids research quality - allows for open and early peer-review of study objectives and methods and their refinement.</li> <li>❖ Aids guideline development and evidence synthesis/systematic review.</li> <li>❖ global collaboration between researchers – more multicentre studies.</li> </ul>
Editors and peer-reviewers	<ul style="list-style-type: none"> <li>❖ Compare study findings with registered study protocol.</li> <li>❖ Evidence-based medicine.</li> </ul>
Commissioners, funders and wider society	<ul style="list-style-type: none"> <li>❖ Reduce unnecessary duplication and saving precious funds and finite resources.</li> </ul>
Institutions	<ul style="list-style-type: none"> <li>❖ Increased collaboration – research that's more global, multicentre and more interdisciplinary.</li> </ul>
Patients and the public	<ul style="list-style-type: none"> <li>❖ Can find out about research of interest to them (e.g. HIV treatments).</li> <li>❖ Respect, dignity and ethics – people who enter studies expect a permanent record of it, that should be publicly available.</li> </ul>

The other aspect we must acknowledge is the lessons lost and the learning that wasn't disseminated to the wider research community. Kasenda et al found that 24.9% of 1,017 RCTs were discontinued with the most frequent reason being poor recruitment.<sup>105</sup> These 'failures' are often not reported. But learning from them and disseminating problems encountered together with possible solutions could help prevent others repeating the mistake. Was it poor recruitment, costs, a flawed hypothesis or lack of equipoise that led to the studies demise. We can learn from these valuable experiences and they should be added to the ever-expanding corpora of knowledge in our field.

We need to know what works and what doesn't work in order to drive research in the correct direction, aid collaboration, prevent duplication and wasted resources. Other issues our community grapples with, is underpowered studies, poor statistical methods, poor reproducibility and external validity, poor methodology and reporting of studies.<sup>106</sup> Publishing Protocols and negative results brings the focus away from the results themselves to the research questions, the hypothesis and the robustness of the methodology used to investigate it.

In 1999, Chalmers and Altman stated that medical journals should consider publishing protocols to aid with the primary prevention of poor medical research.<sup>107</sup> In the intervening period, transparency has become a major part of the healthcare research discourse. The Declaration of Helsinki (DoH) is in support of explicit research protocols:

*"The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol."*

## Existing Trial Registries

In 1989, Robert Simes called for an international registry of clinical trials to deal with the growing problem of publication bias.<sup>108</sup> Simes performed a comparison between published clinical trials found in a literature search and those found in a review of registered trials contained in a cancer trials registry.<sup>108</sup> He attempted to answer two questions:

1. Impact on survival of initial alkylating agent (AA) Vs combination chemotherapy (CC) in advanced ovarian cancer.
2. Impact on survival of AA/prednisone v CC in multiple myeloma.

In answer to the first question, a survival impact for CC was demonstrated by a review of the published trials, but none was found when registered trials were pooled. With respect to the second question, a pooled analysis of published trials showed a survival advantage for CC and this was also shown in the pooled analysis of registered trials. However, the magnitude of the effect was reduced, from a median survival ratio of 1.26 to 1.11.<sup>108</sup>

Simes used his analysis demonstrating publication bias, as the basis for a call for an international registry of clinical trials.<sup>108</sup> However, it was not until 2000 that the first one launched with ClinicalTrials.gov.<sup>109</sup> There are 17 registries that are recognised as primary registries by the World Health Organisation (WHO) and which submit data to its International Clinical Trials Registry Platform (ICTRP).<sup>110</sup> They meet specific criteria set by the WHO ICTRP and International Committee of Medical Journal Editor (ICMJE) for content, quality, validity, accessibility, unique identification, technical capacity and administration.<sup>110,111</sup> These are listed below:

- ❖ Australian New Zealand Clinical Trials Registry (ANZCTR)
- ❖ Brazilian Clinical Trials Registry (ReBec)
- ❖ Chinese Clinical Trial Registry (ChiCTR)
- ❖ Clinical Research Information Service (CRiS), Republic of Korea
- ❖ ClinicalTrials.gov
- ❖ Clinical Trials Registry - India (CTRI)
- ❖ Cuban Public Registry of Clinical Trials(RPCEC)
- ❖ EU Clinical Trials Register (EU-CTR)
- ❖ German Clinical Trials Register (DRKS)
- ❖ Iranian Registry of Clinical Trials (IRCT)
- ❖ International Standard Randomised Control Trial Number (ISRCTN)
- ❖ Japan Primary Registries Network (JPRN)
- ❖ Thai Clinical Trials Registry (TCTR)
- ❖ The Netherlands National Trial Register (NTR)
- ❖ Pan African Clinical Trial Registry (PACTR)
- ❖ Peruvian Clinical Trial Registry (REPEC)
- ❖ Sri Lanka Clinical Trials Registry (SLCTR)

Most of the registries listed above are focused on a single country or group of countries rather than having a global outlook. Their websites are not typically in English but in the local language. There are two major international registries in this group which have attracted registrations from a broader global base; ClinicalTrials.gov and ISRCTN. They both publish trials and observational research and allow for studies to be registered at any time (although registration prior to the recruitment of the first patient is what is advised).

ClinicalTrials.gov was set up by the National Institutes of Health (NIH) in the USA in 2000.<sup>109</sup> Observational and interventional studies can be registered, and this has been the case since its launch although like ISRCTN the focus has been trials. By 9<sup>th</sup> January 2018, it had 263,083 registrations, with the largest contributions from the USA (41%), European Union (28%) and China (10%).<sup>109</sup>

ISRCTN was set up in 2000 to register RCTs. It is owned by BMC, part of Springer Nature. Over the years this scope expanded to include: “any study designed to assess the efficacy of health interventions in a human population”<sup>112</sup> By 9<sup>th</sup> January 2018, it had 16,540 registrations and 55% of these are from the UK with most of the remainder from the Netherlands (9.5%), Germany (6.5%), Canada (3.8%) and Spain (3.3%).<sup>112</sup>

### **Drive to Increase Registration**

Journal editors have been influential in raising awareness about these issues. In 2004, the International Committee of Medical Journal Editors (ICMJE) made registration of clinical trials a requirement for publication in their member journals.<sup>113</sup> This led to a sharp increase in the number of trials being registered which did not occur when the US Federal Drug Administration (FDA) called for it in 2002 (see figure).<sup>114</sup> In 2008, the Declaration of Helsinki (DoH) made registration of Clinical Trials mandatory and hence it became an ethical requirement in addition to a regulatory one.<sup>116</sup>

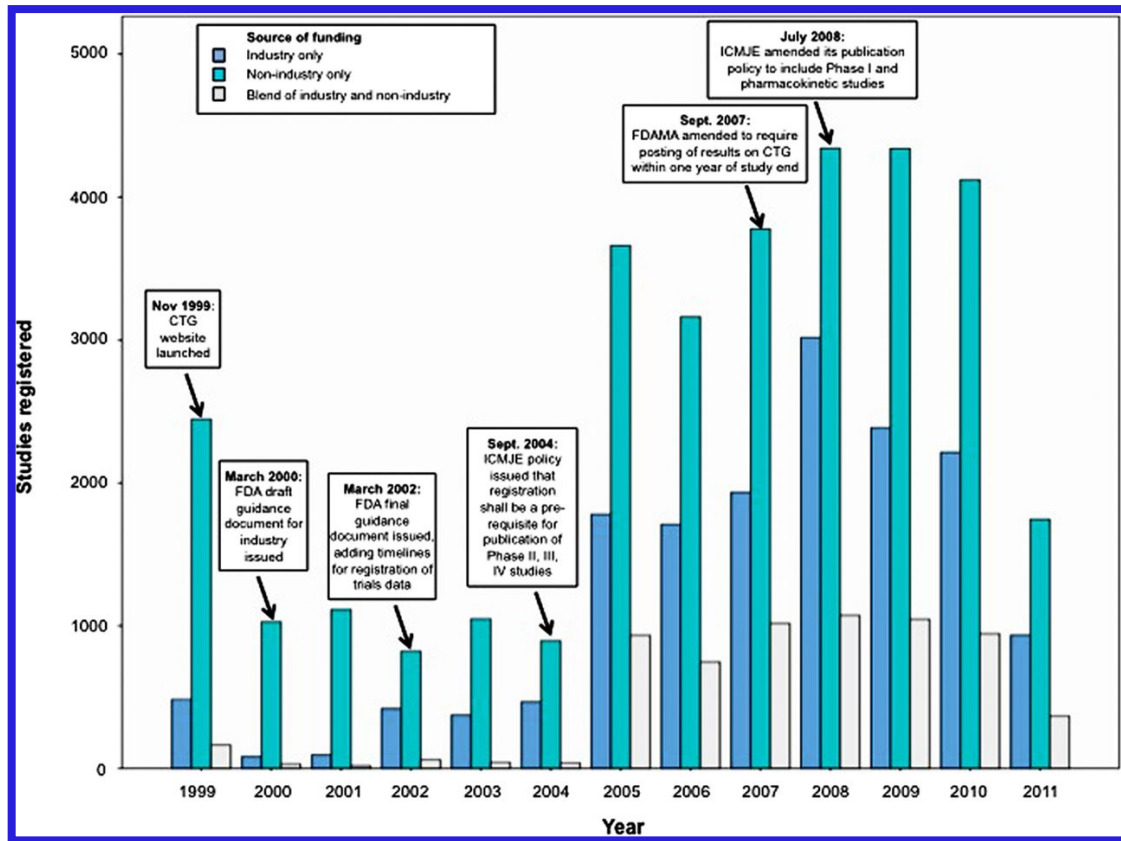


Figure 2.4: Studies registered on Clinicaltrials.gov, by year and funding source (taken from Gill, 2012<sup>114</sup>).

### Rise of Observational Research

Whilst the focus in the past has been on registering clinical trials, there has been tremendous growth in observational studies (case series, cohort, case-control, cross-sectional, etc), many of which are not registered. Whilst some trial registries do allow for the registration of observational studies, only a small fraction are actually registered. Nearly 80,000 observational studies were published in the period 1990-2000 across all fields, according to Thomson Reuters as reported in the Wall Street Journal (figure 5.2).<sup>115</sup> In the following period, 2001-2011, this tripled to 263,557.

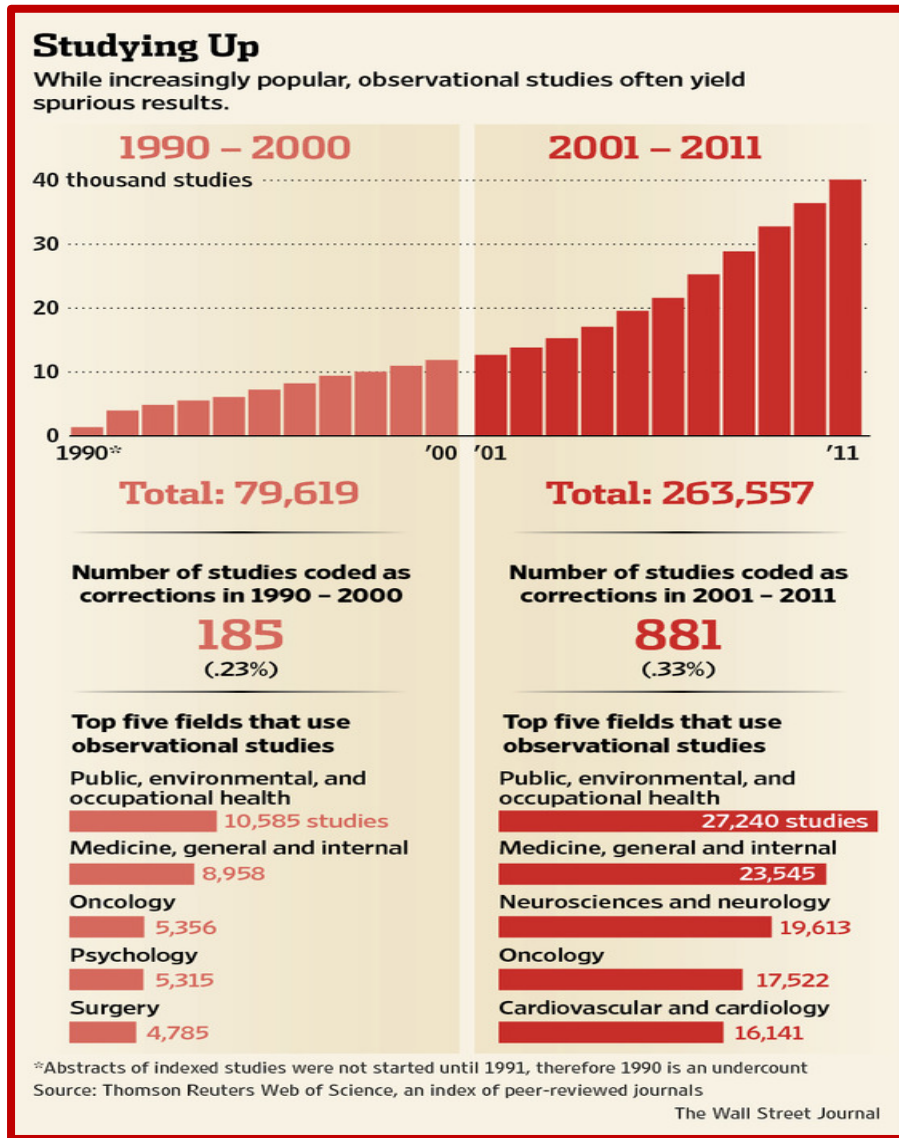


Figure 2.5: Observational studies published in journals indexed by Thomson Reuters Web of Science index (source: Wall Street Journal<sup>115</sup>).

### The Declaration of Helsinki 2013

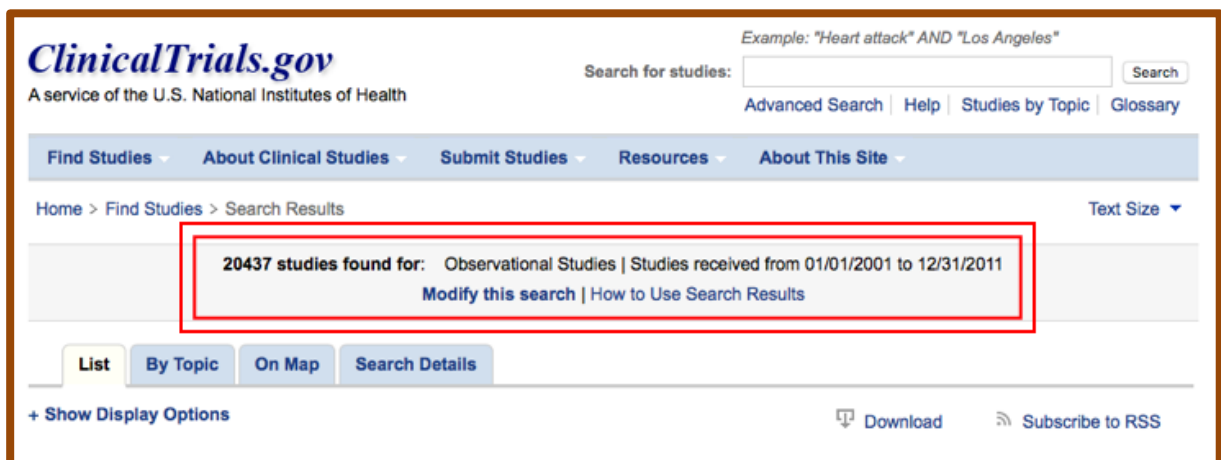
Why is this important? In 2013, the DoH<sup>116</sup> changed to state:

*“Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.....Negative and inconclusive as well as positive results must be published or otherwise made publicly*

*available.....Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.”*

This move away from just clinical trials in the 2008 version and broadening to “*every research study*” has important ramifications. Observational research must now be registered to comply with the DoH. During the period 2001-2011, ClinicalTrials.gov listed a total of 20,437 studies classified as observational (see figure 5.3).<sup>117</sup> Hence, taking the denominator of 263,557 from figure 5.2, ClinicalTrials.gov registered less than 8% of observational studies during the period 2001-2011 ( $20,437/263,557 = 7.8\%$ ).

Other major global research registries like ISRCTN, have only 1,193 observational studies in their entire database at the time of writing and hence don’t add significantly to these numbers.<sup>118</sup> It’s reasonable to say that 90% of observational studies published by journals indexed in the Thomson Reuters web of science index are unregistered. With global scientific output doubling every nine years, there are of course many thousands of traditional subscription-based and new open access journals that have not been indexed yet, so if anything, this may be an underestimation.<sup>119</sup>



**Figure 2.6:** Number of observational studies registered with ClinicalTrials.gov in the period 2001-2011.<sup>117</sup>

This situation is equivalent to only have car number plates (i.e. registration) for Rolls Royce, Ferrari, Bentley and high-end vehicles (left side of figure 2.7 below) rather than the Fords, Vauxhall's, Toyota's, Honda's and other cars that the majority of people drive (right side of figure 2.6).



**Figure 2.7:** Photos of high-end cars (left side of the black line) and standard cars (right side of black line).

This has in part because the mandate and set-up of many of these registries was centred around clinical trials (RCTs) and not a wide variety of research study designs. Lack of awareness is an issue too. Barriers include the practical difficulties of registering a study, with some requiring the researcher to determine who their institutional account manager is, poor usability and charging high fees to register a study are other issues (the ISRCTN registry charges £214 + VAT to register).<sup>120,121</sup>

Further evidence of the gap is provided in an article written by those working at ClinicalTrials.gov itself titled: *Registration of observational studies: Is it time?* Where they acknowledge a lack of focus and attention in this area.<sup>122</sup> This adds to several other

recent calls to register protocols for observational research.<sup>123,124</sup> Indeed Chalmers et al have written specifically on how to increase value and reduce waste when research priorities are set. One of their recommendations was that research funders and regulators should strengthen and develop sources of information about research that is in progress, ensure that they are used by researchers, insist on the publication of protocols at study inception, and encourage collaboration to reduce waste.<sup>125</sup>

Peer-review of protocols allows for independent external feedback at an important stage and allows for important course corrections that could save significant time, money and resources spent on a study that was asking the wrong research question or which deployed methodology that could never reasonably be expected to answer it. Institutions and funding bodies would certainly appreciate it, they often organise it themselves anyway for institutional review board approval and grant funding respectively. Once published, it may facilitate collaboration leading to a multicenter study with greater power and external validity. It also gives the research team greater assurance on the likelihood of publication of the final paper, if they stick to the protocol. Of course, this does not preclude exploratory or additional analyses, as long as the final paper mentions these in a transparent manner.

**OBJECTIVE TWO**

To determine the rates of study registration and protocol publication in the Plastic Surgery literature.

**OBJECTIVE THREE**

To build and implement a new global research registry to boost study registration prior to submission to a surgical journal.

**OBJECTIVE FOUR**

To determine the barriers to research registration.

**Reporting Quality in Plastic Surgery**

The Consolidated Standards of Reporting Trials or CONSORT was one of the first reporting criteria developed in a systematic way and has aided in the assessment of RCTs since its launch in 2001 and subsequent updates.<sup>126</sup> CONSORT has opened a new field of meta-research, examining the quality of research and its reporting. Prior work by the author and colleagues has demonstrated the deficiencies in reporting quality of RCTs in Plastic Surgery<sup>127</sup> but also in other surgical specialties including Trauma<sup>128</sup>, urology, vascular, orthopaedic, hepatic, gastrointestinal and cardiovascular.<sup>129</sup>

However, the majority of studies within the plastic surgery literature, are observational by design such as cohort or case studies. Whilst high quality RCTs provide evidence with the least amount of bias, observational studies still have an important role to play. They are

useful for assessing new techniques early in their development, for studying rare conditions or where it is not practical to do an RCT such as emergencies. RCTs are also very expensive and resource intense, requiring the necessary team with the set-up and skills to see it through.

The reporting of any study should be complete, clear and transparent. This is important for subsequent evidence synthesis. The author's work looking at the reporting quality of RCTs in Surgery and Plastic Surgery in particular has shown significant deficiencies. Of 57 RCTs identified from 2009-11 the median CONSORT score was 11.5 out of 23 mandatory items.<sup>2</sup> The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was published in 2007 and aimed to improve the reporting quality of observational studies.<sup>130</sup> It was developed through a Delphi Consensus Exercise by a multidisciplinary group of editors, statisticians, methodologists, clinicians from Europe and North America. It consists of a 22-point checklist of items considered as mandatory for inclusion when reporting such observational studies.

**OBJECTIVE FIVE**

To determine the reporting quality of observational studies in Plastic Surgery.

**OBJECTIVE SIX**

To determine the reporting quality of systematic reviews in Plastic Surgery

## **The Role of Journals in Enhancing Reporting Quality**

Journals have an important role in enhancing transparency and implementing reporting guidelines in their processes. Editors and peer-reviewers are guardians of the scholarly literature. Discerning the best research from what they receive and ensuring its reporting is optimal. In the author's experience peer-reviewers often became bogged down with asking questions about information that authors should have included in the first place – this is where reporting guidelines like CONSORT, STROBE and so on can be so useful. Given the aforementioned evidence on poor reporting, it's reasonable to look for solutions on how this could be improved.

A Cochrane systematic review published in 2012 assessed this issue.<sup>131</sup> It compared the reporting quality of RCTs in those journals endorsing CONSORT with those that didn't. It showed that 25 outcomes improved with CONSORT endorsement with five being statistically significant. The review concluded by saying that reporting quality was still sub-optimal and journals need to take further action to facilitate complete, transparent and accurate reports.<sup>131</sup>

Listing reporting guidelines that authors should comply with in the journal's instructions to authors is an important first step. Journals can go further, for instance insisting that authors submit a completed reporting guideline checklist (where they mention the page number where compliance has been achieved) with their manuscript. This would be available to editors and peer-reviewers and open up scrutiny of their compliance. This aims to boost the reporting quality of the article prior to peer-review, thus allowing peer-reviewers to focus on what information is there, not what's missing.

**OBJECTIVE SEVEN**

To determine the existing support for reporting guidelines within surgical journals.

**OBJECTIVE EIGHT**

Assess the impact of the mandatory implementation of reporting guidelines in a surgical journal.

*The reporting of surgical case reports – the need for guidance development*

Since the time of Hippocrates, case reports have been popular within the medical literature.<sup>132</sup> In recent decades however, their importance has decreased as focus has shifted to randomised controlled trials. Such studies minimise the bias that's inherent in looking at a single patient or even a series of them and are hence able to answer research questions more reliably. Indeed, some even feared their extinction due to low citation rates, negative effects on journal impact factor and restricted page budgets.<sup>133,134</sup> As a result, many journals stopped publishing case reports altogether.<sup>133,135</sup>

The rise of electronic publishing and open access models have led to a resurgence of the clinical case report. In 2008, the International Journal of Surgery (IJS) stopped accepting case reports for publication and in 2010 launched a sister journal specifically devoted to them – IJS Case Reports.<sup>135</sup> In 2015, IJS Case Reports became the largest publisher of surgical case reports globally according to Scopus.

Vandenbrouke outlined how case reports further medical progress: *“they permit discovery of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine.”*<sup>136</sup>

Case reports have specific relevance within the surgical literature. The IDEAL recommendations call for structured case reports for reporting a “first-in-man” study – i.e. the first time a new surgical technique is used, in stage 1 of their framework.<sup>57,137</sup> This has been exemplified in recent times by case reports of facial transplantation and other innovative techniques.<sup>138</sup>

The Case Report or CARE Guidelines were developed in 2013 to provide a framework that supports transparency and accuracy in the publication of case reports and the reporting of information from patient encounters.<sup>139</sup> They have been adopted by multiple journals and compliance with them has been mandatory at the IJS Case Reports. However, they are not tailored to surgery and a number of areas are missing e.g. discussion around patient selection, the reporting of any pre-operative optimisation, where the surgeon performing the operation is on the learning curve (if established) or what their experience with the technique in question is, post-operative instructions and care, reporting complication rates and length of follow-up (supported by photos, scan results and multimedia as appropriate).

#### **OBJECTIVE NINE**

To develop a reporting guideline for surgical case reports.

*The reporting of surgical case series – the need for guidance development*

A case series is an uncontrolled study of a group of patients with a particular disease, or condition who undergo a particular treatment with subsequent outcome(s). They are commonly a retrospective review of a string of interesting cases, often with a unifying feature - be that exposure, intervention, treatment or outcome. They are frequent within the medical literature but are also present within social sciences and the humanities. In a 2005 report, Dalziel et al, outlined that case series are used in 30% of Health Technology Assessments (HTA) - assessments used in the provision and suitability of care. In the summer of 1999, the use of a case series in the recognition of a new disease was exemplified by the epidemic of West Nile encephalitis in New York City.<sup>140</sup> Historically case series were important in identifying the dangers of Thalidomide and alcohol for pregnant women and the role of vitamin C in preventing scurvy.<sup>141,142</sup>

However, no standardised reporting criteria developed within a robust methodological framework exist for case series. In the on-going drive to improve the evidence base for clinical practice, a number of tools have been developed to improve the quality of reporting research. For example, publication of CONSORT (Consolidated Reporting Standards of Randomised controlled Trials) has seen the quality of articles in some fields improve significantly.<sup>143</sup> A wide variety of reporting guidelines are now available across different research study types, except for case series. Problems in the reporting of case series have been highlighted to us from recent experience during a systematic review of fat grafting for breast reconstruction. In this study, 25 of the 31 included studies were case series, yet 20% did not mention the age of the participants and 48% did not mention whether the participants had had radiotherapy.<sup>144</sup>

Readers need complete clear and transparent information and failure to provide this short circuits critical appraisal and any assessment of external validity and whether for instance a surgeon should change their practice.<sup>145</sup> The author's aim is to close this gap and help produce a reporting guideline for case series that is methodologically robust and easy to use. Important in this work will be defining what exactly a case series is – semantics are important here, as these guidelines need to be distinguished from the STROBE guidelines for cohort, case-control and cross-sectional studies. Furthermore, such work may also lead to the development of a surgical extension of the existing CARE guidelines on the reporting of case reports.

**OBJECTIVE TEN**

To develop a reporting guideline for surgical case series.

**2.9 SUMMARY**

The literature gaps discussed above have generated a number of research questions and led to ten objectives for this thesis. In the subsequent chapters, the author will introduce each chapter and the research questions, the methods used to answer them, the results which will lead into a scholarly discussion and the conclusions that can be drawn from the data and the methods.

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# **CHAPTER 3**

## **LEVELS OF EVIDENCE IN PLASTIC SURGERY: BIBLIOMETRIC TRENDS AND COMPARISON WITH FIVE OTHER SURGICAL SPECIALTIES**



**BALLIOL**  
**COLLEGE**  
UNIVERSITY OF OXFORD

A summary of the following chapter has been published in the European Journal of Plastic Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback from others. The author had assistance from five medical students (MD, KW, AJF, RC and GW) in data acquisition and was supervised by Prof. Orgill and Prof. McCulloch. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

### **3.1 BACKGROUND**

Evidence-based medicine (EBM) is the integration of the best available research evidence with clinical expertise and patient values.<sup>1</sup> Part of determining the ‘best available research evidence’, is to categorise research into the appropriate level of evidence (LOE) as defined by the American Society of Plastic Surgeons (ASPS, table 3.1 below).<sup>2</sup> This aids searching for evidence, transparency, with higher LOE associated with less bias and greater validity if performed well.<sup>3</sup> LOE therefore also helps direct researchers as to the best available evidence and what ‘value’ to place on different research, when considering whether to change their practice. Indeed, when considering what grading or strength of recommendation to place on a particular aspect of management within a clinical guideline, authors consider the LOE pertinent to that specific aspect. For precisely these reasons, in

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<sup>1</sup> Agha RA, Devesa M, Whitehurst K, Fowler AJ, Coe R, Wellstead G, Orgill DP and McCulloch P. *Levels of Evidence in Plastic Surgery - bibliometric trends and comparison with five other surgical specialties*. European Journal of Plastic Surgery 2016;39(5):365-70.

January 2011, a specialty wide EBM initiative in Plastic Surgery was launched. This included the listing of the LOE on all articles amenable to the LOE grading.<sup>3</sup> Doing so allows for ease of communication and also for comparison of LOE at a particular point in time for different specialties and also see how such trends have changed over time. This could potentially be used to evaluate the effect of such EBM initiatives.<sup>4</sup>

Loiselle et al, examined changes in the published LOE in the journal Plastic and Reconstructive Surgery from 1983 to 1993 and 2003.<sup>5</sup> They found a slight improvement in the mean level of evidence published from 4.42 in 1983 to 4.16 in 2003, with the majority of research, uncontrolled and descriptive in nature. They concluded that the plastic surgery literature has responded to the call for higher LOE, albeit slowly and that the field will likely never enjoy the high level of evidence of medical fields.

### **3.2 AIMS AND OBJECTIVES**

The objective was to assess how the LOE in plastic surgery have changed from 2003 to 2013 to see if this trend has continued. In addition, the author assessed how this trend compared with five other surgical specialties.

### 3.3 METHODS

A search of all articles published in the top three plastic surgery journals by 2013 Thomson Reuters Impact Factor (IF) was conducted for 2003 and 2013.<sup>6</sup> IF represents the average citation rate for a journal in a given year for articles published in the previous two years, it provides a standardised measure against which to compare the journals.<sup>6</sup> The search was systematic and issue-by-issue, with articles then being labeled as LOE 1-5 as defined by the American Society of Plastic Surgeons (table 3.1).<sup>2</sup>

<b>TABLE 3.1. LEVELS OF EVIDENCE FOR THERAPEUTIC STUDIES AS DEFINED BY THE ASPS</b>	
<b>LEVEL OF EVIDENCE</b>	<b>QUALIFYING STUDIES</b>
<b>1</b>	High quality, multi-centred or single-centred, randomised controlled trial with adequate power; or systematic review of these studies
<b>2</b>	Lesser-quality, randomised controlled trial; prospective cohort or comparative study; or systematic review of these studies
<b>3</b>	Retrospective cohort or comparative study; case-control study; or systematic review of these studies
<b>4</b>	Case series with pre/post-test; or only post test
<b>5</b>	Expert opinion developed via consensus process; case report or clinical example; or evidence based on physiology, bench research or “first principles”

Editorials were excluded, as were any animal or cadaverous studies. The same procedure was carried out for the following surgical specialties; Vascular Surgery (KW), Orthopaedic Surgery (MD and KW), Maxillofacial (GW and RC), Ear, Nose and Throat (ENT, GW and RC) and Neurosurgery (AJF). These five specialties were chosen for the

purposes of broad comparison between Plastic Surgery and specialties defined by region (Maxillofacial, ENT and Neurosurgery) and system (Vascular Surgery and Orthopaedic Surgery).

Results were populated into a Microsoft Excel® database (Microsoft, Redmond, WA, USA). Bar charts were used to compare 2003 and 2013 figures across the LOE for each specialty. The mean LOE was also calculated in 2003 and 2013 for each specialty. The relationship between trends in mean LOE 2013 and impact factors of journals were compared using a scatter plot and a Pearson correlation coefficient.<sup>7</sup>

### **3.4 RESULTS**

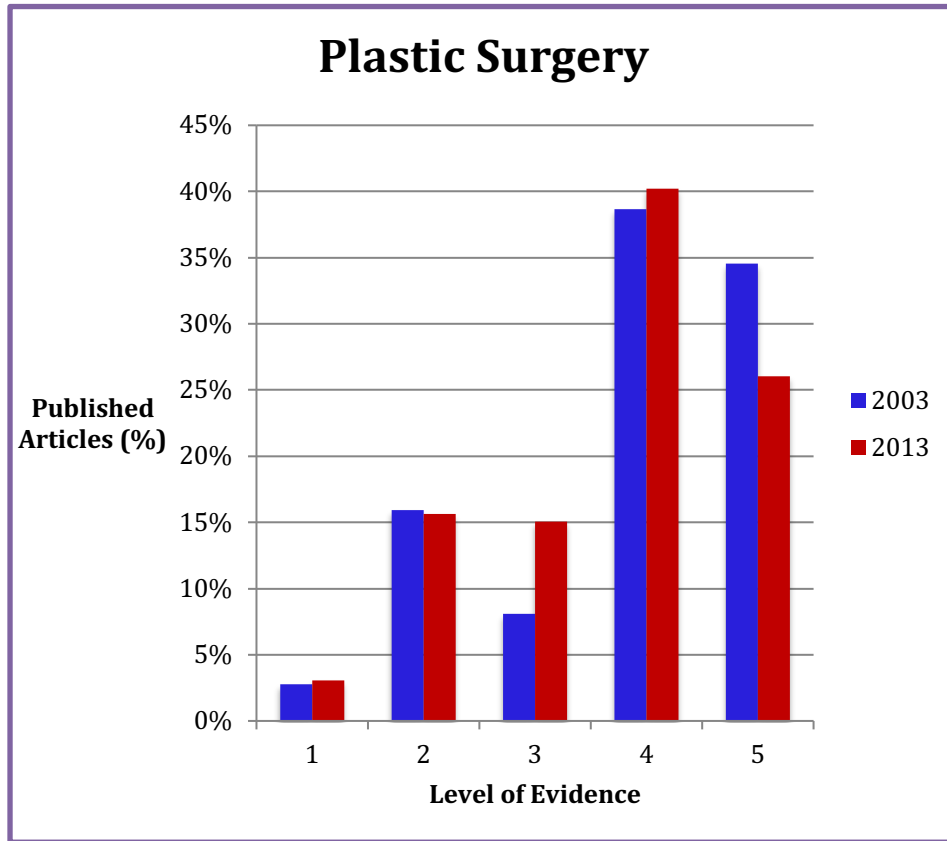
A total of 18 journals were included, spread across the six specialties considered including 4,804 articles. These journals had a mean impact factor of 2.79 and ranged from 1.36 (International Journal of Oral and Maxillofacial Surgery) to 5.58 (Journal of Neurology, Neurosurgery and Psychiatry). Table 3.2 outlines the journals of each specialty along with mean and weighted impact factors, (the latter taking into account the number of papers published by each journal).

When considering the mean LOE from 2003 and 2013, the lowest LOE (i.e. numerically highest) was achieved by Maxillofacial surgical journals in 2003 (4.09), and again in 2013 (3.92). Across the ten-year period of the study, there was an average LOE improvement of 6.2% (range 3.7-10.0%) The mean LOE in 2003 and 2013 across all specialties considered are displayed in table 3.2.

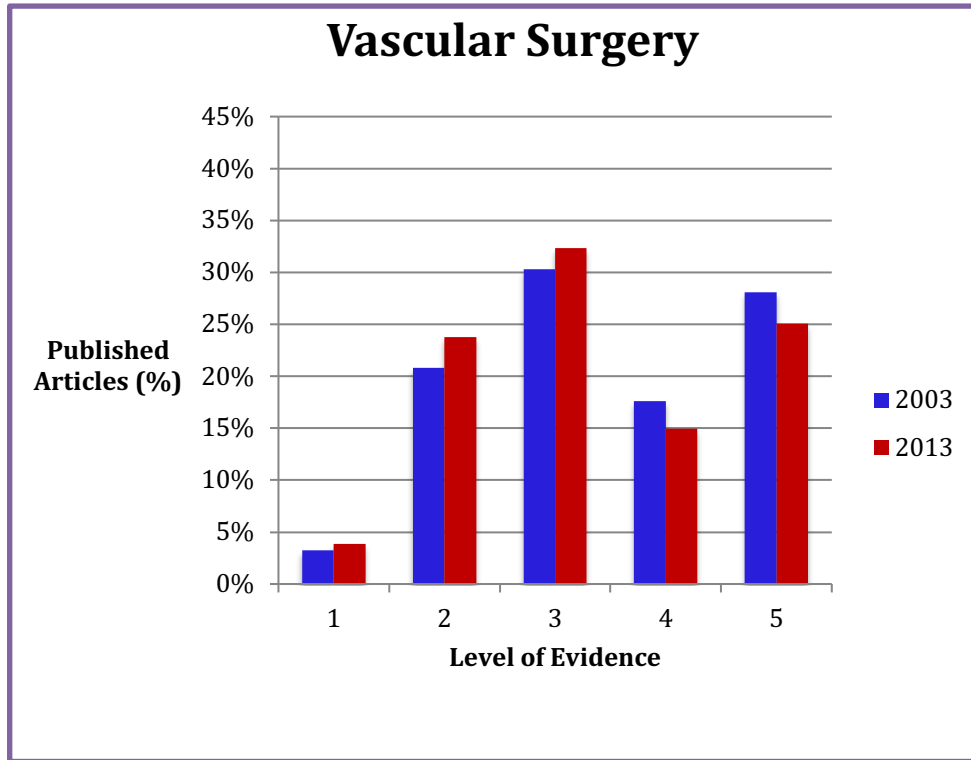
<b>TABLE 3.2. JOURNALS INCLUDED, THEIR INDIVIDUAL, MEAN AND WEIGHTED IMPACT FACTORS IN 2013 <i>n</i> = TOTAL NUMBER OF PAPERS</b>			
<b>SPECIALTY</b>	<b>JOURNALS (IF)</b>	<b>MEAN IF</b>	<b>WEIGHTED MEAN IF</b>
Plastic Surgery ( <i>n</i> = 1330)	<ul style="list-style-type: none"> <li>❖ Plastic and Reconstructive Surgery - PRS (3.328)</li> <li>❖ Journal of Plastic, Reconstructive and Aesthetic Surgery - JPRAS (1.474)</li> <li>❖ Annals of Plastic Surgery - APS (1.458)</li> </ul>	2.401	2.217
Vascular Surgery ( <i>n</i> = 643)	<ul style="list-style-type: none"> <li>❖ Journal of Endovascular Therapy (3.590)</li> <li>❖ European Journal of Vascular and Endovascular Surgery (3.070)</li> <li>❖ Journal of Vascular Surgery (2.980)</li> </ul>	3.213	3.080
Orthopaedics ( <i>n</i> = 815)	<ul style="list-style-type: none"> <li>❖ Journal of Bone and Joint Surgery (4.309)</li> <li>❖ Clinical Orthopaedics and Related Research (2.882)</li> <li>❖ The Bone and Joint Journal (2.801)</li> </ul>	3.331	3.226
Maxillofacial ( <i>n</i> = 600)	<ul style="list-style-type: none"> <li>❖ Journal of Cranio-Maxillofacial Surgery (2.597)</li> <li>❖ International Journal of Oral and Maxillofacial Surgery (1.359)</li> <li>❖ British Journal of Oral &amp; Maxillofacial Surgery (1.696)</li> </ul>	1.696	1.515
ENT ( <i>n</i> = 660)	<ul style="list-style-type: none"> <li>❖ Head and Neck Journal (3.006)</li> <li>❖ JAMA Otolaryngology (1.748)</li> <li>❖ Otolaryngology (1.721)</li> </ul>	2.158	2.302
Neurosurgery ( <i>n</i> = 756)	<ul style="list-style-type: none"> <li>❖ Journal of Neurology, Neurosurgery and Psychiatry (5.580)</li> <li>❖ Journal of Neurosurgery (3.227)</li> <li>❖ Neurosurgery (3.946)</li> </ul>	3.946	3.898

Figures 3.1-3.6 demonstrated the distribution of the LOE in each specialty. There was a weak correlation between the 2013 mean LOE in a journal and 2013 impact factor

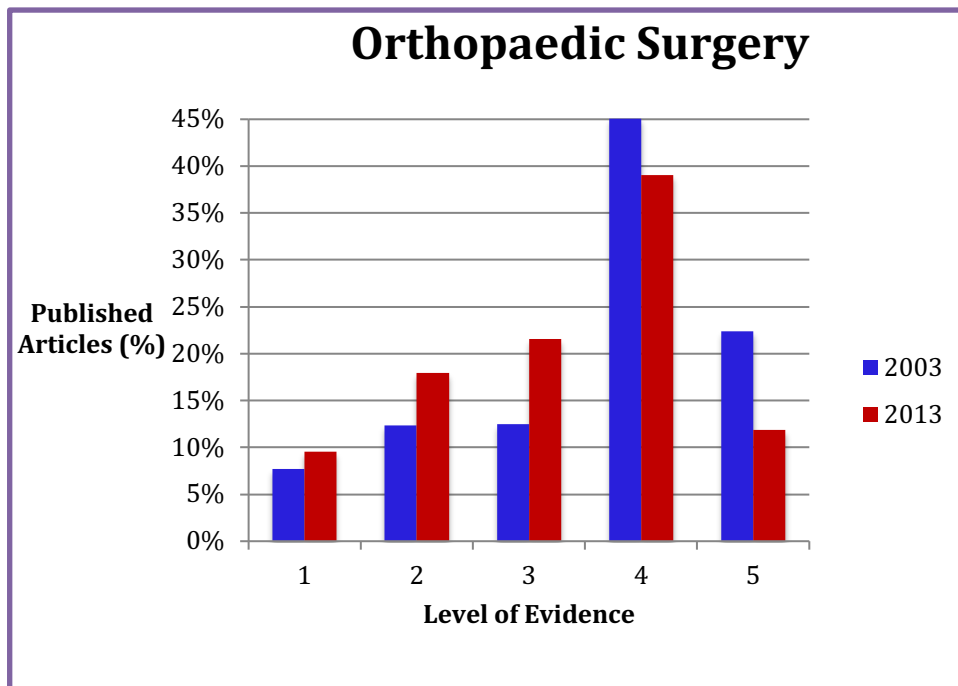
(Pearson Correlation Coefficient = 0.35, figure 3.7).



**Figure 3.1:** LOE in Plastic Surgery in 2003 and 2013.



**Figure 3.2:** LOE in Vascular Surgery in 2003 and 2013.



**Figure 3.3:** LOE in Orthopaedic Surgery in 2003 and 2013.

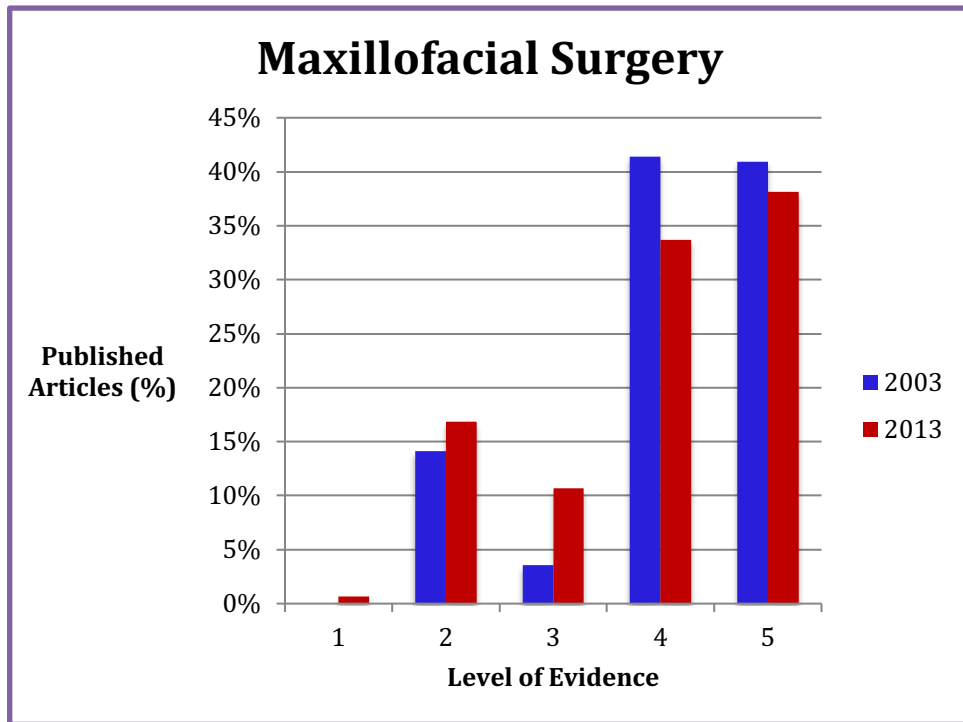


Figure 3.4: LOE in Maxillofacial Surgery in 2003 and 2013.

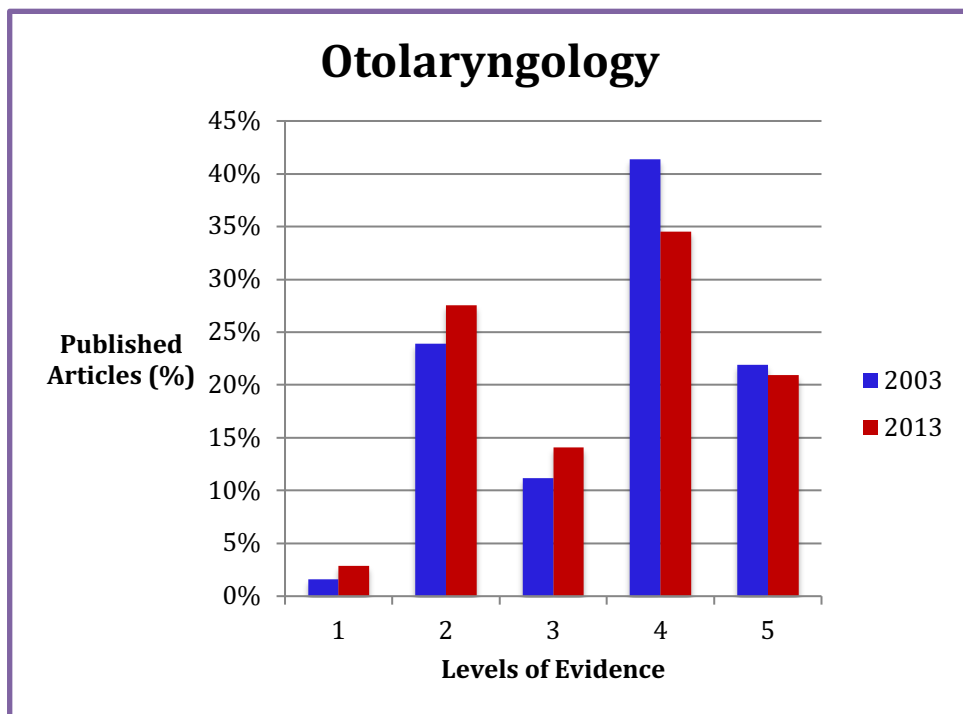


Figure 3.5: LOE in Otolaryngology in 2003 and 2013.

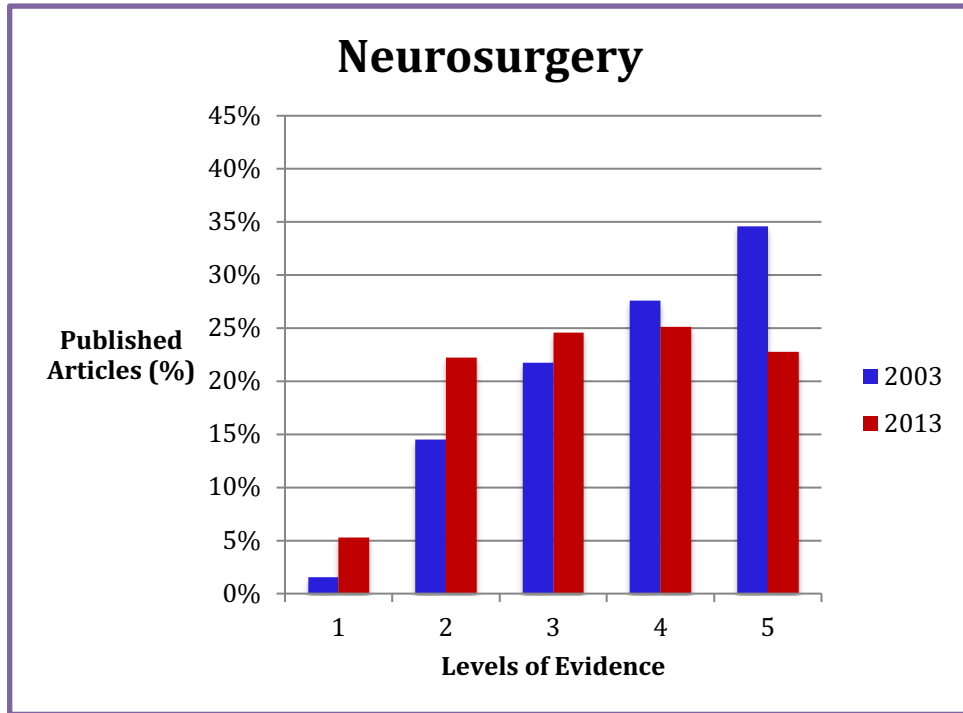


Figure 3.6: LOE in Neurosurgery in 2003 and 2013.

Figure 3.7 below shows a weak correlation between a journal’s mean LOE in 2013 and impact factor for 2013 with a Pearson Correlation Coefficient R of 0.35.

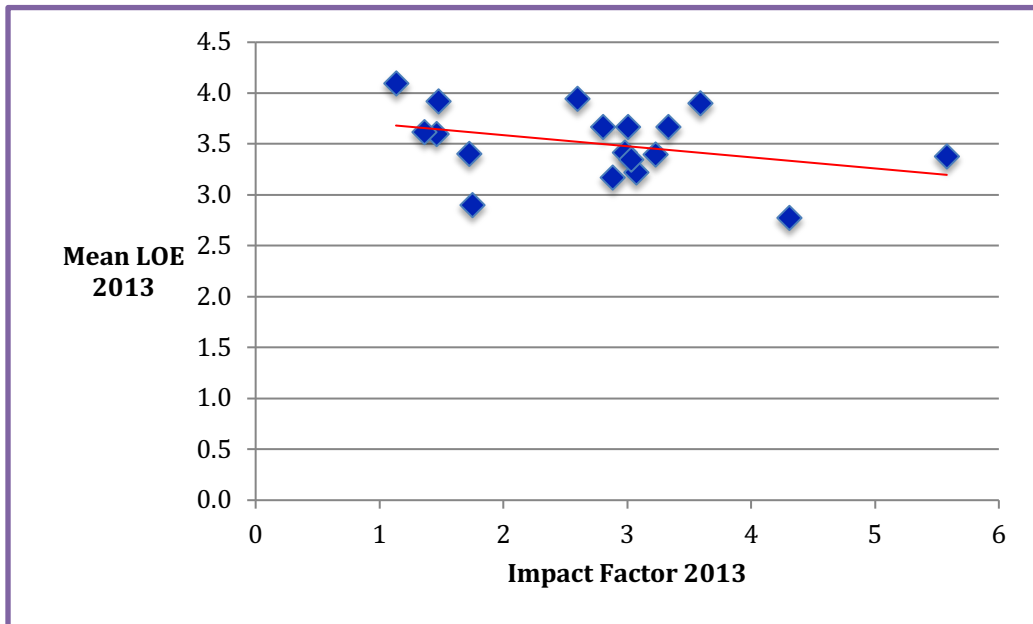


Figure 3.7: A scatter plot of mean LOE in 2013 versus Impact Factor 2013 for all the specialty journals.

### 3.5 DISCUSSION

The results show that the mean LOE for plastic surgery improved by 4.1% from 3.86 to 3.70 in 2003 to 2013 respectively. Journals representing the six surgical specialties included in this study have improved their mean LOE (range 3.7% for vascular surgery to 10.9% for neurosurgery) over the ten-year period (2003 to 2013). The base from which they were starting in 2003 was varied, with 4.09 for maxillofacial surgery to 3.46 for vascular surgery. In order of the mean LOE achieved in 2013, Plastic Surgery ranks five out of six. This is the same position it occupied in 2003. Overall, the specialty journals decreased the proportion of level five evidence they were publishing and increased the proportion of level two and three evidence, except for plastic surgery, where only level three evidence increased significantly (figure 3.1).

The highest proportion of level one evidence was in Orthopaedic surgery at 9.6% and the lowest with Maxillofacial Surgery at 0.7%. There is a weak trend for journals with higher impact factor in 2013 also publishing a lower mean LOE ( $R = 0.35$ ). There may of course be lag effects which impact on this correlation. However, in Plastic Surgery, the APS has the highest mean LOE of all three journals and yet has the lowest impact factor. Citations may not correlate with mean LOE and a wide range of factors influences a journal's impact factor.<sup>8</sup>

Loiselle et al showed that from 1983 to 2003, the mean published LOE improved from 4.42 to 4.16 respectively.<sup>4</sup> The data shows this trend has continued to 2013 with an increase in the proportion of level 3 evidence. Becker et al examined all issues of *Plastic and Reconstructive Surgery* from 1990 to 2010 and found that RCTs were increasing in absolute terms.<sup>9</sup> However, the study shows that level 1 evidence is still proving to be

elusive, hence such increases may have leveled off.

Post et al have shown that approximately 50% of hand surgery articles over the years 1991 to 2011 published in the American and European Journals of Hand Surgery are either case series or case reports.<sup>10</sup> They also pointed to low mean Jadad scores in published level 1 evidence. Chuback et al showed that just 10.3% of 126 podium presentations at three major North American Plastic Surgery meetings in 2010-11 were level 1 or 2 evidence.<sup>11</sup> However, the mean LOE was 3.45 – higher than the published literature the author assessed, perhaps indicating the selection bias towards higher levels of evidence by those assessing abstract submissions.

Higher LOE were associated with multicenter studies. This points to the need for greater collaboration between surgeons encountering similar problems with similar research interests at different centres. This may be something that surgeons are not traditionally used to doing, a cultural change is needed and is indeed underway. The success of trainee research collaboratives in the UK is evidence of this cultural change.<sup>12</sup> In the UK, the creation of the Reconstructive Surgery Trials Network (RSTN) is a step in this direction for RCTs and national audits with the Academic Surgical Collaborative (ASC) doing the same for evidence synthesis/systematic reviews.<sup>13,14</sup>

The author has previously shown that RCTs in plastic surgery require improvement in both methodological and reporting quality.<sup>15-16</sup> The author has also demonstrated this more recently for observational studies.<sup>17</sup> The author's recent systematic review of autologous fat grafting for breast reconstruction – one of the most active research fronts in our field, showed that the majority of studies were low or very low quality and were case

series by design.<sup>18</sup> Determining when a case series is the most appropriate format for a study to take (e.g. rare conditions) is dealt with in chapters 12 and 13.<sup>19-20</sup>

Significant improvements will require ongoing cultural change. This process has already been initiated by the American Society of Plastic Surgeons who have led initiatives to improve understanding of evidence-based medicine amongst their members. Plastic Surgeons will need to plan more methodologically robust studies at higher levels of evidence. Not all questions are suitable for an RCT and case series and case reports will still be needed for rare diseases and interesting technical developments amongst other reasons.<sup>21</sup>

The research question must be clear and relevant and the correct study design should be chosen to answer it. Whatever the study design/LOE intended, the methodological and reporting quality should be high. This will require consultation with a methodologist and/or statistician to ensure the study is adequately powered. Study protocols should be published in advance and authors should take the opportunity to have them independently peer-reviewed to optimise methodological quality up-front.<sup>22-23</sup> Established reporting criteria like CONSORT (for RCTs) and STROBE (for observational studies) will need to be adhered to. Journals, peer-reviewers and editors will need to hold authors to these higher standards as guardians of the scholarly literature.

In their editorial, Sullivan et al stated that publishing the LOE was a simple way to make authors, reviewers and readers aware that EBM and LOE are important.<sup>24</sup> They stipulated that raising awareness of the LOE will help surgeons make better informed decisions with respect to the data quality in the articles they read. This in turn would lead to a gradual

elevation in the LOE and EBM with positive ramifications for patient safety and outcomes. Whilst there has been improvement, the data shows that Plastic and Maxillofacial Surgery have been slower to respond to the call for higher LOE – lagging behind the other specialties included in this cohort. This may represent them starting off from a traditional and technical base held around LOE 4 and 5.

### **3.6 STRENGTHS AND LIMITATIONS**

This work compares six surgical specialties in 2003 and again in 2013, it thus allows both a cross-sectional and a longitudinal analysis. Such analysis across a breadth of specialties with both an anatomical focus (Maxillofacial Surgery, ENT and Neurosurgery) and a system focus (Vascular Surgery and Orthopaedic Surgery) has not been performed before to the author's knowledge. Indeed, Neurosurgery has a system focus – the nervous system, although in practice, a number of specialties work in the area of the peripheral nervous system (Plastic Surgery and Orthopaedic Surgery). These five specialties to compare with provides a broad spread and shows where plastic surgery is within this cohort. Future work could look at a broader sub-set of specialty areas.

Assessing the three highest impact factor journals with the specialty, ignores the fact that a significant amount of content is published in other journals (both specialty ones with lower impact factors and more general journals with higher impact factors). However, this is true for all these specialties. It is also more complex to do such a search and select and 'pidgeon-hole' articles that serve as 'representatives' for the specialty. High quality large RCTs in such journals may incorporate multiple specialties in different treatment arms and so again deciding where such articles go is more complex. Hence the methodology is relatively easy to repeat in a few years.

Very high impact journals tend to publish RCTs, systematic reviews of RCTs and large database-based analyses which drive their citations and hence impact factor. They don't necessarily represent what the 'bread and butter' of a specialty is achieving. The top three specialty journals can act as a useful barometer for assessing the direction of travel within the specialty. Indeed, many of them are journals for the specialty association representing large national and international groups within the specialty. Some journals, such as JBJS have formed their own dedicated case reports journals. Hence the number of case reports published in the main journal drop significantly. This would tend to result in proportionally higher LOE within these journals specifically.

LOE is only a guide to judging a study design's relative quality and bias. High LOE studies can be badly conducted and reported, lack a power analysis and suffer from type two statistical error, conversely low LOE studies may still reliably answer the research question they set out to.<sup>15,16,25</sup> Furthermore, the author would like to highlight that conducting high LOE studies in surgery is challenging. Lack of funding, the need for multicenter collaboration to accrue enough cases and to demonstrate external validity, difficulties with randomisation, allocation concealment, blinding and lack of therapeutic equipoise are just some of the challenges. An RCT may not be the best way to answer every research question. For rare diseases and emergency scenarios a case series may be better. For assessing complications long-term or for surveillance, a registry study may be better.

### **3.7 IMPLICATIONS FOR FUTURE RESEARCH**

In the future, this work could be repeated to assess how things have changed. A suitable timeframe in keeping with prior work would be in 5-10 years i.e. 2018 and/or 2023. These periods could then be compared with our time periods and other studies which have been discussed in this chapter. One could also look at more specialty areas, perhaps all ten recognised surgical specialties according to the Royal College of Surgeons.<sup>26</sup>

When working with medical students in a future study like this, I would prepare a detailed protocol with data extraction instructions and a template database to act as a ‘jump-start’ and quick reference guide to data extraction. Such a document with appropriate telephone or face-to-face communication would support them better. This would allow for smoother working and help facilitate progress through the project for those new to research.

### **3.8 SUMMARY**

The key findings of this chapter can be summarised as follows:

- ❖ EBM is an integral part of safe surgical decision-making and has been heralded as a revolution of modern healthcare.
- ❖ Plastic Surgery is tending towards higher LOE but the pace of change is slow.
- ❖ The specialty must continue to drive towards higher levels of evidence to improve the corpora of research utilised for EBM decision making.

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# **CHAPTER 4**

## **THE USE OF STUDY REGISTRATION AND PROTOCOLS IN PLASTIC SURGERY RESEARCH: A SYSTEMATIC REVIEW**



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A summary of the following chapter is published in the International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, contributing to writing and critically revising the manuscript in light of feedback. The author received assistance from medical students and junior doctors for data collection (TEP, CL, KW, CC, GW and AJF) and writing up the published paper (TEP only) and was supervised by Professor Dennis Orgill. They were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 4.1 BACKGROUND

The publication of a study protocol is an important element in the primary prevention of poor medical research.<sup>1</sup> Poor study design is suspected to be a major contributor to discontinued clinical trials.<sup>2</sup> Submission and subsequent publication of a protocol in a journal allows peer-review of the study research questions and methodology. Thus providing an opportunity for early refinements to improve research quality<sup>3</sup>, saving precious time and resources and potential ‘heartache’ during journal peer-review later in the research cycle.

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<sup>1</sup> Pidgeon TE, Limb C, Agha RA, Whitehurst K, Chandrakumar C, Wellstead G, Fowler AJ and Orgill DP. The use of study registration and protocols in plastic surgery research: A systematic review. International Journal of Surgery 2017;44:215-222.

Prospective study registration in a publicly available research database or registry increases the transparency of any changes made to a study's design and conduct after its commencement.<sup>4</sup> The final study outcomes can be compared to the pre-specified outcomes within the protocol; discouraging the selective reporting of results post-hoc and consequential outcome reporting bias, that permeates the literature with the potentially negative ramifications for clinical decision making and public policy.<sup>5,6</sup>

Even after study completion, fewer than half of trials registered with ClinicalTrials.gov are published two years on.<sup>7</sup> However, registration can facilitate data synthesis from the 'grey' literature; where insights and results from unpublished studies could be utilised if readers were able to contact the authors using the registered protocol.

Protocol registration may prevent study duplication,<sup>8</sup> by alerting authors to registered, unpublished studies that are still to be completed, indeed this may help facilitate collaboration. Registration may have importance to the public, who can freely access registry databases, and may wish to do so if they want to be involved in research or see what studies are on the cutting edge of a particular field.

In recognition of these advantages, clinical trial registration became a compulsory ethical requirement in 2008.<sup>9</sup> However, in October 2013, the World Medical Association announced in the Declaration of Helsinki (DoH) that "*every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject*".<sup>10</sup> The move from every clinical trial to "every research study" was significant, with the corollary being that more studies need to be registered to comply with the DoH. In addition, the Preferred Reporting Instructions for Systematic Reviews and Meta-analyses

(PRISMA), now also mandates protocol registration for systematic reviews and/or meta-analyses.<sup>11</sup>

### ***Rationale***

Reporting and methodological quality of randomised controlled trials in plastic surgery is sub-optimal.<sup>12,13</sup> Only 16% of RCTs in plastic surgery in a recent review had declared a trial registry number.<sup>13</sup> Observational research in plastic surgery fares no better, with articles achieving only moderate STROBE (Strengthening the Reporting of Observation Studies in Epidemiology) scores.<sup>14</sup> Compliance with the Declaration of Helsinki is a major ethical requirement in clinical research. This study assessed whether articles published in leading journals of plastic surgery were compliant with this guidance by examining whether they had registered a protocol with a publicly accessible database, or published a protocol *a priori*.

## 4.2 AIMS AND OBJECTIVES

A systematic review to assess protocol registration and protocol publication rates among published articles in plastic surgery was performed.

### *Primary objectives*

The primary objective was to assess the proportion of studies published in the top three journals (by Thomson Reuters Impact Factor 2013) in the broad field plastic surgery that had registered protocols on selected publicly accessible databases or published their protocols in a peer-reviewed journal.

### *Secondary objectives*

- What study designs have the lowest and greatest rates of protocol registration?
- Was there an improvement in protocol registration over time?
- Had any other form of protocol registration taken place, outside of those databases listed above, but described in the study methods?

### *Hypothesis*

The rate of research protocol registration and publication will be low for studies published in the three plastic surgery journals selected in this study.

### 4.3 METHODS

This review is reported in line with the PRISMA statement.<sup>11</sup> The protocol for this study was registered *a priori* with <http://www.researchregistry.com> (*Unique Identifying Number: reviewregistry12*).

#### *Inclusion and Exclusion criteria*

All research articles with human participants published in three major journals of plastic surgery from 1<sup>st</sup> April 2014 to 31<sup>st</sup> March 2015 were examined (see table 4.1). The Thomson Reuters Impact Factor (IF) 2013<sup>15</sup> showed the top three journals of general plastic surgery to be; Plastic Reconstructive Surgery (PRS, IF=3.328), Journal of Plastic Reconstructive and Aesthetic Surgery (JPRAS, IF=1.474) and Annals of Plastic Surgery (APS, IF=1.458).

Articles not addressed by the Declaration of Helsinki were excluded, and so non-research articles, case reports, and animal or cadaveric studies were not examined (see table 4.2). Systematic reviews were included, as reporting guidance for systematic reviews (PRISMA) recommends protocol registration.<sup>11</sup> This review was confined to published articles only, and so no further study sources were explored.

**TABLE 4.1: INCLUSION AND EXCLUSION CRITERIA**

TABLE 4.1: INCLUSION AND EXCLUSION CRITERIA
<p>Inclusion criteria</p> <ul style="list-style-type: none"> <li>• Original primary and secondary, prospective and retrospective research articles</li> <li>• Human participants</li> <li>• Published from 1<sup>st</sup> April 2014 to 31<sup>st</sup> March 2015</li> </ul>
<p>Exclusion criteria (articles not addressed by the Declaration of Helsinki)</p> <ul style="list-style-type: none"> <li>• Non-research articles (editorials, letters, errata, correspondence)</li> <li>• Case reports</li> <li>• Studies without human participants</li> <li>• Animal or cadaveric-only studies</li> </ul>

### *Search strategy and information sources*

A systematic review of all original research articles engaging human participants published in JPRAS, PRS and APS from 1<sup>st</sup> April 2014 to 31<sup>st</sup> March 2015 was performed.

An electronic issue by issue search was performed for all articles on each of the journal's websites. No electronic database search was required. Title, abstract and full text screening were undertaken by two teams of independent researchers (CL/CC and KW/GW) against the above eligibility criteria, and another author arbitrated when necessary (TEP). Included studies were entered into a pre-formatted database using Microsoft Excel Software (Version 2007; Microsoft Corp, Redmond, WA).

The following research registries and databases were searched for corresponding protocol registrations:

- [ClinicalTrials.gov](http://ClinicalTrials.gov)
- International Standard Randomised Control Trial Number (ISRCTN) <http://www.isrctn.com/editAdvancedSearch>
- WHO (World Health Organisation) International Clinical Trials Registry Platform (ICTRP) <http://apps.who.int/trialsearch>
- The Cochrane Collaboration
- Research Registry <http://www.researchregistry.com>
- PROSPERO <http://www.crd.york.ac.uk/prospero>
- PubMed (i.e. if a protocol was published in a PubMed Indexed Journal)

The above registries were selected because of their attributes and appeal to authors. The WHO registry is a meta-registry of primary registries. The Research Registry allows retrospective study registration. PubMed was searched to identify published protocols. With

each included article a search was performed for the study title text within each of the above listed registration databases. If a protocol was not returned by a search for the title, the search was repeated using the title after removing any non-text characters (:, ;, /, -). The search was again repeated for each database using the lead author's name (this feature was unavailable for ISRCTN and was therefore not performed). For each paper, the introduction, methods sections and reference list were also reviewed to identify if a protocol was referred to in the manuscript but had not been placed on a publicly accessible database. A registration identification number was also sought. When a protocol number was stated in the manuscript, the method of protocol registration was noted.

### *Data extraction and data items*

Two independent teams of researchers performed the data extraction. Disagreements were resolved by consensus, followed by arbitration when necessary (by TEP). Data were entered directly into a pre-formatted database using Microsoft Excel Software (Version 2007; Microsoft Corp, Redmond, WA). The data extracted per study included; date of publication, journal, study design, protocol registration with any of the above databases, where the protocol was registered if not in the main study registration databases, and whether a protocol had been published. Assessment of risk of bias within studies and across studies was not a requirement of this review.

### *Sub-group analysis*

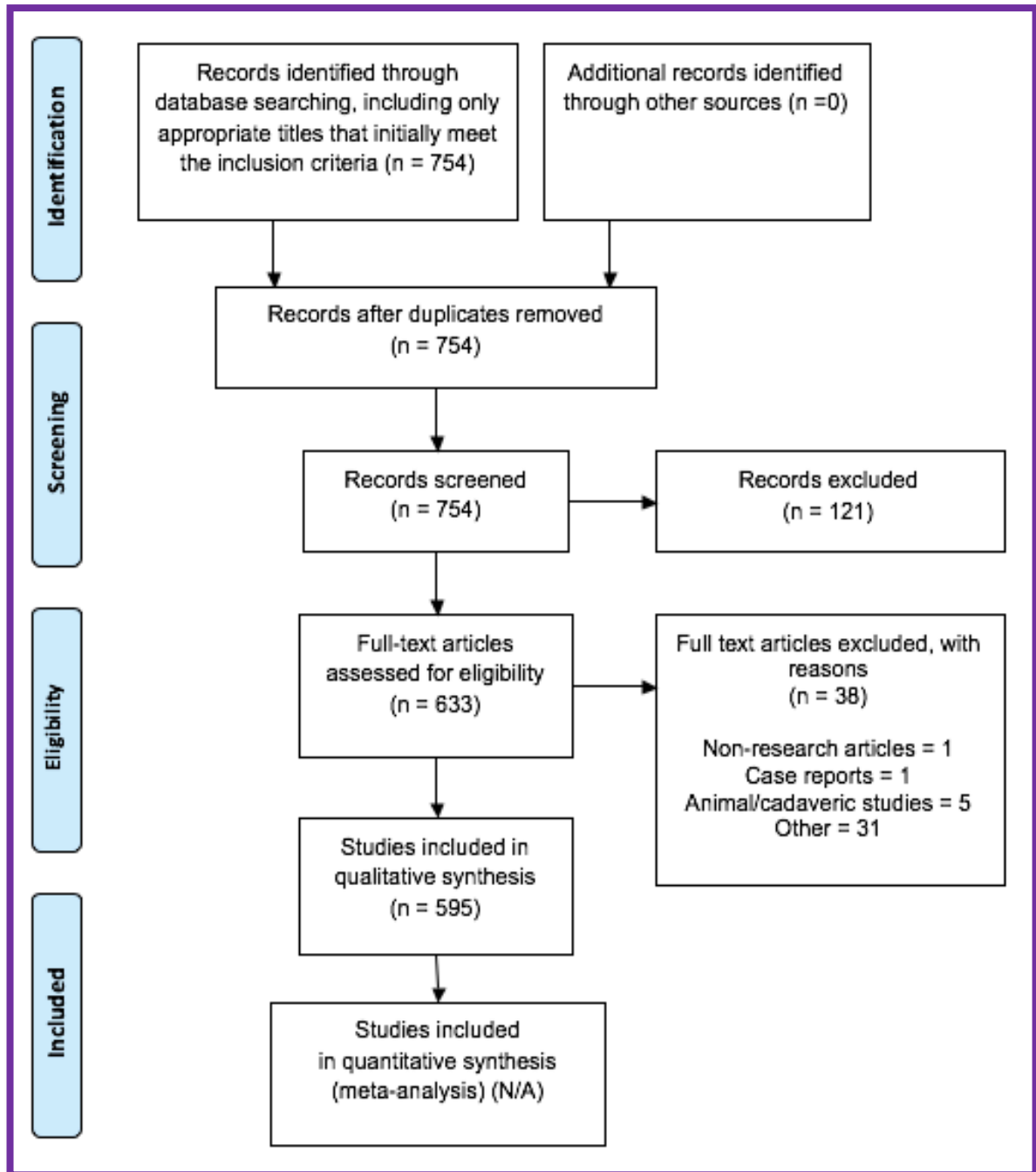
The intent was to analyse articles grouped by study design and date of publication. No sensitivity analyses or meta-regression calculations were pre-specified.

### *Statistical Analysis*

Data were analysed using Microsoft Excel Software (Version 2007; Microsoft Corp, Redmond, WA). Categorical variables were presented as absolute values and as percentages of the total. The summary measure was a percentage value for the number of studies published in journals of plastic surgery that had registered protocols on publicly accessible databases. Binomial symmetrical 95% confidence intervals were calculated (given the binary nature of our data with studies being either registered or not) using a JavaStat calculator available at: <http://statpages.info/confint.html#Binomial>.

## **4.4 RESULTS**

Seven hundred and fifty-four articles were returned by the initial manual search. One hundred and twenty-one were excluded upon review of the abstract. Thirty-eight were excluded upon review of the full text. Five hundred and ninety-five research articles underwent data extraction (see figure 4.1):



**Figure 4.1:** PRISMA Flow diagram (adapted from Moher et al).<sup>11</sup>

Over the year-long publication period, PRS published the most articles that were included (see table 4.2). Of the 595 articles, the most common study designs were case series (n=185, 31.1%), retrospective cohort studies (n=176, 29.6%) and prospective cohort studies (n=47, 7.9%, see table 4.3). There were 24 randomised controlled trials (RCTs, 4.0%):

**TABLE 4.2: NUMBER OF INCLUDED ARTICLES SOURCED FROM EACH JOURNAL**

JOURNAL	<i>n</i>	Proportion of sample (%)
JPRAS	154	25.9% (154/595)
APS	166	27.9% (166/595)
PRS	275	46.2% (275/595)
<b>Total</b>	<b>595</b>	<b>100.0%</b>

**TABLE 4.3: NUMBERS OF EACH INCLUDED STUDY DESIGN IN STUDY SAMPLE**

STUDY DESIGN	<i>n</i>	% of sample
Case series	185	31.1% (185/595)
Retrospective Cohort	176	29.6% (176/595)
Prospective Cohort	47	7.9% (47/595)
Case-control	43	7.2% (43/595)
Systematic review	30	5.0% (30/595)
Other prospective observational study	30	5.0% (30/595)
Other retrospective observational study	24	4.0% (24/595)
RCT	24	4.0% (24/595)
Other prospective interventional study	14	2.4% (14/595)
Other retrospective interventional study	13	2.2% (13/595)
Meta-analysis	9	1.5% (9/595)
<b>Total</b>	<b>595</b>	<b>100%</b>

Out of 595 articles, a total of 24 studies had a protocol registered on a publically accessible database (4.0%, 95% confidence interval 2.6%-5.9%). Four studies registered a protocol in two separate databases. The most common database to register a protocol was with ClinicalTrials.gov (n=17) and with the Cochrane Collaboration (n=7). Three studies

published a protocol in a peer-reviewed journal (0.5%). Twenty-four articles (4.0%, 95% confidence interval 2.6%-5.9%) referred to a protocol in their methods, but had not registered with a database (see table 4.4).

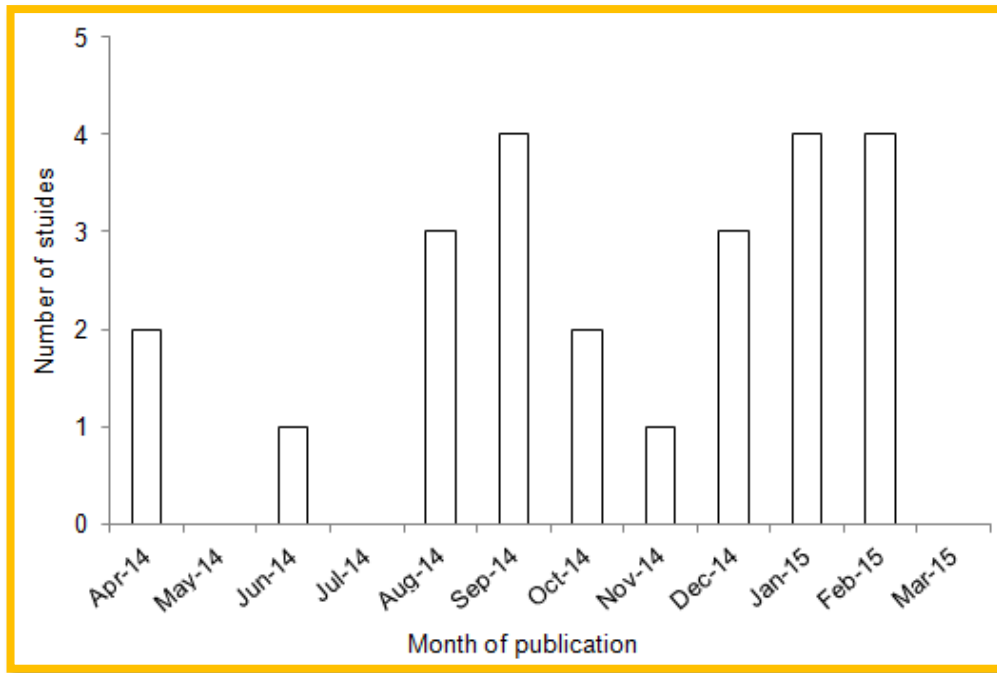
<b>TABLE 4.4: NUMBER OF STUDIES REGISTERED WITH EACH DATABASE</b>		
<b>DATABASE</b>	<i>n</i>	Proportion of sample (%)
<b>ClinicalTrials.gov</b>	17	2.9% (17/24)
<b>ISRCTN</b>	0	0% (0/24)
<b>WHO International Clinical Trials Registry Platform</b>	3	0.5% (3/24)
<b>Cochrane Collaboration</b>	7	1.2% (7/24)
<b>Research Registry</b>	0	0.0% (0/24)
<b>PROSPERO</b>	1	0.2% (1/24)
<b>A PubMed Indexed Journal</b>	0	0.0% (0/24)
<b>Duplicate registrations in more than one database</b>	4	0.7% (4/24)
<b>Protocol referred to in the methods section of the paper but not present on the searched databases</b>	24	4.0% 24/24
<b>Total studies registered</b>	<b>24</b>	<b>4.0%</b>

The study design that most commonly had a protocol registered was the RCT, with eight of 24 protocols registered (33.3%, confidence interval 15.6%-55.3%). The majority of study designs had very low levels of protocol registration (see table 4.5).

**TABLE 4.5: STUDY DESIGNS OF ALL REGISTERED AND UNREGISTERED STUDIES**

<b>STUDY TYPE</b>	<b>Registered (n)</b>	<b>%</b>	<b>Unregistered (n)</b>	<b>%</b>	<b>% of each study design registered</b>
<b>RCT</b>	8	1.3%	16	2.7%	33.3%
<b>Other prospective interventional study</b>	3	0.5%	11	1.8%	21.4%
<b>Meta-analysis</b>	1	0.2%	8	1.3%	11.1%
<b>Prospective Cohort</b>	2	0.3%	45	7.6%	4.3%
<b>Other prospective observational study</b>	1	0.2%	29	4.9%	3.3%
<b>Retrospective Cohort</b>	5	0.8%	171	28.7%	2.8%
<b>Case-control</b>	1	0.2%	42	7.1%	2.3%
<b>Case series</b>	3	0.5%	182	30.6%	1.6%
<b>Systematic review</b>	0	0.0%	30	5.0%	0.0%
<b>Other retrospective observational study</b>	0	0.0%	24	4.0%	0.0%
<b>Other retrospective interventional study</b>	0	0.0%	13	2.2%	0.0%
<b>Total</b>	<b>24</b>	<b>4.0%</b>	<b>571</b>	<b>96.0%</b>	<b>4.0%</b>

There was no clear trend in the number of study registrations occurring over time (see figure 4.2).



**Figure 4.2:** Number of registered studies each month (n=24)

Twenty-four articles (4.0%, confidence interval 2.6%-5.9%) had referred to a study protocol in the manuscript without registration on one of the aforementioned databases (see table 4.6).

<b>TABLE 4.6: SITE OF PROTOCOL REGISTRATION IF NOT WITH A PUBLICLY ACCESSIBLE DATABASE (IRB = INSTITUTIONAL REVIEW BOARD)</b>	
<b>SITE OF PROTOCOL REGISTRATION</b>	<b><i>n</i></b>
Not specified	11
Local/ Regional IRB approval	6
Partners Human Research Office	2
Netherlands Trial Register	2
Brazilian Information System on Research Ethics Involving Humans	1
ClinicalTrials.gov, but protocol not detected by the search	1
Clinical Trials America	1
<b>Total</b>	<b>24</b>

## 4.5 DISCUSSION

This systematic review examined 595 articles published by three leading journals in plastic surgery over a one-year period. The proportion of studies published in journals of plastic surgery that had registered a protocol on a publicly accessible database was 4.0% (confidence interval 2.6-5.8%). Only three studies published a protocol in a journal. The greatest rate of registration was amongst plastic surgery RCTs (33.3%). 4.0% of studies referred to their protocol being registered with other providers (outside the main databases searched). It was not possible to refute the study hypothesis and a low rate of protocol registration among articles published in plastic surgery journals was found.

The requirement to register clinical trials *a priori* has been in place since 2008<sup>9</sup>. This work demonstrated that just 33.3% of RCTs in this cohort had registered a protocol. However, the confidence intervals were quite wide at 15.6%-55.3%, this reflects the low numbers involved i.e. 8 of 24 RCTs. The 33.3% figure could be explained if these other unregistered RCTs began recruitment prior to 2008. However, this “lag” is unlikely to be the case for 66.7% of RCTs, and so a failure to demonstrate compliance with the Helsinki Declaration is likely to have occurred.

Other authors have found that that only 16% of RCTs in plastic surgery declare a trial registry number.<sup>13</sup> However, in RCTs published in surgical journals requiring trial registration for submission, 49-83%<sup>16,17</sup> of studies were registered, although only 18% had been registered prospectively in one study.<sup>17</sup> The difference may lie in the requirement for compulsory trial registration prior to submission of a manuscript to the journal. Only 28% of medical journals currently mandate trial registration,<sup>18</sup> however this work demonstrates that this is a problem affecting plastic surgery.

A recent position statement from the Royal College of Surgeons of England states that clinical trial registration (on a publicly accessible database) is now expected, and that the results of each trial should be published in full to avoid outcome reporting bias.<sup>19</sup> Outcome reporting bias is a recognised feature of surgical publications even when registration has occurred.<sup>16</sup> This review has shown the high volume of plastic surgery publications that exist in the literature, but with a 4.0% registration rate across all studies, risk of outcome reporting bias is high.

Protocol publication in a journal utilises early peer review to improve research quality and helps in the primary prevention of poorly designed studies trying to answer the wrong research question. This will also safeguard against irrelevant work performed as a consequence of the incentive system for clinical research,<sup>2</sup> and will develop research that is fit for purpose. *A priori* registration may protect authors against plagiarism of their research question. The authors can declare their idea in a registered protocol, without needing to wait for publication of the final paper to exhibit their idea.

It is unethical to fail to disseminate research trial findings.<sup>20</sup> Yet Chapman et al showed that one in five surgical RCTs are discontinued early and one in three remain unpublished two years after their conclusion.<sup>21</sup> All studies reported in this review had been published, but there is likely to be an “iceberg” of unpublished, unregistered research in plastic surgery. There is strong evidence that unpublished research findings are common in surgery as a wider speciality.<sup>21</sup> Unpublished research is a waste of resources and could damage the public’s faith and engagement in future research. Lessons must therefore be learned from unsuccessful research. Protocol registration will help in the identification of unpublished research, to better understand what studies are never published and why.

Benefit can still be gained from *retrospectively* registering trials. This will be particularly relevant to important, yet negative studies that remain unpublished, and in the grey literature, as a result of the direction of the observed effect. Retrospective protocol registration of surgical trials could ameliorate the effects of publication bias already present in the literature. Retrospective registration also avoids penalising high quality surgical RCTs that are currently underway but have yet to register a protocol.

A solution to the apparent under-registration of this research may be to encourage all journals within surgery to mandate study registration as a condition of submission. This will result in registration of the study at submission, even if it is ultimately rejected by the journal. This will improve publication bias (unpublished studies will feature on registry databases), but the other benefits of protocol registration *a priori* will not be available. Further efforts, such as this paper, may be required to educate all researchers internationally, and across all healthcare disciplines, on the benefits of early registration. So far, even changes to the Declaration of Helsinki have not succeeded in establishing a culture of mandatory interventional and observational study registration in healthcare research.

Systematic reviews and meta-analyses were included in this study because protocol registration forms part of the PRISMA guidelines.<sup>11</sup> A recent systematic review of PRISMA compliance of systematic reviews in plastic surgery found only 5% had a registered protocol.<sup>22</sup> The results described in this paper are concordant with this poor level of registration, as only 1 of 8 (12.5%) meta-analyses and no systematic reviews were found to be registered in this study.

The majority of published studies examined were case series. This study design does not yet have a set of reporting guidelines and these articles can be published without formal “recruitment”. They may be exempt from DoH guidance, yet they form part of a group of observational studies in the medical literature where the benefits of registration still apply. The efforts of others to improve the registration of observational research<sup>23</sup> should be welcomed. This may require special efforts to encourage this, as the STROBE guidance does not currently incorporate protocol registration.<sup>24</sup> Efforts to include a need to register observational studies could be considered at the next revision of the guidelines.

Twenty-four studies referred to a protocol in their methods but did not formally register as far as the author could determine. This may suggest a perceived difficulty in registering a study with a trial database, poor usability and a set-up that favours RCTs.<sup>3</sup> In the future, improving usability of trial databases, a universal set-up for all study designs and a wider awareness of the latest DoH guidance among authors is advocated.

Some small case series and cohorts are published as correspondence to journals (reporting research in a “non-research article”). Such correspondence was excluded by this paper, as it is not expected for protocols to be published as letters to journals. However, such research findings should be reported formally in the future, and as studies registered *a priori*, and not as letters. This will help increase transparency, as the methodological detail will allow the reader to assess the validity of the study’s findings which may be unclear when results alone are published in a letter with significant restrictions on word count.

## 4.6 STRENGTHS AND LIMITATIONS

This paper describes a PRISMA-compliant, non-commercial systematic review examining a large number of research articles in plastic surgery. This was performed by an experienced team. The accuracy of the data was affirmed by using two independent researchers for both study selection and data extraction. Such work has not yet taken place in other surgical subspecialties.

An assumption was made that searching for the study title and lead author in each database would return the required protocol. This will not be the case where the protocol for a paper is published under a different title or with a different named lead author. However, these protocols should have instead been detected with the review of the full texts.

Although all included studies were published after the DoH update in 2013,<sup>10</sup> some studies may have begun prior to this, but may have been published later due to publication lag time. This lag may be up to 4-6 years among surgical clinical trials.<sup>21</sup> These studies were not sought out in this review, as retrospective protocol registration may have been appropriate for these papers after the DoH was updated. Future research may reveal better uptake of the DoH guidance over time, as current lack of awareness may be impeding study registration.<sup>3</sup>

There was a tendency toward greater numbers of registered protocols in the latter six months of the study period, however this observation is limited because only one year's worth of data were examined. Some authors may have registered their work with a database other than those described above, however such examples were still detected the methodology described (see table 4.6). We sound particular caution on the RCT registration figure of 33.3%, given the low numbers of eight of 24 RCTs registered, with the uncertainty reflected

in the broad confidence interval of 15.6% to 55.3%. A larger sample size would be needed to get tighter confidence of where the true point estimate should be.

#### **4.7 IMPLICATIONS FOR FUTURE RESEARCH**

The author acknowledges that other high-quality plastic surgery articles may register a protocol and go on to publish in a higher impact journal than those addressed by this study. The work was not biased by this as the research question was specific to studies published in plastic surgery journals. However, a future research question could address all plastic surgery articles across a wide set of journals.

An interesting area of further investigation would be whether research that had a protocol published *a priori*, is ultimately better quality? Does that initial peer-review process help add quality and robustness to the methods, that then pays dividends down the line? Anecdotally, the author has benefited from the peer-review and subsequent adjustment of his own systematic review protocol, with previous versions and tracked changes archived [here](#).<sup>25,26</sup>

## 4.8 SUMMARY

The key findings of this chapter can be summarised as follows:

- ❖ Protocol registration and publication rates for studies involving human participants in recent articles published in three well-known journals of plastic surgery is low.
- ❖ There is considerable scope to improve this level of protocol registration and publication in future studies in plastic surgery.
- ❖ This would improve study transparency and reduce outcome reporting bias.
- ❖ The intent of this work is to advocate education, raise awareness and support the adoption of basic principles of research integrity and quality, that if followed, will reflect on the quality of plastic surgery research in the coming decades.

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# **CHAPTER 5**

**THE FIRST 500 REGISTRATIONS OF THE  
RESEARCH REGISTRY: ADVANCING  
THE CAUSE OF RESEARCH  
REGISTRATION IN COMPLIANCE WITH  
THE DECLARATION OF HELSINKI 2013**



**BALLIOL  
COLLEGE**  
UNIVERSITY OF OXFORD

A summary of the following chapter has been published in *Frontiers in Surgery*.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback from other authors. The author had assistance from others (AJF, CL, YA, HS, KK, DJ and MOA) in data acquisition (with two independent teams) and was supervised by Professor Peter McCulloch and Professor Dennis Orgill. They were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 5.1 BACKGROUND

In 2008, the Declaration of Helsinki stated: *“Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject”*. This core ethical guidance was updated in 2013 as follows: *“Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.”*<sup>1</sup>

Registration of research studies is of great importance for the progress of medical research. There are a number of potential benefits to registering a study, firstly that the problem of publication bias (whereby studies are performed but not reported) can be more accurately identified and dissuaded. Chapman et al found that one in five surgical randomised controlled trials (RCTs) are discontinued early and one in three remains unpublished two

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<sup>1</sup> Agha R, Fowler AJ, Limb C, Al Omran Y, Sagoo H, Koshy K, Jafree DJ, Anwar MO, McCulloch P, Orgill DP. *The First 500 Registrations to the Research Registry®: Advancing Registration of Under-registered Study Types*. *Frontiers in Surgery* 2016;3:1-8.

years after their conclusion.<sup>2</sup> We only know this because of RCT registration. Secondly, by registering a study protocol prior to conducting research, it is possible to pre-specify research questions and outcomes and allow peer-reviewers (if also submitted to a journal) and readers to compare these to the published results. Finally, registration of studies reduces duplication of work, a key source of waste in biomedical research.<sup>3</sup>

The registration of clinical trials has been the focus of significant attention.<sup>3,4</sup> However, whilst clinical trial registration has improved with time, there has been little improvement in the registration of observational studies, despite these making up a growing portion of the research landscape.<sup>5</sup> It is estimated that less than 10% of observational studies are registered at present on existing registries and the author has argued the need for a new registry to address this gap.<sup>6</sup> In addition, current registries have cost and time implications, and there is often a significant bureaucratic process to register studies.<sup>6</sup> As a result, the Research Registry® ([www.researchregistry.com](http://www.researchregistry.com)) was built by the author in December 2014 and formally launched in February 2015 and is free for all users to register and is open access.

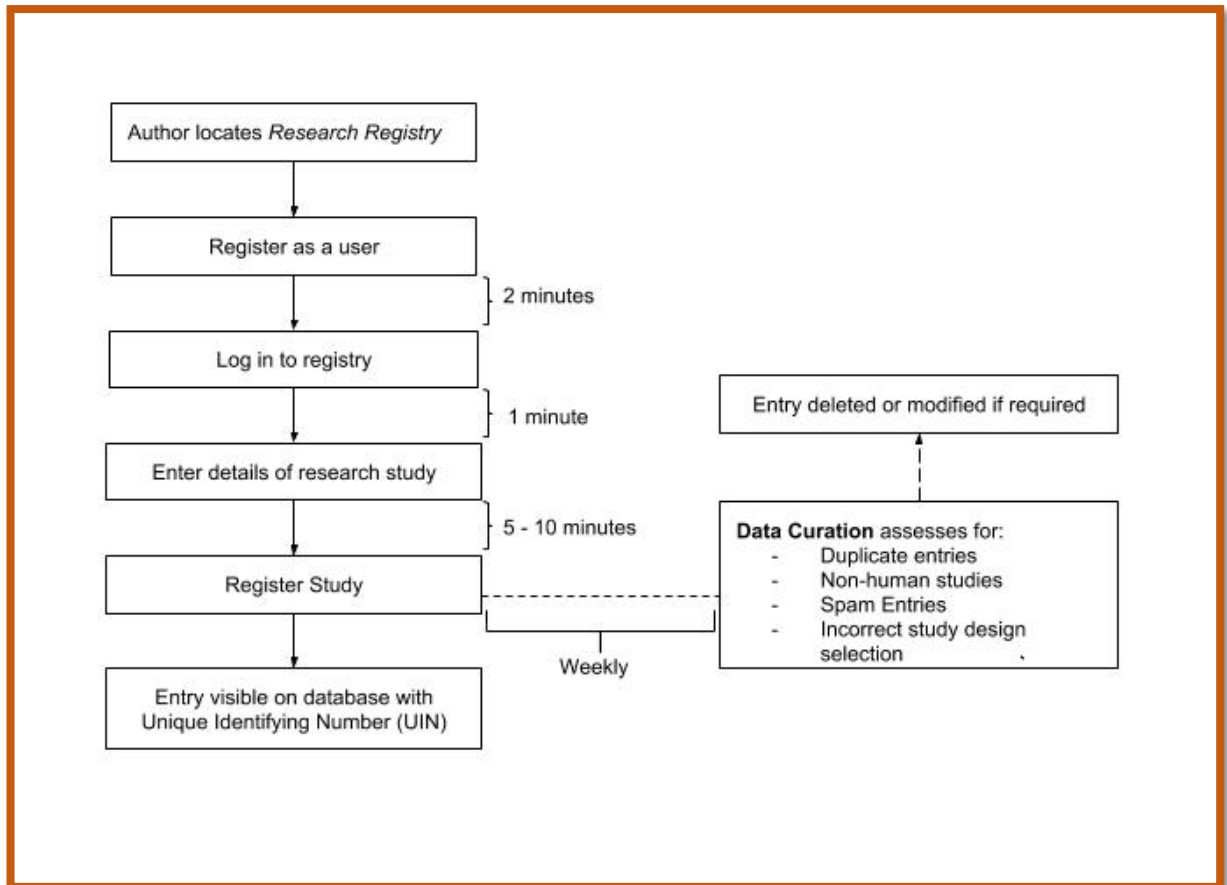
The *Research Registry* enables free registration of any research study involving human participants, it takes a few minutes to register and researchers get immediate visibility of their registration, and a retrospective data curation process has been developed to remove or modify inappropriate registration. The registry allows prospective and retrospective registration. In other words, it will not only register research prospectively (as is best practice), but also retrospectively. This is because if a study is not prospectively registered, subsequently performed and then rejected by a journal and not published, no record of it will exist. The author wishes to address this by allowing retrospective registration for all

those studies not prospectively registered prior to recruitment of the first participant and which have not yet been published in a journal. This is not to say that such a practice is actively encouraged by the author, over time with increased awareness, it is intended that the proportion of prospective registrations would rise.

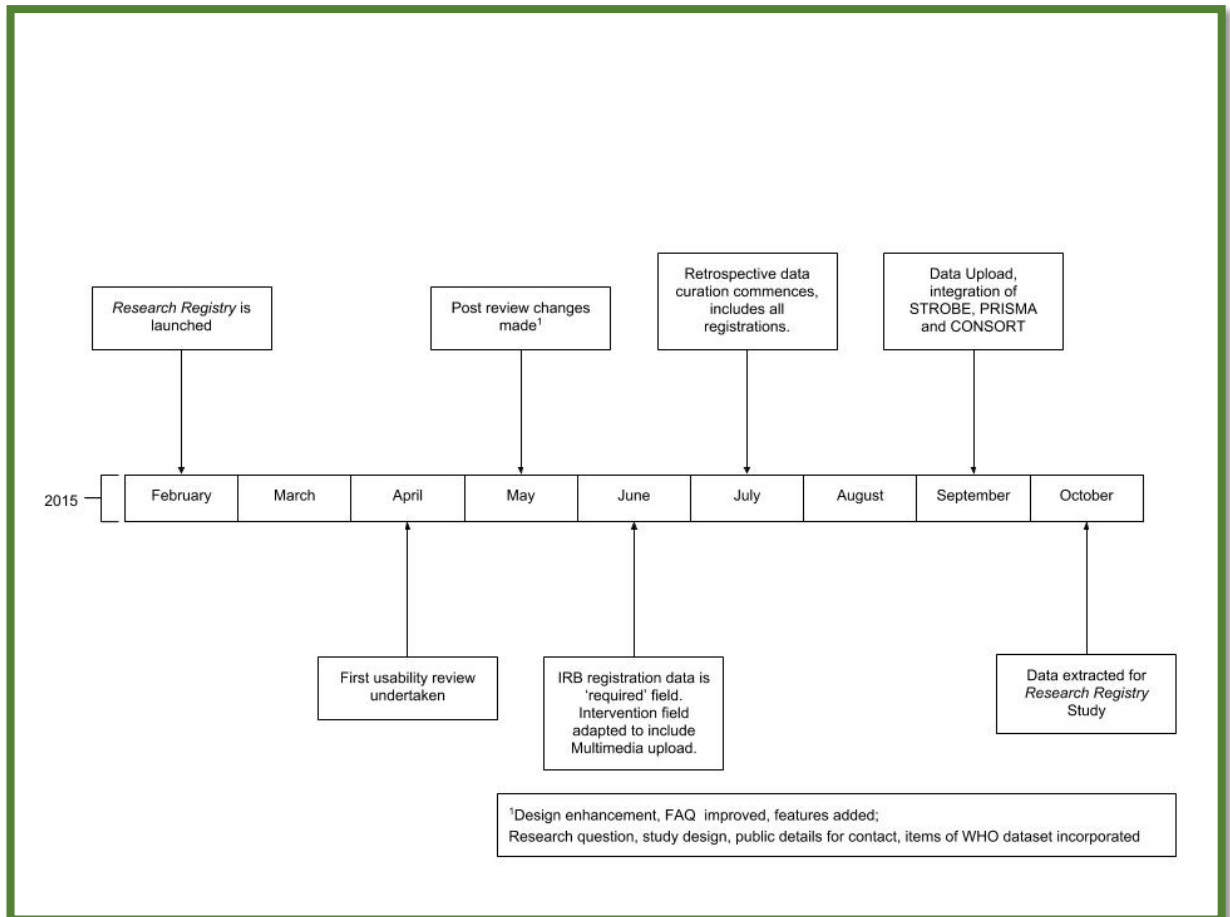
Figure 5.1 highlights the process of registration. Data collected is in line with the World Health Organisation (WHO) 20-item dataset for trial registration.<sup>7</sup> In addition, key elements of reporting guidelines have been integrated into the registration forms. Modifications to the registry have occurred following usability studies (figure 5.2).

## **5.2 AIMS AND OBJECTIVES**

This paper presents the findings of the first 500 registrations from the *Research Registry*, their nature, data quality and curation findings.



**Figure 5.1:** Process of registration and data curation on the *Research Registry*.



**Figure 5.2:** Timeline of development of *Research Registry*. All months are in 2015. IRB: Institutional Review Board, WHO: World Health Organisation.

### **5.3 METHODS**

This study was a retrospective database analysis of the *Research Registry*, and involves no human participants directly, so was not registered itself.

#### **Technical Development of the Research Registry**

The registry took one month to develop and refine prior to a soft launch in mid-January 2015 (with the formal launch in February 2015). Technical development of the ‘back-end’ (database) and ‘front-end’ (the website that people see) occurred separately. The back-end was developed first and took the majority of the development time and effort. This involved the creation of a database containing the records, rules and the processes by which the unique identifying number (UIN) is issued to each record in sequence (the main rule being, that UINs are not issued twice, so remain unique, even if a record is subsequently deleted).

In the database an interface was developed allowing for the input of each data item seen when completing a registry record (title of research, key research questions and objectives, primary investigator, etc). The database is based on open source software known as MongoDB which utilises JavaScript and is deployed by companies like eBay and YouGov.<sup>8</sup> MongoDB is free to download and the author utilised tutorials on how to build a database from it, which are freely available.<sup>9-10</sup> The database is hosted on the Amazon Web Services (ACS) – Cloud Computing Services (<https://aws.amazon.com>). To allow for secure encrypted information transfer a secure socket layer (SSL) certificate was installed on the server.<sup>11</sup>

The front-end was developed on Weebly (<https://www.weebly.com>), a website development platform founded in 2007. There are now 40 million websites developed on Weebly around

the world with 325 million unique visitors coming to them per month.<sup>12</sup> Weebly provides guidance on how to develop a site, getting started and ‘how to’ guides on using their website builder.<sup>13-14</sup> Essentially one selects a template and then opens the website builder to iteratively develop the website, label menus, add content (text and images), create hyperlinks between pages and other websites. For the registry, a version of the ‘Clean Lines’ theme was used.

### *Baseline data*

The *Research Registry* database (accessible at <http://www.researchregistry.com/browse-the-registry.html>) was extracted when 500 complete registrations were reached on the 17<sup>th</sup> October 2015. The following demographics were calculated based on the 500 extracted studies. The number of registrations per calendar month, total number of patients enrolled in registered studies, was calculated together with median number of patients per registration. The study location, which is entered by authors upon registration, was also extracted as well as the types of studies registered. Where authors did not specify study design by selecting ‘Other’, and then entered a study design subsequently in the free text box, in these cases studies were allocated to the most appropriate study design after discussion between two curators (AJF + CL).

The registry clearly explains why people should register their research on this page: <https://www.researchregistry.com/why-register.html>. When registering, the form includes a drop-drop down of the types of research that can be registered and these include those listed below:

- ❖ Randomised controlled trials
- ❖ Non-randomised trial

- ❖ Prospective Cohort Studies
- ❖ Retrospective cohort studies
- ❖ Before and after study
- ❖ Cross-sectional study
- ❖ Diagnostic study
- ❖ Economic evaluation
- ❖ Tumour marker prognostic study
- ❖ Case-controlled study
- ❖ Feasibility study
- ❖ Case series
- ❖ Quality improvement study (originally termed audit)
- ❖ First in man case reports (IDEAL stage 1)
- ❖ IDEAL stage 2
- ❖ IDEAL stage 3
- ❖ IDEAL stage 4
- ❖ Qualitative study
- ❖ Mixed methods research
- ❖ Other (to be specified further in a separate free text field)

The registry also has a separate area dedicated to systematic review registration

(<https://www.researchregistry.com/browse-the-registry.html#registryofsystematicreviewsmeta-analyses/>), but this data was not extracted.

### *Data Curation*

Retrospective data curation is the means by which all registrations in *Research Registry* are reviewed on a weekly basis. A standardized policy was followed by all curators on a rolling rota. Curators identify inappropriate registrations (figure 5.1). Each curation team then generated a data curation report for that week. These reports included the number of registrations with identified problems, and the reasons for inappropriate registration are documented.

Data curation began prospectively in July 2015, but a full retrospective ‘sweep’ back to the first registration in January 2015, was also performed to ensure the integrity of the database. Once inappropriate registrations had been highlighted, these were forwarded to and removed by the author (RA) if he agreed. At the end of the study period, after baseline data for the first 500 curated registrations to *Research Registry* were obtained, data curation reports were retrieved and data extracted.

### *Data Quality*

The quality of data within the *Research Registry* was assessed using quality criteria that were developed alongside the registry. These are based on Sir Austin Bradford Hill’s criteria for what an account of a research study should convey, and each of the four key questions is linked directly to fields in the database (table 5.1).<sup>15</sup> Studies were scored out of nine using these quality criteria (see right hand side of table 5.1); receiving one point for each criterion met. Two teams of researchers (CL / MA / HS and YA / KK / DJ) scored each registration independently and compared results. Individual discrepancies in scoring were referred to the lead researcher for each group (CL or YA) for adjudication, and where consensus was

not reached, the decision was escalated to the lead author (RA). The proportion of quality criteria met per registration was expressed as a percentage.

<b>TABLE 5.1. QUALITY INDICATOR SCORE FOR REGISTRATIONS</b>	
<b>QUESTION</b>	<b>Relevant field of the registration form</b> <a href="http://www.researchregistry.com/browse-the-registry.html#home/addregistration/">http://www.researchregistry.com/browse-the-registry.html#home/addregistration/</a>
1. <i>Who did the research?</i>	<ul style="list-style-type: none"> <li>• Primary Investigator</li> </ul>
2. <i>Where did they do the research?</i>	<ul style="list-style-type: none"> <li>• Participating Institutions</li> <li>• Countries recruiting</li> </ul>
3. <i>Why did they do it?</i>	<ul style="list-style-type: none"> <li>• Key Questions and Objectives</li> </ul>
4. <i>What did they do?</i> This can be expanded to include the PICO items.	<ul style="list-style-type: none"> <li>• Patient Population</li> <li>• Intervention</li> <li>• Control or Comparator</li> <li>• Primary Outcomes (and secondary if used)</li> </ul>
5. <i>When did they do it?</i>	<ul style="list-style-type: none"> <li>• Dates of enrolment</li> </ul>

An alternative would have been to use the 24-item WHO data set <http://www.who.int/ictpr/network/trds/en/>. However, during this early phase of development of the registry i.e. the first 500 registration, the author was still adding and adjusting fields and hence it is difficult to ‘lock-down’ quality criteria at such an early phase. This is recognised as an important limitation of this study, as well as an area for further research and hence are has been further discussed in sections 5.6 and 5.7.

### *Statistical Analysis*

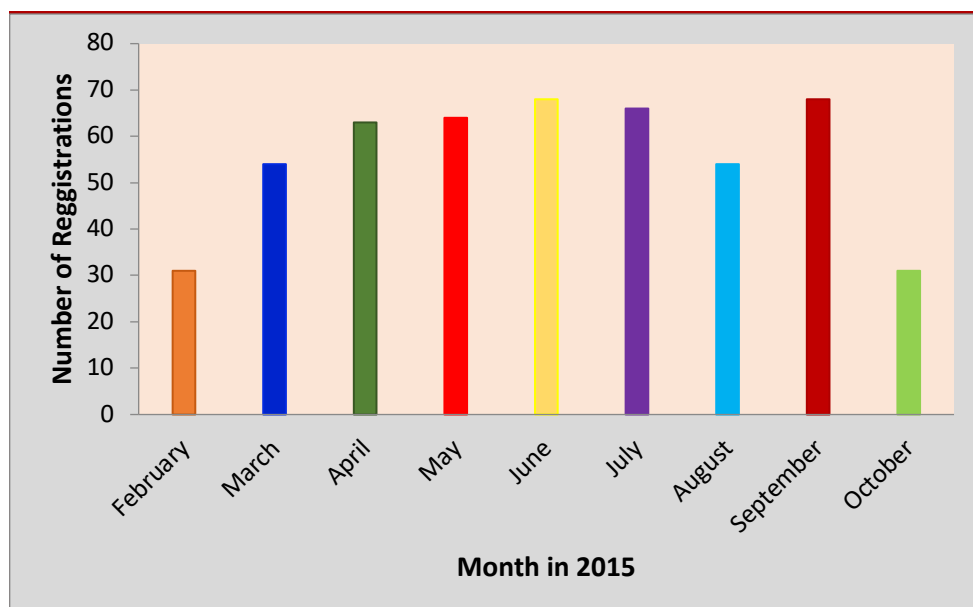
Descriptive data were calculated for the number of registrations, country of registration and type of study. Total number of patients was calculated by addition of the number of patients

reported in the study registration for all 500 registrations. Inter-rater reliability was calculated for the quality criteria, and quality of registrations were presented on a month by month basis. An independent samples Kruskal-Wallis Test was performed to ascertain if there was any difference between month by month quality scores, and this was presented with a box plot. All data were managed using Microsoft Excel 2013 (Microsoft, Redmond, VA), statistical analysis was performed using IBM SPSS Statistics for Window, Version 22.0 (IBM Corp., Armond, NY).

## 5.4 RESULTS

### *Number of Study Registrations*

From the launch of the *Research Registry* in February 2015, a nine-month period passed until the registration of 500 research studies. On 17<sup>th</sup> October 2015, the database was extracted for analysis. The number of registrations per calendar month is shown in figure 5.3. There has been a mean growth of 6% in registrations per month since the launch of the registry in February 2015.



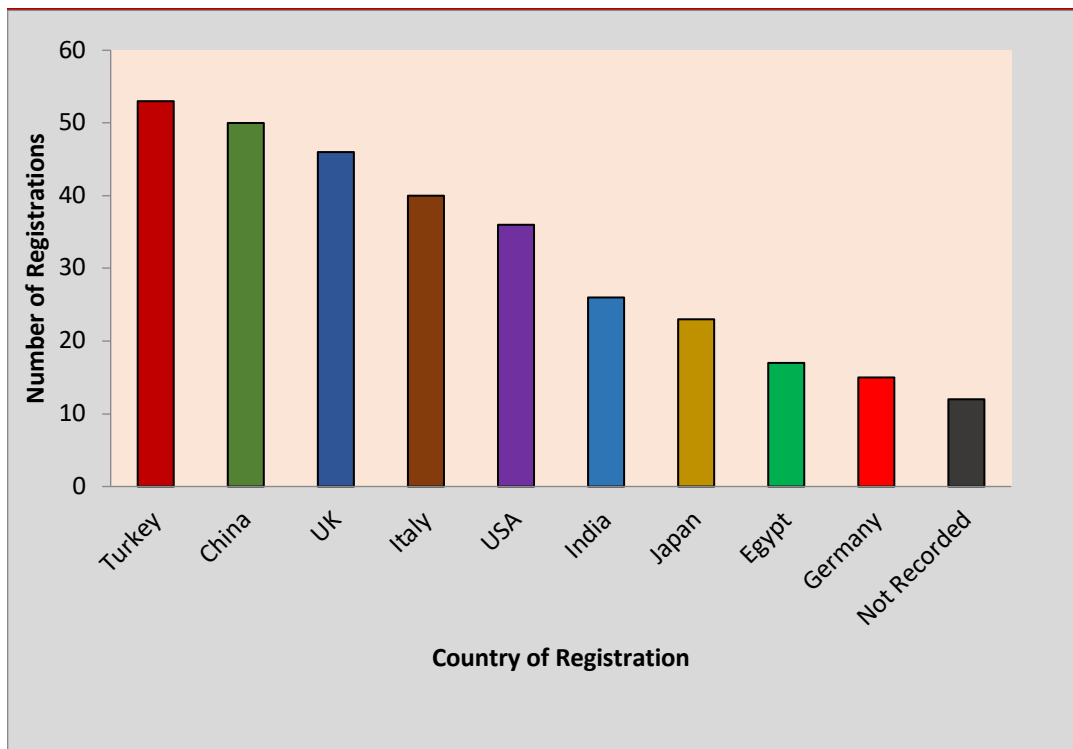
**Figure 5.3:** Number of study registrations to *Research Registry* per calendar month. 500 Registrations were reached by 17<sup>th</sup> October 2015.

### ***Number of included patients***

87.2% (436 of 500) registrations reported the number of patients included in their studies. Across these, a total of 1.77 million patients were enrolled. The median number of participants per study was 79 (Inter Quartile Range: 30 to 200)

### ***Source of registrations***

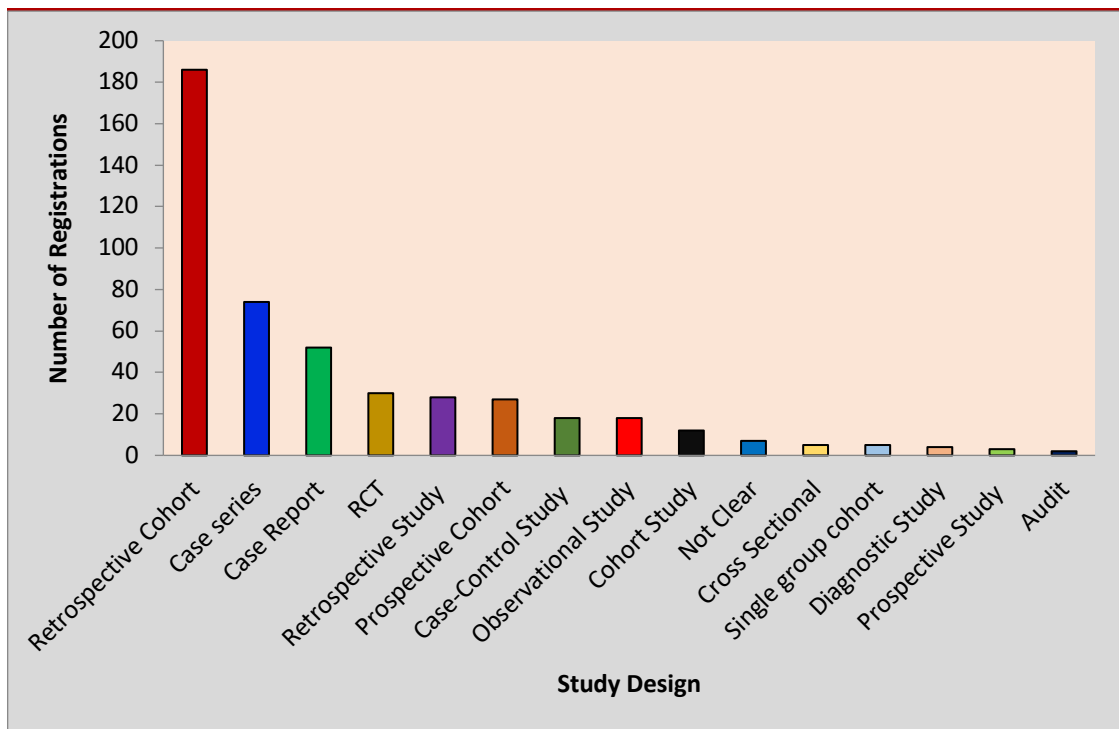
Registrations originate from 57 countries, of which the top 10 countries are shown in figure 5.4. Turkey registered the most studies (52 of 500, 10.4%), followed by China (50 of 500, 10%) and the United Kingdom (46 of 500, 9.2%). The top ten countries made up 329 of 500 studies (65.8%) and the mean number of studies registered by these countries was 30 (standard deviation 14.9).



**Figure 5.4:** Top ten countries of origin for studies that were registered.

### ***Types of studies registered***

Of the 500 studies registered on the *Research Registry*, the commonest study type was retrospective cohort studies (186 of 500, 37.2%). Case series also made up a large proportion of registered studies (74 of 500, 14.8%). The third largest population was first-in-man case reports (52 of 500, 10.4%, figure 5.5).



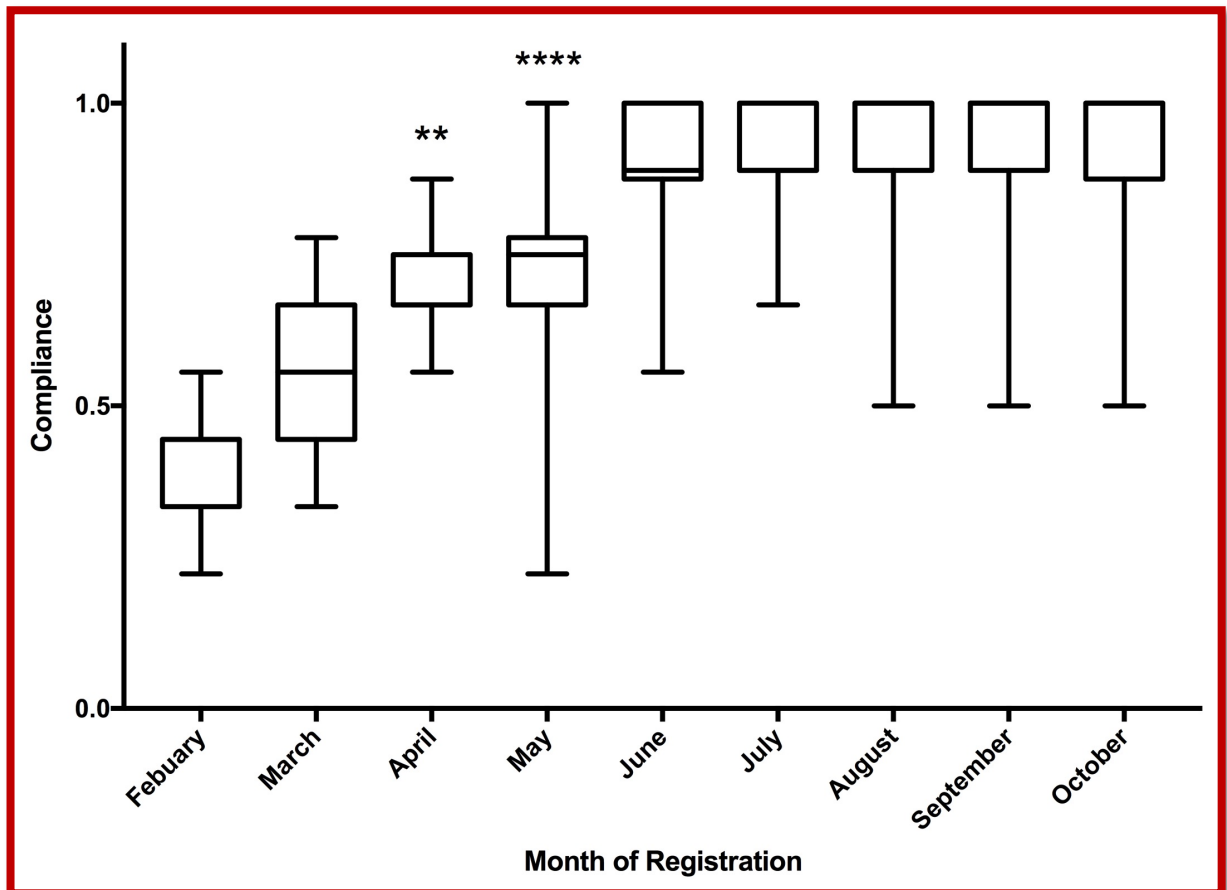
**Figure 5.5:** Bar chart of the types of studies registered in *Research Registry*.

### ***Data Curation***

Retrospective weekly data curation resulted in 88 studies being deleted. 80 studies were registered but not within the scope of the *Research Registry* e.g. animal studies or case reports that were not first-in-man (91% of 88 studies deleted) and there were eight duplicate studies that were deleted (9% of 90 studies deleted).

## Quality Criteria

The quality criteria score increased significantly over the course of the first 500 registrations (figure 5.6). The median quality score of the first 50 registrations was 44% (4 of 9 criteria fulfilled) and gradually increased to 100% (9 of 9) for the last 50 registrations in the cohort of 500. When compared on a month-by-month basis, the median score improved month on month and the Kruskal-Wallis test demonstrated significant improvement in median quality scores over the study period ( $p < 0.001$ ). The inter-rater agreement of quality scoring was 66.4% (complete score matches are achieved in 332 of 500 scores).



**Figure 5.6:** Boxplot of median score including inter quartile range and minimum/maximum scores. The difference in median compliance between months is compared using the Kruskal-Wallis test, with Dunn's multiple comparisons \*\*:  $p < 0.01$ , between February and April (no statistically significant difference between February and March), \*\*\*\*:  $p < 0.0001$ , between February and May (and increasing statistical significance thereafter).

## 5.5 DISCUSSION

Over the first 500 registrations at the *Research Registry*, studies have been registered from over 57 countries, accounting for over 1.77 million patients who were otherwise in unregistered studies. Registrations per month gradually increased over the study period overall. Objective quality indicators have improved over the course of the first 500 registrations.

Turkey, China and the UK were the commonest country of registration. This reflects in part submissions to two journals where study registration is mandatory, and reference is made to the *Research Registry* (although not exclusively) as a venue for registration (*International Journal of Surgery* and *Annals of Medicine and Surgery*). Concerns were initially raised as to whether clinicians would be willing to register their study as a necessary step during the submission process. This concern was unfounded, and authors have engaged well with the process, with no drop in the number of manuscripts being received at IJS or AMS. There were 80 submissions deleted for being incorrectly registered and these were mostly case reports. The IDEAL framework (discussed more in chapter 14) to improve the quality of surgical research encourages the registration of first-in-man case reports.<sup>16</sup> These should reflect the first time a particular surgical technique is utilised clinically, however some authors incorrectly registered a case report involving well established surgical techniques or treatments with *Research Registry*.

A gradual increase in registrations per month has been observed from launch in February 2015 to the end of the study period in October 2015, with the exception of August. This is likely due to the reduced number of papers submitted for publication during August and therefore less authors directed to the registry. During the study period, over 1.77 million

patients were included in registered studies and prior to the launch of *Research Registry*, many of these studies would not have had a venue of registration. The breadth of countries from which registrations have been received demonstrates the global impact of *Research Registry* and the breadth of research registration that can be achieved.

It has been estimated that less than 10% of all observational studies are registered at present.<sup>6</sup> When establishing *Research Registry*, observational studies were a key focus, and this is evidenced in the study breakdown. Over 37% of the registrations during the study period were retrospective cohort studies – studies which previously would have limited options for registration, and if registered retrospectively, there would be no venue for registration, prior to the launch of *Research Registry*. Given other registries have found the registration of observational studies challenging, the example of utilising a journal to boost compliance may be a way forward to improve registration of such studies.

The registry has evolved from its surgical roots and recent registrations include an intervention to improve nutritional intake and physical activity in women who have had treatment for breast cancer and a pilot study of tremor disruption in Parkinson's Disease.<sup>17,18</sup> Through an agile and iterative approach, new features have been added. These include unique features such as the ability to upload multimedia to demonstrate interventions, for example videos of surgical procedures. In September 2015, the function to deposit data and results, as well as the ability to update entries was added. The author has also integrated key reporting criteria from STROBE, CONSORT and PRISMA into the registration forms.

## 5.6 STRENGTHS AND LIMITATIONS

This analysis has a number of limitations, it is limited to a solitary database and the challenges posed are similar to other established registries.<sup>19</sup> Initially, there was difficulty with inappropriately filled fields in registrations and this reflects the poor-quality score initially (figure 5.6). This was improved with the combination of mandatory fields and careful data curation. Overtime, the registration form has been improved both with formal reviews of the database, and with suggestions from data curators as they review registrations on a weekly basis. There have also been technical difficulties, such as the ‘search the database’ function initially using a Google based search, which was prevented by a national firewall in China.<sup>20</sup> This was rectified by using a non-Google search facility and this aspect of the site has been functioning well in China since July 2015, and during the study period, China provided over 10% of registrations.

The author allowed for the retrospective registration of research i.e. research that had already been completed could also be registered. This decision had clear ethical reasoning. If a study is not registered, submitted to a journal and then subsequently rejected, the author could ‘mothball’ the study with no record of it having existed. It could potentially never be published at the behest of the author and so doing this, helps in part address the publication bias against negative studies, which is one of the goals of research registration.<sup>6</sup>

We utilised five points for auditing the registry data for quality (table 5.1), as opposed to using the 24-item WHO data set (recently increased from 20-items).<sup>21</sup> Whilst the current Research Registry contains all of the 24 items, we only audited against five specific questions, which includes up to 10 specific points (table 5.1). This is because the registry during the first 500 registrations was still evolving and subject to rapid iteration, with new

fields being added based on feedback or the author's analysis and this is somewhat expected in agile development projects like this. Whereas the five areas we selected were included from launch in the registry, so provide a reliable indicator of change in quality, especially given they are core items to understanding a registration.

The limitations created by establishing a quality score retrospectively should also be recognised. Once a registration is completed, it is essentially finalised. So, if additional fields are developed and then added to the database, the field will show up as not completed in previous entries. In practice the people completing the form never had a chance to complete that particular field, as it didn't exist at the time they registered. Going forward, as discussed in section 5.7 below, we could extend the scope of our audit of completeness of registration and quality by looking at all 24 items in the WHO dataset. This would require additional human resources with the time and commitment to undertake this and increased funding.

Finally, there is a limitation in one conceiving, developing and then evaluating one's own registry. The author has done his utmost to minimise this conflict of interest, by making the evaluation of the registry more independent, by not participating in data collection on the registry's performance, only analysing and interpreting it. In the future the evaluation of the registry could be made even more independent, by having the evaluation done entirely by external people/organisations. This may necessitate the registry developing more robust funding to allow for this to happen. In addition, the data could be made open access, allowing others to analyse it as well, this fits well with the open data movement, which in part aims to increase integrity in science.<sup>22</sup> This conflict of interest has been declared in the

relevant published papers related to the registry and all oral presentations pertaining to it as well.

## **5.7 IMPLICATIONS FOR FUTURE RESEARCH**

Going forward, the plan is to continue developing the platform in line with user feedback, data curator feedback and usability studies. Technology developments will likely be needed as the platform scales. Future research will assess a larger cohort of studies, with plans to assess 3,000 records when the registry reaches that level. This will provide a much larger database which the author can analyse, to see how the registry is developing and how registry developments and recognition, influence the developing content of the registry, the mix of study types, geographic distribution and so on. Future research could also look at auditing the registry against the 24-item minimum dataset that the WHO uses, rather than the more abbreviated instrument we have used. This would necessitate the appropriate resourcing to do such an audit.

## **5.8 SUMMARY**

The key findings of this chapter can be summarised as follows:

- ❖ The *Research Registry*® has established itself as a new registry with a clear focus on areas not well represented in existing registries, such as observational studies and those registering retrospectively.
- ❖ The author aims to establish *Research Registry* as a pan-research registry, addressing unmet demands and providing additional functionality.
- ❖ Ultimately, this registry will be used to improve compliance with the *Declaration of Helsinki 2013* through supporting the registration of all research studies involving human participants.

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# **CHAPTER 6**

## **SURVEYING OPINIONS OF 149 REGISTRANTS TO THE RESEARCH REGISTRY®: AWARENESS OF AND ATTITUDES TOWARDS RESEARCH REGISTRATION**



**BALLIOL  
COLLEGE**  
UNIVERSITY OF OXFORD

A summary of the following chapter has been published in the International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback. The author had assistance from medical students (DJ, MVB, CL, TKO, MCM and AJF) in data acquisition (with two independent teams) and was supervised by Professor Peter McCulloch and Professor Dennis Orgill. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 6.1 BACKGROUND

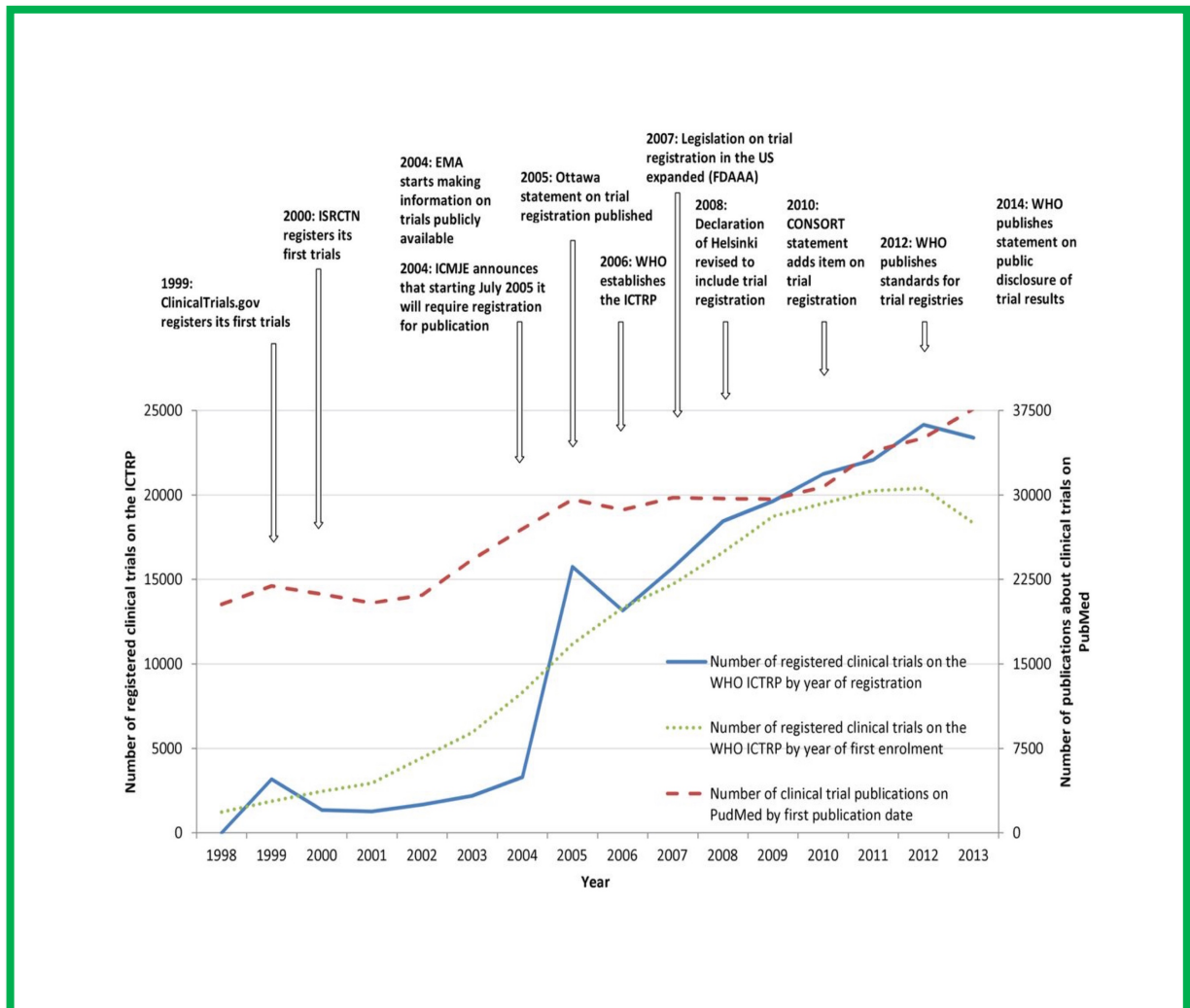
In 1986, Simes called for the creation of an international registry of clinical trials in part to help fight publication bias – that is the increased likelihood that positive or promising results would be published, compared to equivocal or negative results.<sup>1</sup> The development of such a registry was not started until 2000 when the US Congress authorised the creation of ClinicalTrials.gov. In the same year, the ISRCTN registry was established by BioMed Central. However, trial registration rates remained low despite this initial enthusiasm.<sup>2</sup>

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<sup>1</sup> Agha RA, Jafree DJ, Vella-Baldacchino M, Limb C, Kusu-Orkar T, Millip MC, Fowler AJ. *An analysis of the perceived barriers to research registration: surveying 1074 registered studies in the Research Registry*. International Journal of Surgery 2017;39:182-187.

In 2004, the International Committee of Medical Journal Editors (ICMJE) made registration of clinical trials a requirement for publication in their member journals.<sup>3</sup> This led to a sharp increase in the number of trials being registered, which did not occur when the US Federal Drug Administration (FDA) called for it in 2002.<sup>2</sup> In 2008, the Declaration of Helsinki (DoH) made registration of Clinical Trials mandatory, and hence registration became an ethical, in addition to a regulatory, requirement.<sup>4</sup>

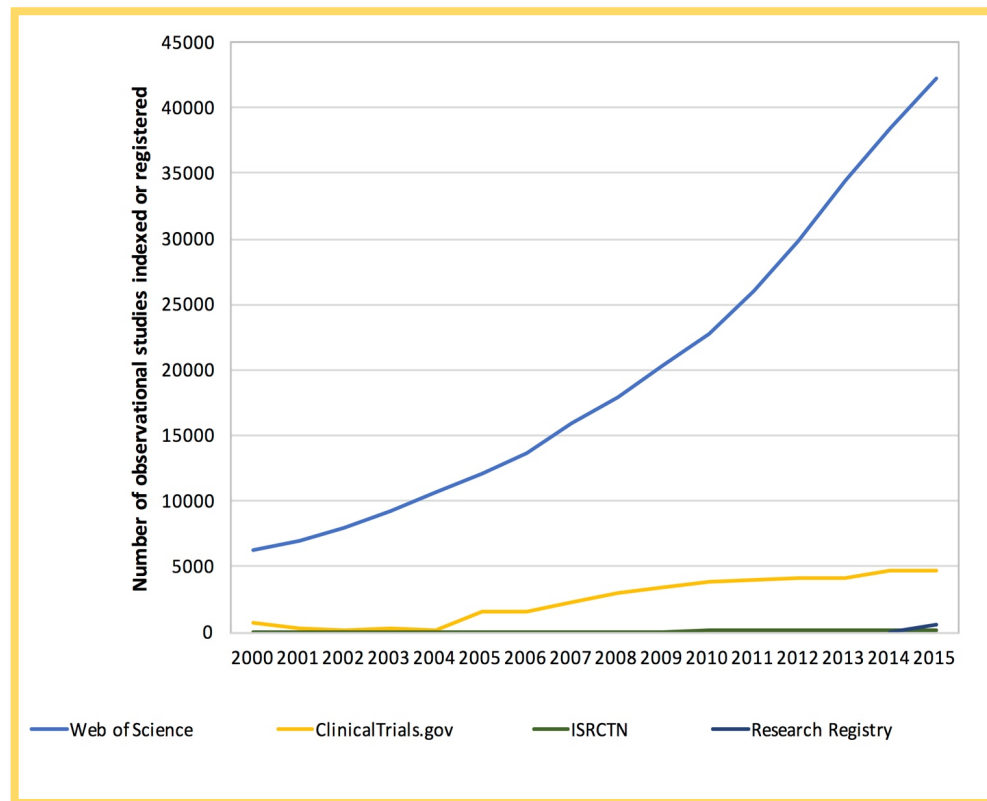
In 2007, Section 801 of the Food and Drug Administration Amendments Act (FDAAA) mandated the sponsors of applicable clinical trials to register and report basic summary results at ClinicalTrials.gov.<sup>5</sup> Despite this, only 13.4% of trials reported summary results within 12 months of trial completion.<sup>6</sup> Such calls for the registration of research, and uploading of results after completion of the study, have recently been underscored by a World Health Organization (WHO) statement. These trends are summarised in figure 6.1. This shows that the number of clinical trials registered has increased five-fold since 2004, relative to the number of publications of clinical trial research.<sup>7</sup>



**Figure 6.1:** Annual numbers of registered clinical trials on the International Clinical Trials Registry Platform (ICTRP) and annual numbers of publications about clinical trials on PubMed from 1998 to 2013. The first trials in the ICTRP database were registered in 1994; 15 trials registered from 1994 to 1997 are not shown (all registered at the Australian New Zealand Clinical Trials Registry (ANZCTR)). CONSORT, Consolidated Standards of Reporting Trials; EMA, European Medicines Agency; FDA, Food and Drug Administration; FDAAA, Amendments Act; ICMJE, International Committee of Medical Journal Editors; ICTRP, International Clinical Trials Registry Platform; ISRCTN, International Standard Randomized Controlled Trial Number Register. Taken from Viergever and Li, 2015.<sup>5</sup>

Lack of compliance with research registration is clearly still an issue. With the change in the DoH in 2013 to require the registration for *all research* involving human participants,

not just all trials, the scope of registration needed has greatly expanded.<sup>4</sup> However, it is estimated that less than 10% of observational research is actually registered.<sup>8</sup> The trends in the registration of observational research are shown in figure 6.2.



**Figure 6.2:** Number of observational studies indexed by Web of Science and numbers registered in ClinicalTrials.gov, ISRCTN and Research Registry® over the period 2000-2015.

Clearly, registries need to adopt a user-centric approach to improve compliance with research registration. However, there is little objective evidence to assess how research registration can be changed to meet the needs of users. Viergever and Li suggested that low compliance may be due to barriers to research registration, including a lack of local measures in low-income countries. For example, a lack of; funding and research

organizations, local legislation, local-language clinical trial registries, policies from local journal editors and ethics committees.<sup>5</sup> The author recently demonstrated, using the first 500 registrations to a global research registry, Research Registry® ([www.researchregistry.com](http://www.researchregistry.com)) that a registration policy enabling the registration of any study type involving human participants encourages registration from a wide variety of countries.<sup>9</sup> As such, the Research Registry® provides an opportunity to assess the needs of users. The author hopes to adapt the Research Registry® according to feedback, and further develop the registry to boost compliance with the DoH.

## **6.2 AIMS AND OBJECTIVES**

Using a global research registry, the Research Registry® ([www.researchregistry.com](http://www.researchregistry.com)), the author sought to gain insight into the demographics of registrants, awareness of research registration, perception of important elements of registration and users' motivation for registering their research.

### 6.3 METHODS

Data from all the registrations on the Research Registry® (n=1432) was exported into a Microsoft Excel® database (Microsoft, Redmond, WA, USA) in September 2016. These registrations were made by study investigators from the launch of the registry, in January 2015 to the end of the study period, in August 2016. From the database, email addresses were extracted, and participants were sent a link to complete a survey on Google Forms (Google, Mountain View, CA, USA).

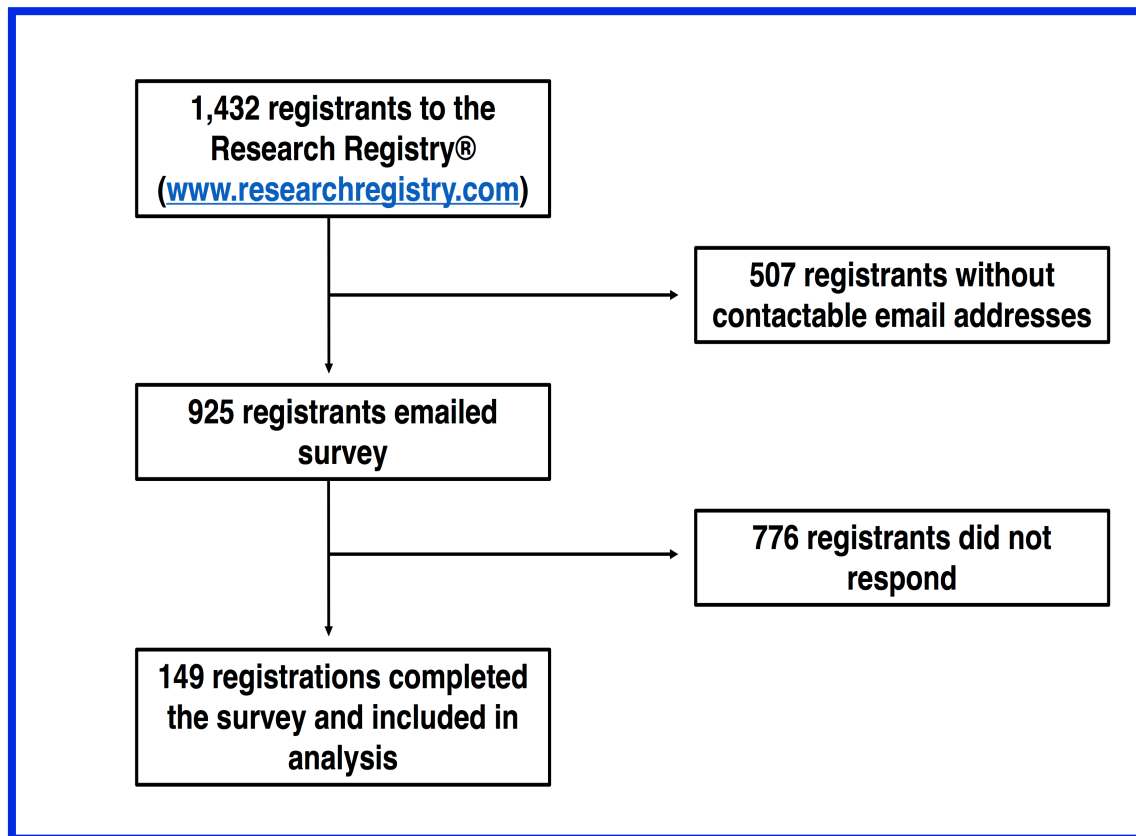
The survey consisted of three sections and 17 questions with multiple choice, checkbox, linear scale and free text answers (available at: <http://goo.gl/forms/P44wQrZNx6>). The questions would determine the demographics or types of registrations being made by the respondent, their awareness of the research registration, what they viewed as important elements of research registration and their motivation to register. Non-responders would be sent reminder emails (up to three).

Results were analyzed using Microsoft Excel®. Answers to multiple choice questions were analyzed using descriptive statistics, and free-text was analysed using a thematic analysis (by RA and DJ). This involved tagging the free text responses with codes which were representative of specific themes and then counting the codes to see how strongly particular themes were evident in the data.<sup>10</sup> The codes were generated by an initial pass of the data by the author to assess what themes were being represented in the results.

## 6.4 RESULTS

From 1,432 registrations, 925 (64.6%) emails were extracted, as not every registrant included an email address. The survey was initially piloted to 200 registrants, of which 146 (73.0%) had valid email addresses. From the pilot period, 20 out of 146 (13.7%) responses were obtained. During the pilot, the author identified a need to include a field in which registrants could input their name, as this way one would know who had completed the survey, and therefore who to send reminders emails to.

After the pilot, questions were added to the section on how important certain elements are when registering (“recording all the relevant study details in the registry entry” and “publication of the registry unique identifier in the eventual journal paper”). As such, the response rate was lower for the new questions, as these questions were included post-pilot. The author emailed 925 registrations with email addresses, requesting each registrant to complete the survey. A response rate of 149 out of 925 (16.1%) was achieved (figure 6.3).

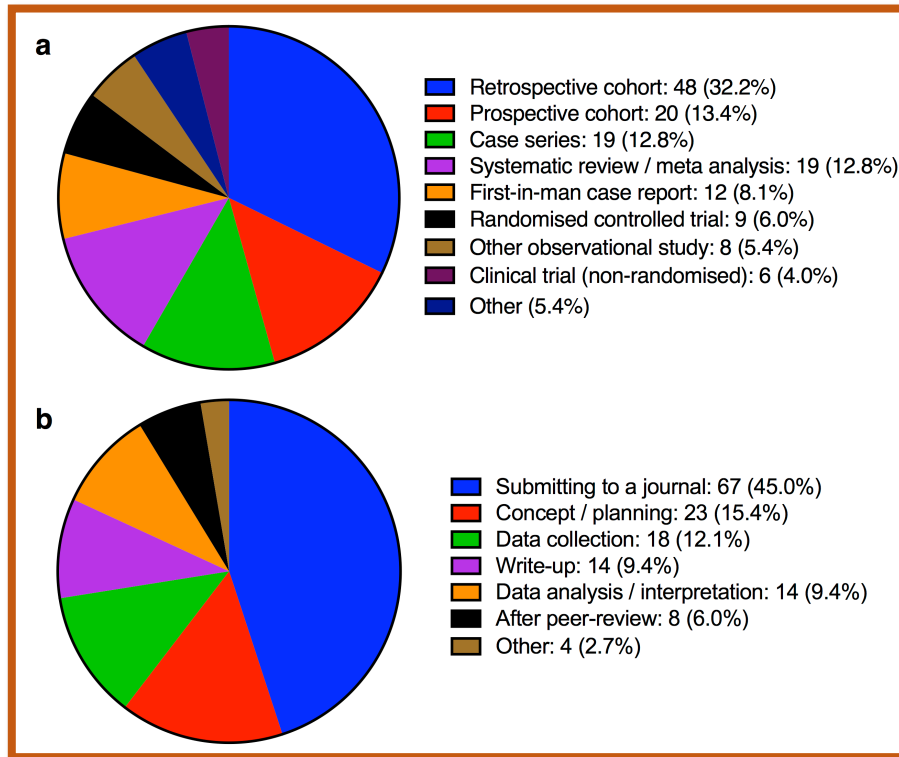


**Figure 6.3:** Flow diagram of participant involvement in the study.

## Demographics of registrations

Users first identified the type of studies that they had registered on the Research Registry® (figure 6.4a), and the stage of the study during which the registration was made (figure 6.4b). From the 149 respondents, the most commonly registered study type was Retrospective cohort (n=48, 32.2%), followed by Prospective cohort (n=20, 13.4%) and Case series (n=19, 12.8%). A majority of the 149 registrants registered their study at the time of submission to a journal (n=67, 45.0%) and only 23 registrants (15.4%) submitted during the concept or planning stage, prior to study commencement. Only 112 registrants declared whether they had previously conducted research that was unregistered or not. 51

out of the 112 registrants (45.5%) that answered this question declared that they had performed research that was not registered in a publically accessible database.

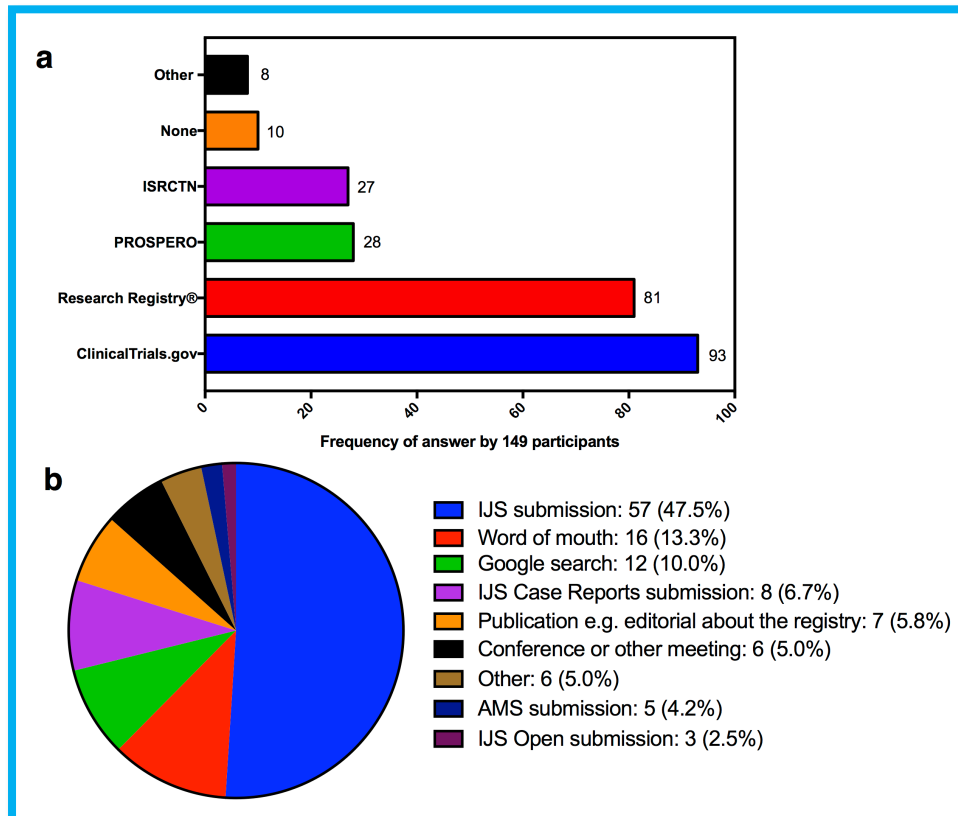


**Figure 6.4:** The study types registered (a) and the stage at which participants registered their study to the Research Registry® (b).

### Awareness of registration

Users were asked to indicate the registries that they were aware of prior to registration at the Research Registry® (figure 6.5a). The author asked the means by which the users became aware of the Research Registry® (figure 6.5b). The three most popular registries were ClinicalTrials.gov (n=93), Research Registry® (n=81) and PROSPERO (n=28). Of the 149 users, most had become aware of the Research Registry® through submission of a manuscript to the International Journal of Surgery (IJS, n=57, 47.5%). The second and third

most common methods by which users were made aware of the Research Registry® were through word of mouth (n=16, 13.3%) and through Google search (n=12, 10.0%).

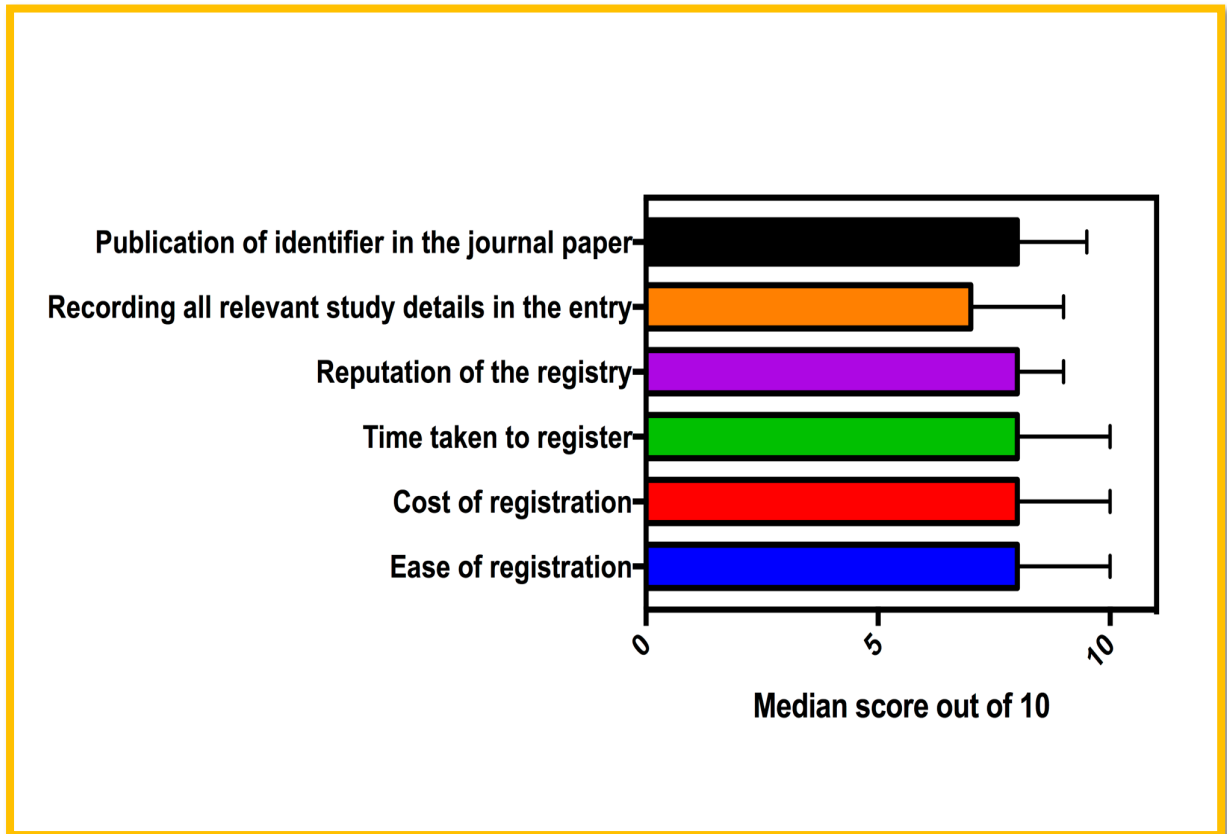


**Figure 6.5:** Which registries participants were aware of prior to their registration (a) and the means by which participants became aware of the Research Registry® (b).

## Important elements of registration

The 149 users were asked to score their perception on the most important elements of research registration out of 10, where 1 was of least importance, and 10 was of most importance. These elements were selected prior to study commencement by the senior investigators (RAA, AJF, CL). The median score out of 10 was calculated for each element

(figure 6.6). All elements were identified as equally important (median=8), with the exception of recording all relevant study details in the registry entry (median=7).

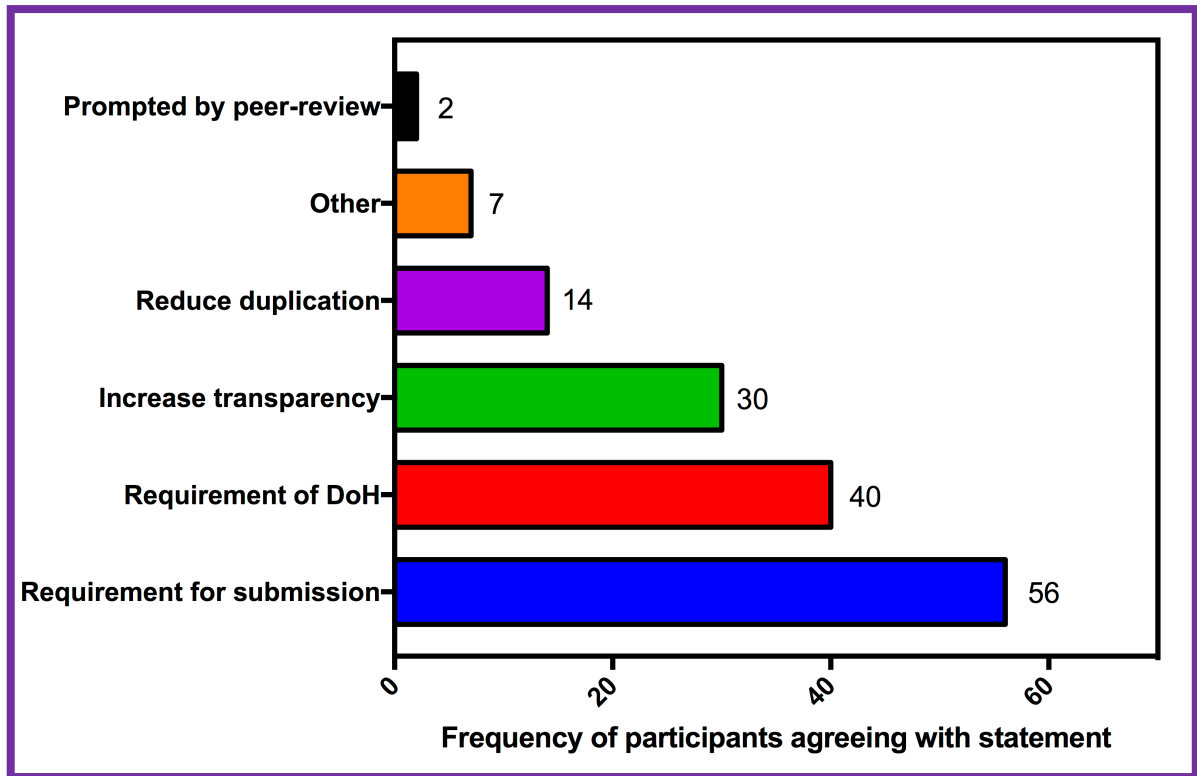


**Figure 6.6:** Motivation for registration by participants at the Research Registry®. Scores are given as median, and error bars indicate interquartile ranges.

### Motivation for registration

The final section of the survey concerned the user's motivation for registration. Firstly, the user's reasons for registration of their research was assessed using a multiple-choice question defined by the senior investigators (figure 6.7). Overwhelmingly, the common reason given for registration was as a requirement of journal submission (n=56). The next

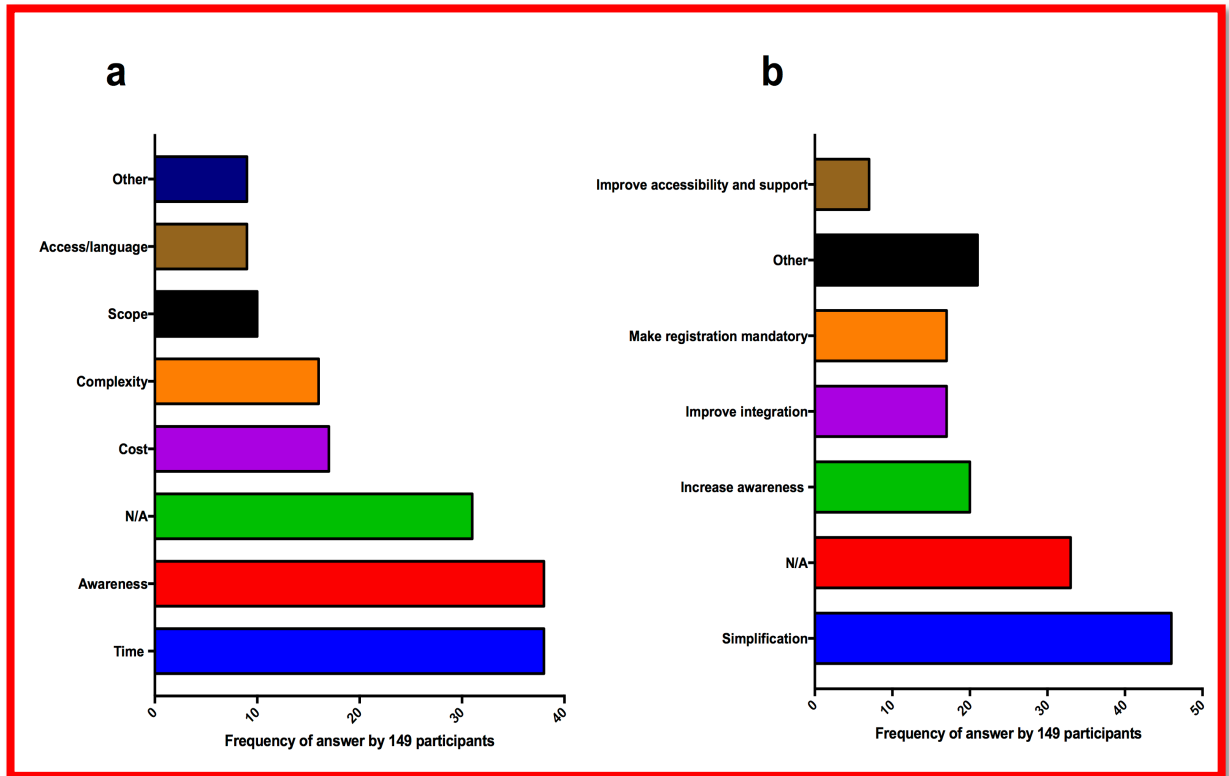
two most common reasons given for registration were as a requirement of the DoH (n=40) and to increase transparency of research (n=30).



**Figure 6.7:** Participants attitudes towards how registration could be improved at the Research Registry®.

Thematic analysis of free-text answers was performed to assess the user's perception of the barriers to research registration (figure 6.8a), in addition to their opinion on how to improve research registration (figure 6.8b). The most commonly identified themes which users perceived as barriers to research registration were awareness of registration (n=38), time taken to register (n=38), cost (n=17) and complexity (n=16) of registration. However, a considerable proportion of users also identified that research registration did not need to be improved (n=31). Users most commonly felt that simplification of the registration process would improve concordance (n=46) in addition to increasing awareness of registration

(n=20), improving integration with journals and ethics committees (n=17) and making registration of research studies mandatory (n=17).



**Figure 6.8:** Thematic analysis of users' attitudes towards the barriers to research registration (a) and how registration can be improved (b).

## 6.5 DISCUSSION

In this survey-based study, the author attempted to contact all the registrants to the Research Registry® with email addresses (n=925) in order to ascertain the demographics of registrants, their awareness of and their motivation for the registration of research. The primary finding of this study is that the most importantly perceived elements of registration were its ease, time and cost. Supporting this, thematic analysis revealed that time taken to register, cost and complexity were featured highly as barriers to research registration, and that simplification of registration would improve concordance. These data suggest that the convenience of registration, including time, cost and complexity of registration, could be exploited by registries.

The WHO Trial Registration Data Set advocates 20 items (at the time of conducting this study), meeting the minimum amount of information to deem a research study to be fully registered. At the Research Registry®, the author has included these 20 items in a logical fashion and kept registration free so as to maximise the convenience of registration for users.<sup>8</sup> In essence, registries should focus on simplifying their required dataset, minimising the time and money required to register, with the aim of increasing concordance with registration of research.

From the 149 registrants analysed in this study, the author found that a majority of users declared that they were registering observational research including and retrospective (32.2%) and prospective (13.4%) cohort studies. The author recently reported the

demographics of the first 500 registrations to the Research Registry®, and collectively, it is clear that the predominant form of studies registered at the Research Registry® are observational and retrospective in nature.<sup>9</sup> Strikingly, despite the Declaration of Helsinki mandating the registration of all research prior to recruitment of the first participant, only 15.4% of users made registrations during the conception and planning stages of the research studies.<sup>4</sup> This, combined with the fact that 45.5% users declared that they had performed unregistered research before, supports the need for the Research Registry® to serve as an avenue for the registration of study types that were previously difficult, or even impossible, to register elsewhere.

The lack of awareness around registration was highlighted. Thematic analysis revealed this to be a commonly perceived barrier, and that increasing awareness would improve registration rates. Moreover, thematic analysis indicated that improved integrations with journals or ethics committees would improve registration. Interestingly, 47.5% had been made aware of the Research Registry® through IJS submission.

Research Registry® has an ongoing partnership with the IJS family of journals, and all studies submitted for publication with the IJS journals have to be registered in a publically accessible database. As such, a high proportion of users were first introduced to the Research Registry® through submission at one of the IJS journals. The seamless integration between the Research Registry® and the IJS journals is integral to increasing awareness of the Research Registry®, and registries and journals should work in cooperation to increase

concordance with research registration. However, whilst registration for all research has been advocated in the DoH, this is not policy for the International Committee of Medical Journal Editors (ICMJE) or the vast majority of journals publishing such research.<sup>11</sup> This is a position that the author hopes will eventually be revised, and we have already see movements in this direction.<sup>12</sup>

## **6.6 STRENGTHS AND LIMITATIONS**

A strength of the study is the author's knowledge and familiarity with both the Research Registry® itself, and Google Forms, having used the latter in recent reporting guideline development work. However, a very low response rate of 149 out of 925 (16.1%) was achieved. The author appreciates that this low response rate significantly impairs the validity of the conclusions drawn, as the proportion of registrants who completed the survey may not be representative of registrants as a whole. Indeed, Fincham argues that below a 60% response rate, there is the potential for a significant non-response bias, which can affect both the reliability and validity of the survey findings, with only those who feel strongly about an issue responding.<sup>13</sup> Some journals won't publish a survey below a 70% response rate.<sup>14</sup> One way to limit this is to weight the sample surveyed to different constituencies and then only draw conclusions for those segments for which you have a good response rate.<sup>14</sup> This was not done in our study. The constituencies that use the registry are not yet defined and of course the author couldn't have predicted a low response rate.

The initial pilot of the questionnaire was sent to 200 registrants, of which 146 (73.0%) had valid email addresses. From the pilot period, 20 out of 146 (13.7%) responses were obtained. This 13.7% figure is not too dissimilar from the 16.1% achieved for the larger survey (149 responses from 925 emailed the questionnaire). In hindsight, it would be better to have confirmed the email addresses for the larger group as there could well be a number of email addresses which simply don't work as they were entered incorrectly or bounce or have changed or simply went into the recipient's junk mail. This would help give us the true denominator for such a survey, as it would mean we knew how many people actually received the survey for sure.

The author did follow many of the principles to good survey design espoused by others in the literature e.g. piloting, simple layout, being concise and so on, but there were some changes we could have mind in hindsight that would improve our response rate.<sup>15</sup> There were 18 people who replied to state that they registered their research study many months ago and couldn't now remember the experience of using the registry, hence couldn't complete the survey. Of course, there could be many others who feel the same way and simply deleted the email. So, a future survey of this kind may benefit from being done monthly, on those who registered that month and then sum the results over the course of a year. Using mailing software like MailChimp (<https://mailchimp.com>) may also be better than emailing people using MS Outlook one at a time from personal email accounts. This would also help tell us about the number of click-through's to the survey i.e. the number of people who click on the survey link in the email. We could then compare with the numbers of people who actually completed it and this would give more information about those who could have completed the survey but didn't. This is valuable learning for the future.

The low response rate raises important concerns. It is critical that researchers engage with their registration as a dynamic process - as studies progress changes to the study protocol should be reflected in the registry. Contrary to this process, Dwan and colleagues showed that, in the case of clinical trials, substantial discrepancies exist between registered and reported analyses.<sup>16</sup> This issue may well be prevalent in observational studies where there has been a widening gap between studies performed and those registered. The low response rate raises the question as to how study investigators engage with their registration after it is made, and this should be investigated further to determine how registration can be maintained as a dynamic process.

The registry allows for the retrospective registration of research i.e. research that had already been completed could also be registered. This decision had clear ethical reasoning. If a study is not registered, submitted to a journal and then subsequently rejected, the author could 'mothball' the study with no record of it having existed. It could potentially never be published at the behest of the author and so doing this, helps in part address the publication bias against negative studies, which is one of the goals of research registration.<sup>8,17</sup> A similar policy is followed by ClinicalTrials.gov and ISRCTN registries.<sup>18,19</sup> Doing this also may 'condition' authors to register their research prospectively going forward and raises awareness of registration, in line with the Declaration of Helsinki 2013.<sup>4</sup> However, it should be stressed, the Research Registry supports the Declaration of Helsinki and ICMJE/FDA in calling for research or trials respectively to be registered prior to recruitment of the first participant and this is made clear on the website.<sup>8</sup>

## **6.7 IMPLICATIONS FOR FUTURE RESEARCH**

The next phase of this line of research is to utilise the findings to further enhance and develop the Research Registry®. Other registries should consider the results of these studies going forward in development, and the author advocates that other registries apply this methodology for their own users. Moreover, a study such as this could be repeated in future years to reassess how users' opinions on the registration of research have changed. Strategies should be implemented to try and engage more with researchers so as to increase response rate, and perhaps an ongoing study, whereby participants register and are immediately sent a survey to complete or if it is done on a rolling basis month by month as described in section 6.6 above. These results could then be summed over the course of a year to give the results for that year. Using specialist mailing software like MailChimp and confirming email addresses would be useful methodological changes that could improve our response rate.

## **6.8 SUMMARY**

The key arguments and findings of this chapter can be summarised as follows:

- ❖ Research registration rates, especially for observational research, continue to remain low.
- ❖ Moreover, a large proportion of registration occurs immediately prior to journal submission.

- ❖ This is despite numerous calls from national and international agencies to increase registration of all study types, prior to the recruitment of the first participant.
- ❖ Understanding the opinions and requirements of registry users is critical to boosting research registration. In order to achieve this, registries will need to evolve by developing a user-centric approach, collaborating with journals, gathering and listening to feedback from users and developing an agile approach to their future development which focuses on ease of use, speed and low cost.

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# **CHAPTER 7**

## **THE REPORTING QUALITY OF OBSERVATIONAL STUDIES IN PLASTIC SURGERY NEEDS IMPROVEMENT: A SYSTEMATIC REVIEW**



A summary of the following chapter has been published in the *Annals of Plastic Surgery*.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback. The author had assistance from three medical students (SL, KJLJ and AJF) in data acquisition and was supervised by Professor Dennis Orgill. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 7.1 BACKGROUND

The author has recently examined and described the shortfall in methodological and reporting quality of randomised controlled trials (RCT) in Plastic Surgery (see appendix I).<sup>1,2</sup> However, the majority of studies within the plastic surgery literature are observational by design such as cohort or case studies. Whilst high quality RCTs provide evidence with the least amount of bias, observational studies still have an important role in the literature. They are useful for assessing new techniques early in their development, for studying rare conditions or where it is not practical to do an RCT such as emergencies. RCTs are also very expensive and resource intense, requiring a team with the necessary infrastructure and skills to see it through.

The reporting of any study should be complete, clear and transparent. This is important

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<sup>1</sup>. Agha R, Lee S, Jeong KJL, Fowler AJ and Orgill DP. *Reporting Quality of Observational Studies in Plastic Surgery Needs Improvement: A Systematic Review*. *Annals of Plastic Surgery* 2016;76(5):585-9.

for subsequent evidence synthesis and to ensure that all facets of the work are available for interpretation. The author's work looking at the reporting quality of RCTs in Surgery and Plastic Surgery in particular has shown significant deficiencies (see appendix II). Of 57 RCTs identified from 2009-11 the median CONSORT score was 11.5 out of 23 mandatory items.<sup>2</sup> The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was published in 2007 and aimed to improve the reporting quality of observational studies. It was developed through a Delphi Consensus Exercise by a multidisciplinary group of editors, statisticians, methodologists, clinicians from Europe and North America. It consists of a 22-point checklist of items considered as mandatory for inclusion when reporting such observational studies.

## **7.2 AIMS AND OBJECTIVES**

The objective was to determine the compliance of observational studies in plastic surgery with the STROBE statement.

## 7.3 METHODS

### Search Methods

Two researchers (SL and KJLJ) independently conducted a search of five major plastic surgery journals; Plastic and Reconstructive Surgery (PRS), Journal of Plastic Reconstructive and Aesthetic Surgery (JPRAS), Annals of Plastic Surgery (APS), Aesthetic Surgery Journal (ASJ) and European Journal of Plastic Surgery (EJPS). Whilst this does not represent the entirety of Plastic Surgery publications, these journals are long established and do represent a significant output for the field.

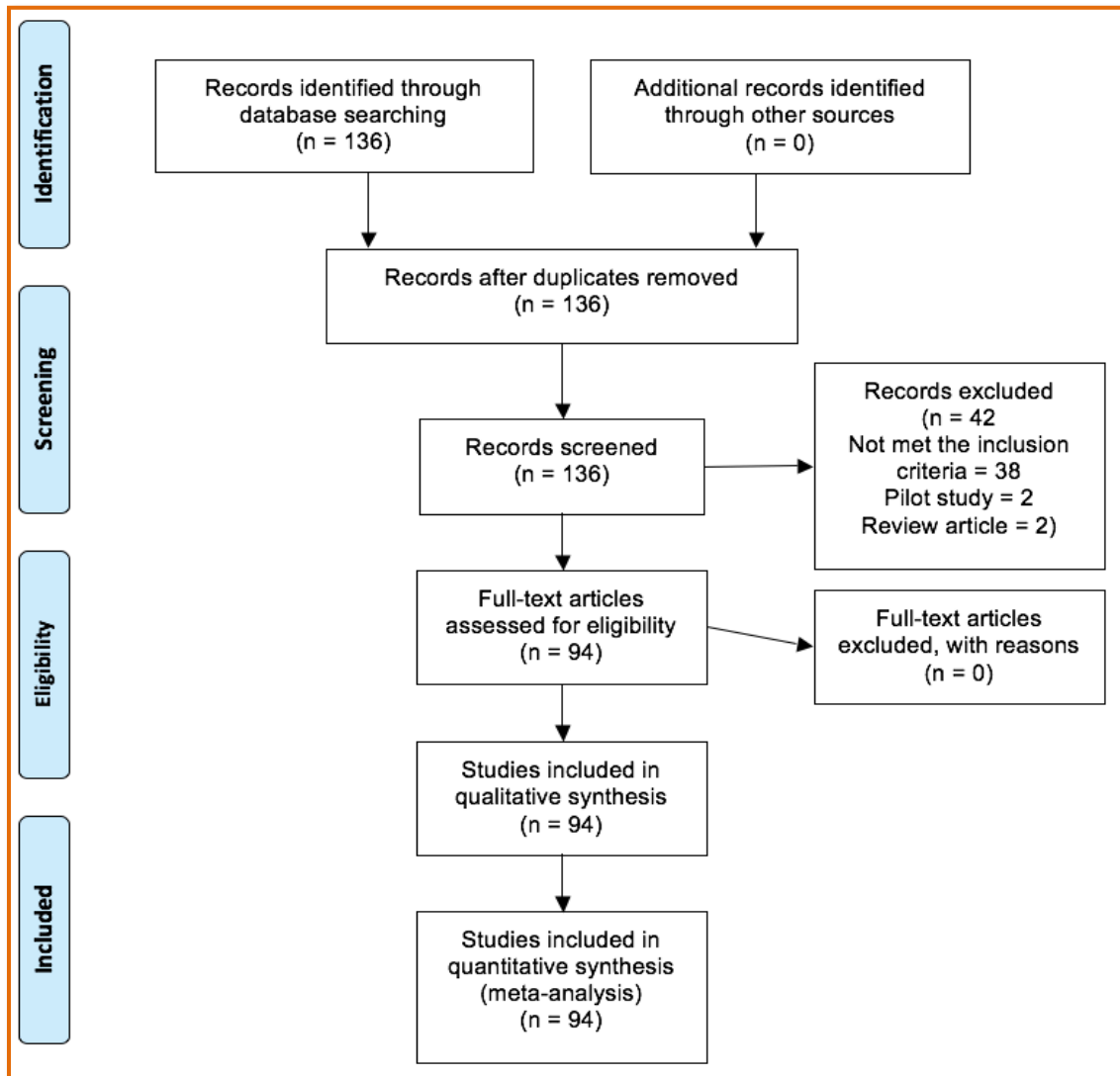
The search was restricted to the year 2013 and to cohort, cross-sectional and case-control study designs (which the STROBE criteria are specifically aimed at). Articles not meeting these criteria were excluded, which included pilot studies, review articles, the articles related to surgical topics but assessment method or technique were not surgical, financial studies, studies about the patient satisfaction, radiological studies, psychological studies, trend studies, and studies about training (figure 7.1). To conduct the search, the abstracting databases MEDLINE® and EMBASE® were used, the search strategy is shown below (table 7.1):

**TABLE 7.1. SEARCH STRATEGY FOR OVID MEDLINE® USED FOR PRS, JPRAS, APS AND ASJ**

1	plastic & reconstructive surgery.jn. (14495)
2	"journal of plastic reconstructive & aesthetic surgery jpras".jn. (3765)
3	"annals of plastic surgery".jn. (5073)
4	(aesthetic surgery journal or aesthetic plastic surgery).jn. (2795)
5	1 or 2 or 3 or 4 (26128)
6	limit 5 to yr="2013" (1630)
7	Cohort Studies/ (141762)
8	Cross-Sectional Studies/ (145810)
9	Case-Control Studies/ (159313)
10	7 or 8 or 9 (425093)
11	6 and 10 (133)

**TABLE 7.2. SEARCH STRATEGY FOR EMBASE® USED FOR EJPS**

1	"european journal of plastic surgery".jn. (1781)
2	limit 1 to yr="2013" (151)
3	cohort analysis/ (165171)
4	cross-sectional study/ (110402)
5	case control study/ (83352)
6	3 or 4 or 5 (346265)
7	2 and 6 (3)



**Figure 7.1:** PRISMA flow diagram, illustrating how articles were selected (adapted from Moher et al.).

## Scoring

Once selected, articles were scored independently against the 22 items of the STROBE checklist by two researchers (SL and KJLJ). The resulting score out of 22 was termed the “STROBE Score”. Items were scored only when all the information detailed for the item was reported in the article.

For the items with sub-sections, fractional points were scored, depending on the number of

sub-items met. For example, if an article thoroughly described the statistical analysis and fulfilled the required information in item 12 but only failed to perform subgroup analysis (item 12b), the mark of 4/5 would be applied. If an item was not applicable, the item was removed from the denominator. If there was disagreement between the two scorers, the matter was forwarded to another member of the team (AJF) who made a final decision. A Cohen's Kappa Statistic was calculated using Microsoft Excel 2011 (Microsoft, Redmond, VA).

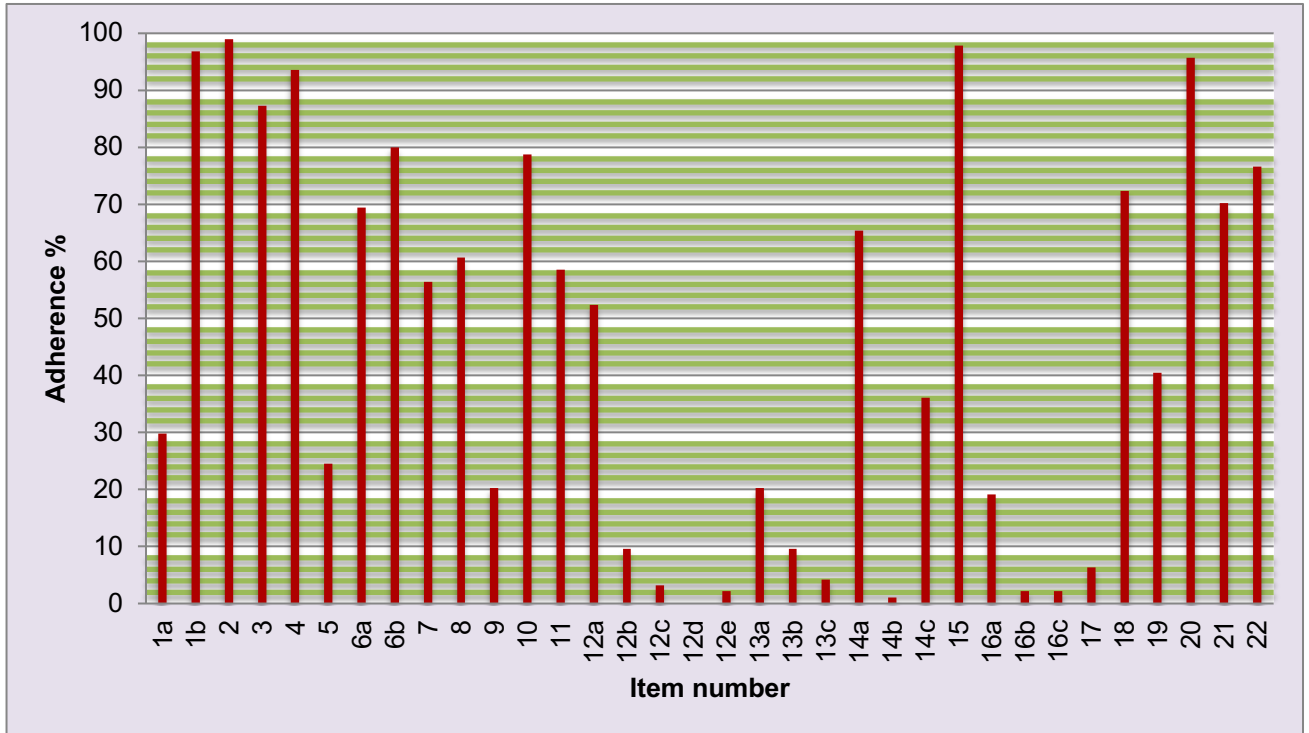
## 7.4 RESULTS

The MEDLINE® and EMBASE® search identified an initial set of 136 articles, of which 94 were then selected following abstract assessment, which excluded pilot studies (two articles), review articles (two articles), and other articles, that did not meet the inclusion criteria (38 articles, figure 7.1). A total of 2068 points were scored (94 articles multiplied by 22 items). Arbitration occurred with respect to 14 articles for inclusion and 57 marking points across 43 articles. The Cohen's Kappa statistic was 0.39 indicating moderate agreement.<sup>3</sup> Following discussion between the two scorers, no disagreements remained.

The mean STROBE score was 12.4 out of 22 items (56%; range 2—20.1) with a standard deviation of 3.36. The compliance with the items in the STROBE statement is shown in table 7.3.

Compliance between individual items showed high variability (figure 7.2). It was poorest for items relating to the description of the loss of follow-up (Item 12d, 0%) and the number of participants with missing data (item 14b, 1%), while being highest for scientific

background and explanation of rationale (item 2, 99%) and reporting the outcomes of the data (item 15, 98%).



**Figure 7.2:** Adherence of articles to the individual items of the STROBE checklist

The compliance with the items in the STROBE statement is shown in table 7.3. Limiting these results to the five most concerning items is shown in table 7.4.

<b>TABLE 7.3. ADHERENCE TO THE STROBE REPORTING CRITERIA</b>			
<b>SECTION</b>	<b>ITEM NO</b>	<b>RECOMMENDATION</b>	<b>Adherence (%)</b>
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	30% (28/94)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	97% (91/94)
<b>Introduction</b>			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	99% (93/94)
Objectives	3	State specific objectives, including any pre-specified hypotheses	87% (82/94)
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	94% (88/94)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	24% (23/94)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	69% (65/94)
		(b) For matched studies, give matching criteria and number of exposed and unexposed	80% (75/94)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	56% (53/94)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	61% (57/94)
Bias	9	Describe any efforts to address potential sources of bias	20% (19/94)

Study size	10	Explain how the study size was arrived at	79% (74/94)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	59% (55/94)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	52% (49/94)
		(b) Describe any methods used to examine subgroups and interactions	10% (9/94)
		(c) Explain how missing data were addressed	3% (3/94)
		(d) If applicable, explain how loss to follow-up was addressed	0% (0/94)
		(e) Describe any sensitivity analyses	2% (2/94)
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	20% (19/94)
		(b) Give reasons for non-participation at each stage	10% (9/94)
		(c) Consider use of a flow diagram	4% (4/94)
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	65% (61/94)
		(b) Indicate number of participants with missing data for each variable of interest	1% (1/94)
		(c) Summarise follow-up time (e.g., average and total amount)	36% (34/94)
Outcome data	15*	Report numbers of outcome events or summary measures over time	98% (92/94)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision	19% (18/94)

		(e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	2% (2/94)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	2% (2/94)
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	6% (6/94)
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	72% (68/94)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	40% (38/94)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	96% (90/94)
Generalisability	21	Discuss the generalisability (external validity) of the study results	70% (66/94)
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	77% (72/94)

**TABLE 7.4. TOP FIVE STROBE ITEMS MOST POORLY ADHERED TO.**

SECTION	STROBE ITEM	ABBREVIATED DESCRIPTION	ADHERENCE (%)
<b>Title and Abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	30% (28/94)
<b>Methods</b>	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	24% (23/94)
<b>Methods</b>	9	Describe any efforts to address potential sources of bias	20% (19/94)
<b>Results</b>	13 and 16	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	20% (19/94)  10% (9/94)  4% (4/94)
<b>Discussion</b>	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	40% (38/94)

## 7.5 DISCUSSION

This study found that no observational studies in 2013 met all criteria laid out in the STROBE 2007 statement, with a relatively low mean score of 12.4 of 22. The mean adherence of all items was 56%; only five items (1b, 2, 4, 15, and 20) showed the compliance above 90%, while 14 items (including sub-items) showed an adherence less than 25%. In particular, items relating to the description of potential bias (Item 9, 20% and Item 19, 40%). It seems to be surprising that, so few studies addressed bias issues, since this is a critical component to scientific publications and nearly all journals require a disclosure statement prior to publication. However, it must be noticed that the marks were given only if the article reported their efforts to address potential source of bias or discussed their limitation. Therefore, even if the study was thoroughly designed to avoid bias, they did not get marks if they failed to adequately describe such efforts.

The results demonstrate that observational studies in the 2013 cohort of five major plastic surgery journals have poor compliance with STROBE criteria. This poses a challenge to the plastic surgical community. Calls for a more evidence-based approach within Plastic Surgery have been growing.<sup>4,5</sup> However, the evidence base in plastic surgery is still dominated by observational studies and calls for more RCTs have been made.<sup>6,7</sup> Poor reporting 'short circuits' proper critical appraisal, prevents inclusion in systematic reviews and meta-analyses, and resulting clinical judgments could be misleading and potentially dangerous.

Much focus has been given to shortfalls in the reporting of RCTs in plastic surgery<sup>2</sup>, surgery more broadly<sup>5</sup> and medicine.<sup>8</sup> Whilst RCTs represent the criterion standard for evaluating the effectiveness of an intervention, the majority of studies are observational in nature. Shortfalls in the reporting of observational studies have also been demonstrated. In stroke

research, 17 of 49 articles or 35% did not specify eligibility criteria.<sup>9</sup> In psychiatry, few reports of case-control studies explained the methods used to identify cases and controls.<sup>10</sup>

In surgery, interest in assessment of reporting quality using STROBE is developing. Nesvick et al assessed the STROBE adherence of 32 case-control studies and determined that the average STROBE score was 15.8 out of 22.<sup>11</sup> The major reporting deficiencies included; reporting of bias (28%), missing data (55%), and funding (44%). Even more concerning, the authors reported that the majority of studies in the neurosurgical literature that identify themselves as "case-control" studies are, in fact, labeled incorrectly.<sup>10</sup>

Sorensen et al assessed STROBE adherence for hand surgery articles between 2005 and 2011.<sup>12</sup> The STROBE score over this period increased from 38% to 58% (or 8.4 to 12.8). Their 2011 STROBE adherence figure of 12.8 is similar to the 12.4 in the present study. Key deficiencies included; presenting the study design in the abstract (20%), matching criteria for case-control studies (25%), addressing bias (3%), providing a power analysis (17%), and addressing missing data (6%). These overlap with some of the key deficiencies found in this study. Seasoned peer-reviewers will recognise the missing items in table 7.4 above and immediately realize one potential value of the checklist – to boost reporting quality pre-submission. This will ensure that peer-reviewers and editors have the necessary information to make an accurate assessment of the manuscript and focus on the science.

One solution is to hard-wire compliance with STROBE by making the checklist a mandatory item for submission for cohort, case-control and cross-sectional studies. This would allow

further scrutiny by editors and peer-reviewers. Such a policy was adopted by the International Journal of Surgery in January 2013 (see chapter 10).<sup>13</sup>

## **7.6 STRENGTHS AND LIMITATIONS**

The limitations of this study included only searching five journals and not the full breadth of the literature related to Plastic Surgery. Database searching is not a perfect science and is known to be time consuming, tiring and can lead to disinterest.<sup>14</sup> An alternative approach would have been to electronically ‘hand search’ the journals i.e. going issue by issue on each journal’s website. This could mean we would be less likely to miss an article due to a database search error or any minor inadequacy with the search strategy. Many higher quality studies in the field of plastic surgery will be published in other specialty journals or more broad scope surgical or medical journals. However, these five journals do represent a broad cross-section of plastic surgery research and illustrate the problem of poor reporting quality well.

It is also possible that within these five journals studies may have been missed, if they did not show up in the electronic database searches. By using two independent data extractors and a third to make decisions on scoring disagreements, more accurate scoring of the 94 papers that met the inclusion criteria would occur. However, human error throughout this process cannot be eliminated completely, only minimised.

A number of items within the checklist are not always required but should be reported “if applicable”. Scoring of these items (for example, sensitivity analysis) was impossible, as there is no way of determining if a sensitivity analysis is required. Finally, by restricting to

2013 only, the review is cross-sectional in nature and provides a snapshot of the literature at that time. One cannot comment on trends in the quality of observational studies.

## **7.7 IMPLICATIONS FOR FUTURE RESEARCH**

The author supports calls for the better education of plastic surgeons at all levels in clinical research methods, EBM and improved funding/support of plastic surgical research. The efficacy of educational interventions is also an area that requires further exploration. How do we make it easier for people to do the right thing? How can post-graduate education programmes, specialty associations, Royal Colleges or other national institutes help drive forward better reporting? Raising awareness is certainly important, but interventions could be coupled with this to achieve robust, long-lasting results. These are areas that require much research and the input of EBM and medical educationalists as well as surgeons.

How should journals change? How many mention reporting guidelines in their instructions to authors? How could compliance be improved were journals to mandate that authors comply with reporting guidelines and submit a completed checklist as part of the submission, with that checklist available to the reviewers and editors to scrutinise. Such research questions are explored further in chapters 9 and 10 of this thesis.

This study could be repeated in the future to assess if things have improved. Methodological changes to be considered would include either electronic ‘hand searching’ a select number of journals, perhaps a larger cohort or searching under the Medical Subject Heading (MeSH) “Surgery, Plastic” in the Medline database and consider a similar approach to searching other databases like Scopus, EMBASE, etc.

## 7.8 SUMMARY

The key findings of this chapter can be summarised as follows:

- ❖ The reporting quality of observational studies in Plastic Surgery needs improvement.
- ❖ The mean STROBE score was 12.4/22 or 56%, demonstrating poor compliance with a well-established reporting guideline.
- ❖ The top five most commonly missed items were; identifying the study design in the title/abstract, describing the setting and recruitment in detail, any efforts made to address potential sources of bias, numbers of individuals at each stage of the study and discussing the limitations of the work.
- ❖ This could potentially be improved through better education, awareness amongst all stakeholders and ‘hard-wiring’ compliance into electronic journal submission systems.

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# **CHAPTER 8**

## **THE REPORTING QUALITY OF SYSTEMATIC REVIEWS IN PLASTIC SURGERY NEEDS IMPROVEMENT: A SYSTEMATIC REVIEW**



**BALLIOL**  
**COLLEGE**  
UNIVERSITY OF OXFORD

A summary of the following chapter is published in JAMA Facial Plastic Surgery.<sup>1</sup> The author was involved in; concept and design, data analysis and interpretation, writing and revising the paper. The author worked with five medical students who assisted in data acquisition (LSY, HS, KW, GW, AF), analysis and writing up (SYL only). The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 8.1 BACKGROUND

A systematic review should be an attempt to answer a clearly formulated research question by assessing and synthesising the relevant and available research evidence. They have become increasingly important in healthcare, by replacing traditional narrative reviews and expert commentaries in summarizing research evidence.<sup>1</sup> They are dependent primarily on the quality of the studies they synthesise but can be more useful than primary studies alone as they may account for bias within individual studies by looking at broader populations. Similarly, they may quantify the heterogeneity in available data, and allow for results from multiple studies to be pooled into a meta-analysis to increase power, and hopefully identify the correct treatment for a particular clinical paradigm.<sup>2</sup>

Clinicians, researchers and policy makers use systematic reviews and meta-analyses to

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<sup>1</sup> Lee SY, Sagoo H, Whitehurst K, Wellstead G, Fowler A, Agha RA and Orgill DP. *The Reporting Quality of Systematic Reviews in Plastic Surgery Needs Improvement: A Systematic Review*. JAMA Facial Plastic Surgery 2015;17:1-5.

keep up to date with their field, to inform decision-making in clinical practice and in preparation of future studies. As with any study, its conduct, methodological design and quality of reporting is paramount.<sup>3</sup> In order to accurately appraise a study, readers need complete, clear and transparent information. A number of reporting guidelines have been established to improve the reporting quality of clinical research. The author has previously shown the poor compliance of randomised control trials (RCTs) and observational studies in plastic surgery with the Consolidated Standards of Reporting Trials (CONSORT) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements respectively.<sup>4-6</sup>

In 2009 the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was published. It consists of a 27-item checklist covering each section of the article and a four-phase flow diagram, aiming to help authors improve the reporting of systematic reviews and meta-analysis.<sup>3</sup>

## **8.2 AIMS AND OBJECTIVES**

The aim of this study was to determine the compliance of systematic reviews and meta-analyses in plastic surgery with the PRISMA statement.

### 8.3 METHODS

This systematic review was conducted according to the recommendations outlined in the Cochrane Handbook version 5.1.0 for Systematic Reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>3</sup> This review is also registered with the research registry – UIN: reviewregistry18 ([www.researchregistry.com](http://www.researchregistry.com)).

#### Search Methods

The electronic search was conducted using the MEDLINE and EMBASE databases (appendix 1) for systematic reviews published in 2013 and 2014 by five major plastic surgery journals: *Plastic and Reconstructive Surgery*, *Aesthetic Plastic Surgery*, *Archives of Facial Plastic Surgery*, *Journal of Plastic Reconstructive and Aesthetic Surgery*, and *Annals of Plastic Surgery*. They were the journals with the highest impact factor among plastic surgery journals, according to the Thomson Reuter Impact Factor 2013.<sup>7</sup> Although they are not representative of all plastic surgery publications, they do represent significant output for the field. The search strategies are shown in the appendix.

Three researchers (SYL, KW and HS) then independently sorted the articles by abstract screening. The search was restricted to the years Jan 2013 to Dec 2014 and to systematic reviews and/or meta-analyses. Only non-systematic reviews and non-meta-analyses were excluded. Any discrepancies in article selection were resolved by consensus first, and if still unsolved, referred to another member of team (RAA) for the final decision.

## **Scoring**

Articles were scored independently by two researchers (HS and KW/GW; works were divided between KW and GW) against the 27 checklist items in the PRISMA 2009 statement, with each item weighted equally. The resulting score out of 27 was termed the 'PRISMA score'. Items were only scored if the article had reported all the information detailed for the item, reflecting the latest PRISMA 2009 statement.<sup>8</sup> However at the same time, any efforts that fulfilled the requirement of the item were accepted. For example, even if the article did not specifically mention the word 'bias', the article gained marks if the description relating to the bias could be found. Any disagreements between the scorers were forwarded to the third member (SYL) who made the final decision.

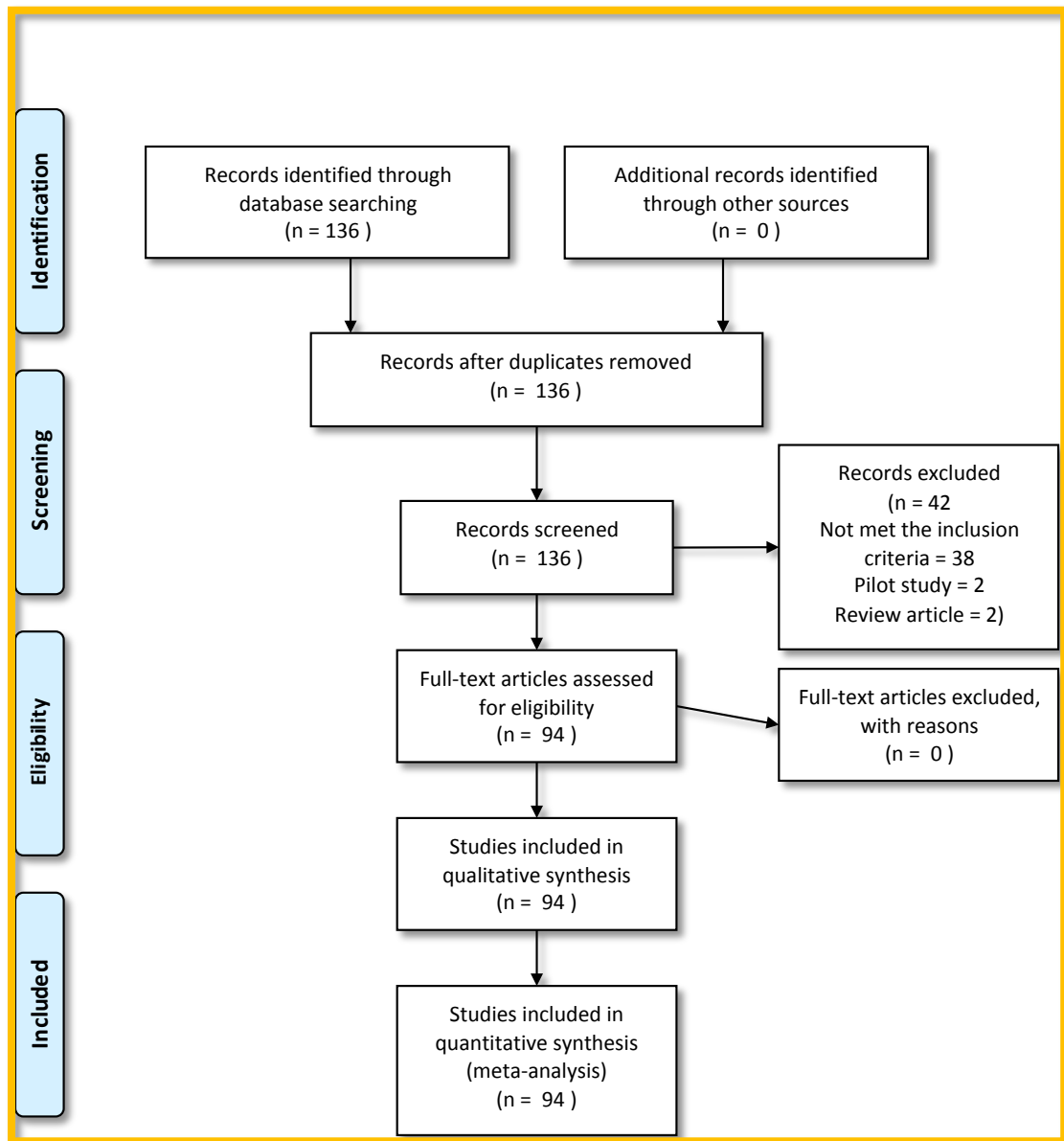
## **Statistical Analysis**

Descriptive statistics were calculated including the median and range for categorical variables. 95% confidence interval (CI) for the median was also calculated. The compliance of individual items with the statement was also calculated. Inter-observer correlation was determined using Cohen's Kappa score, a statistical measure of magnitude of agreement beyond that of chance alone.<sup>9</sup> All statistical analyses were performed using Microsoft Excel® 2011 (Microsoft, Redmond, WA, USA).

## 8.4 RESULTS

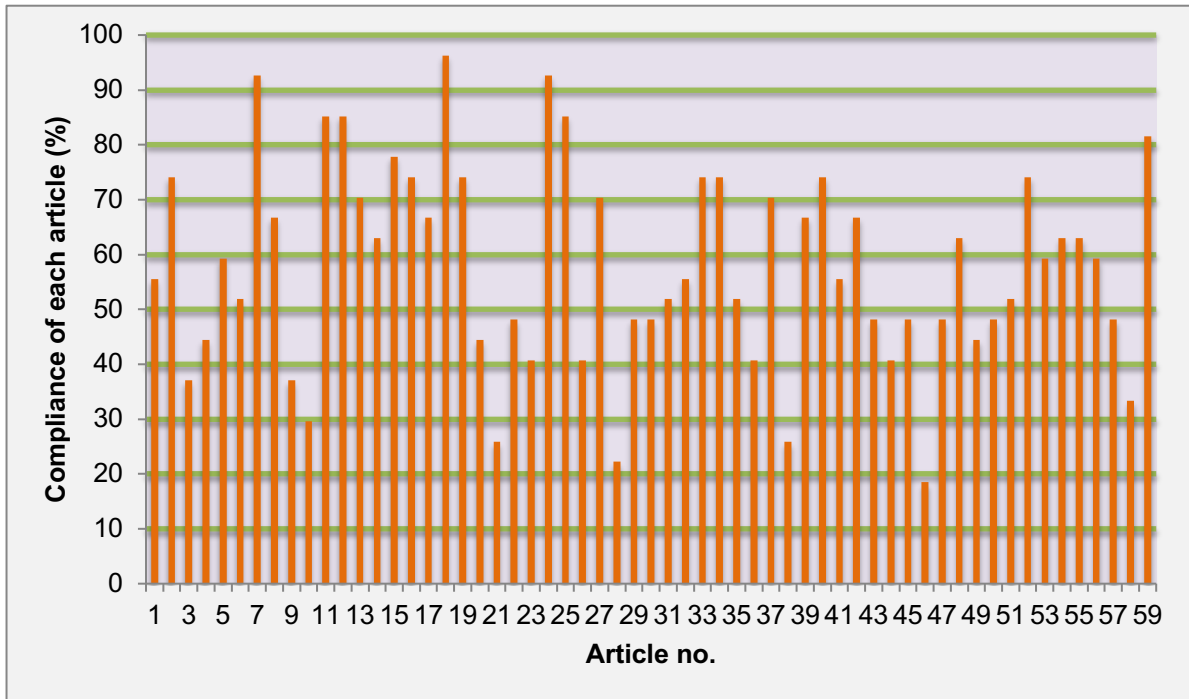
The electronic search identified in an initial set of 163 articles, of which 79 met the inclusion criteria (figure 8.1). A total of 1231 points were scored. Arbitration occurred regarding the inclusion of 22 articles. Disagreement occurred over 431 marking points across the 79 articles, while the Cohen's Kappa statistic was 0.60, indicating substantial agreement between scorers.

The median PRISMA score was 16 out of 27 items (59.3%; range 6-26, 95% CI 14-17). The compliance with each item in the checklist is shown in table 8.1 below, while figure 8.2 shows the number of articles according to their overall compliance to the PRISMA criteria.

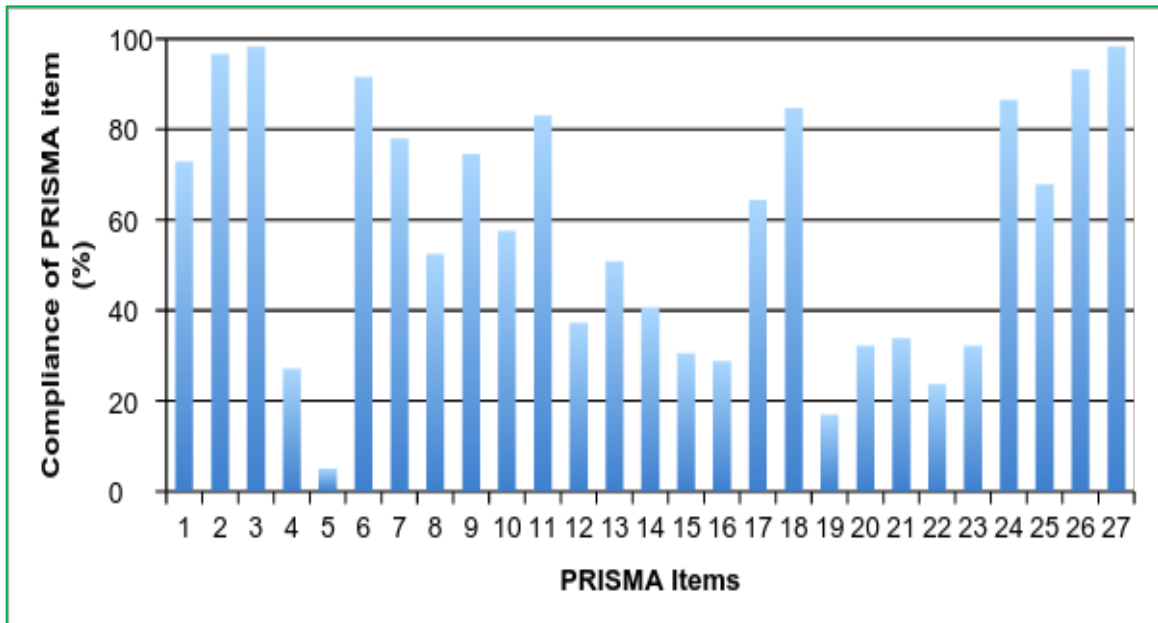


**Figure 8.1:** PRISMA flow diagram, illustrating how articles were selected

(adapted from Moher et al.<sup>9</sup>).



**Figure 8.2:** The percentage compliance of each article with the PRISMA statement.



**Figure 8.3:** The percentage compliance with each PRISMA item.

<b>TABLE 8.1. THE COMPLIANCE WITH PRISMA CHECKLIST ITEMS</b>			
(table adapted from PRISMA checklist, from Moher et al <sup>8</sup> ).			
<b>Section/Topic</b>	<b>No.</b>	<b>Brief description of the item</b>	<b>Compliance</b>
<b>TITLE</b>			
Title	1	Identification of the report	57 (72%)
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary	75 (95%)
<b>INTRODUCTION</b>			
Rationale Objectives	3	Background rationale	78 (99%)
Objectives	4	Description of PICOS (Participants, Interventions, Comparisons, and Study design)	26 (33%)
<b>METHODS</b>			
Protocol and registration Eligibility criteria Information sources Search	5	Indication of review protocol & registration information	4 (5%)
Eligibility criteria	6	Specification of study and review characteristics as eligibility criteria	72 (91%)
Information sources	7	Describe all information sources and date last searched.	63 (80%)
Search	8	Present repeatable full electronic search strategy for at least one database	41 (52%)
Study selection	9	State the process for selecting studies	62 (78%)
Data collection process	10	Describe method of data extraction	50 (63%)
Data items	11	Report all variables and any assumptions and simplifications made.	63 (80%)
Risk of bias in	12	Describe methods used for assessing risk of bias	30 (38%)

individual studies		of individual studies	
Summary measures	13	State the principal summary measures	41 (52%)
Synthesis of results	14	Describe the methods of handling and analysing data	32 (41%)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence	20 (25%)
Additional analyses	16	Describe methods of additional analyses	20 (25%)
<b>RESULTS</b>			
Study selection	17	Give numbers of studies at each stage of the study.	52 (66%)
Study characteristics	18	For each study, present characteristics for which data were extracted	64 (81%)
Risk of bias within studies	19	Present data on risk of bias of each study	14 (18%)
Results of individual studies	20	Report the summary of each data intervention group and estimates of confidence intervals.	29 (30%)
Synthesis of results	21	Present results of each meta-analysis	26 (33%)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies	19 (24%)
Additional analysis	23	Give results of additional analyses	24 (30%)
<b>DISCUSSION</b>			
Summary of evidence	24	Summarise the main findings including the strength of evidence	69 (87%)

Limitations	25	Discuss limitations at study and outcome and review-level	53 (67%)
Conclusions	26	Provide a general interpretation of the results	74 (94%)
<b>FUNDING</b>			
Funding	27	Describe sources of funding & other support	75 (95%)

Compliance between individual PRISMA items showed high variability. It was poorest for items related to the use of review protocol (item 5; 5%) and presentation of data on risk of bias of each study (item 19; 18%), while being the highest for description of rationale (item 3; 99%) and sources of funding and other support (item 27; 95%), and for structured summary in the abstract (item 2; 95%).

## 8.5 DISCUSSION

This study looked at 79 plastic surgery articles and found that none of these articles met all 27 criteria laid out in the PRISMA 2009 statement. Overall, there was a relatively low median score of 16 out of 27 (59.3%), which is lower than the previous studies that looked at adherence with the PRISMA checklist in other fields.<sup>3,10,11</sup>

Compliance between individual items showed high variability. Four items showed compliance over 90%, whereas 11 items had compliance below 40%. Items relating to the description of review protocol, additional analyses and risk of bias showed the lowest compliance (table 8.1).

The poor compliance in reporting of bias has been noted in the author's previous work looking at the reporting quality of randomized controlled trials and observational studies.<sup>4-</sup>

<sup>6</sup> Moreover, a review of 300 systematic reviews identified that just under a quarter (23.1%) of authors reported assessing possible publication bias.<sup>12</sup> It is important to note that this does not suggest poor design or conduct of the study itself; the PRISMA statement was not intentionally developed to improve the conduct of systematic reviews and meta-analyses, rather their reporting quality.<sup>13</sup> The marks were given solely based on the items reported in the article, so even if the study was thoroughly designed and conducted to avoid bias, marks were not awarded if these efforts were not described.

In addition, most of the articles involved in this study lost marks by lacking the additional details in the description relevant to each item. For example, many articles were not awarded marks for item 4 as they failed to refer to PICOS (Patient/Population, Intervention, Comparison and Outcome), but most of them stated the aim of the study.

This is very important because the purpose of publication is to provide clear, transparent information where all aspects of the work are available for interpretation and critical appraisal, and this study shows that many articles have been failing to do so.

Poor reporting in systematic reviews and meta-analyses prevents robust critical appraisal in these fields, from which resulting clinical judgments and policy making could be misguided and even potentially dangerous. There have been increasing calls for using an evidence-based medicine approach across all of medicine, and specifically within plastic surgery. It is hoped that the universal implementation of guidelines such as PRISMA should address suboptimal reporting by researchers.<sup>3,6</sup> The use of PRISMA as a guideline can benefit researchers not only by ensuring they report the essential research components, but also by helping to develop research questions as well as the structured summary and rationale for the study.<sup>14</sup>

The low level of PRISMA compliance has been recognized across other specialties as well. Gagnier et al assessed the PRISMA adherence of 76 systematic reviews and meta-analysis from five Orthopaedic journals with the highest impact factor.<sup>11</sup> The study showed the average PRISMA compliance of 68%, with the major deficiencies identified included the description of risk of bias across studies (9%), the analysis of risk of bias in the results section (37%) and the reporting of a protocol and registration (18%). Fleming et al assessed the PRISMA adherence of 109 systematic reviews published in 5 orthodontic journals between January 2000 and July 2011,<sup>10</sup> and demonstrated an overall compliance of 64.1%.

Key deficiencies included description of risk of bias across the studies (3%), methods used for assessing the risk of bias (26%), and the information of review protocol and registration number (27%). These overlap with the key deficiencies identified in this study, as well as with the deficiencies identified with other types of study design, such as RCTs and observational studies.<sup>4-6</sup> Especially the reporting of a protocol and registration information (item 5) showed very low compliance of 5% in this PRISMA study. This is perhaps due to the fact that systematic review registration is not yet widely recognised, however it is still important as a protocol provides better communication between authors and readers, and registration of the review helps to improve transparency of the review process.<sup>3,15</sup> The author suggests the use of a relevant registry such as PROSPERO<sup>15</sup> or the Research registry<sup>16</sup> to improve this point.

Enforcing the guideline at time of journal submission may lead to an improvement in quality of reporting and endorsement has been shown to improve adherence.<sup>13</sup> It has been recently demonstrated that there is an improvement in the endorsement of reporting guidance among journals in their guide to authors between 2011 and 2014 (10% vs. 19%).<sup>17</sup> The author suggests the use of the PRISMA checklist as a mandatory item during the electronic submission of systematic reviews and meta-analyses. It should go forward into the peer-review process along with the manuscript and be open to scrutiny by peer-reviewers and editors.

The checklist can be published as a supplementary item online, allowing for greater transparency and scrutiny by readers. Indeed, the higher rates of compliance amongst items for sources of funding (item 27, 95%) and structured summary in the abstract (item

2, 95%) may indicate that journals have addressed these issues at submission now through guides for authors and manuscript administrators.

## **8.6 STRENGTHS AND LIMITATIONS**

This study has several limitations. Using the results from five journals means that this study does not represent the full breadth of literature related to Plastic Surgery. The use of five journals with the highest impact factor in the specialty is expected to represent a broad cross section of plastic surgery research. Also, by restricting to articles published in 2013-2014, the review is cross-sectional in nature, which provides a snapshot of the literature, preventing us from commenting on trends in the quality of reporting systematic reviews over time. However, this study has its significance in evaluating the current state of the reporting quality of systematic reviews in plastic surgery.

An alternative would have been a search of MEDLINE and EMBASE databases looking for plastic surgery systematic reviews. As of March 2015, MEDLINE indexes more than 5,000 journals and more than 20 million citations, and EMBASE covers more than 29 million indexed records, so they should include a sufficient breadth of the plastic surgery literature<sup>18,19</sup> This would of course increase the complexity of the search strategy as here too articles could be missed and it may not always be easy to determine what is plastic surgery although the medical subject heading (MeSH); “Surgery; Plastic” would be a reasonable place to start.<sup>20</sup>

Database searching is not a perfect science and is known to be time consuming, tiring and can lead to disinterest.<sup>21</sup> An alternative approach would have been to electronically ‘hand

search' the journals i.e. going issue by issue on each journal's website as this may mean we would be less likely to miss an article due to a database search error or any minor inadequacy with the search strategy as was also discussed in the previous chapter.

Using two independent data extractors and a third to make decisions on scoring judgment, would likely reduce bias and increase the accuracy of scoring all papers meeting the inclusion criteria, again this doesn't mean that human error can't occur.

## **8.7 IMPLICATIONS FOR FUTURE RESEARCH**

Further study is required to assess any other potential barriers to compliance with PRISMA among key stakeholders in plastic surgery, i.e. authors, journal reviewers and editors, funders, institutions, and readers, while support is added to previous calls for the better education of plastic surgeons at all levels in evidence-based medicine. Further study assessing barriers with the compliance of the PRISMA statement is required.

This study could be repeated in the future to assess if things have improved. Methodological changes to be considered would include either electronic 'hand searching' a select number of journals, perhaps a larger cohort or searching under the MeSH heading "Surgery, Plastic" in the Medline database and consider a similar approach to searching other databases like Scopus, EMBASE, etc.

## 8.8 SUMMARY

The key findings of this chapter can be summarised as follows:

- ❖ The reporting quality of systematic reviews and meta-analyses in plastic surgery needs improvement.
- ❖ Four items showed compliance over 90%, whereas 11 items had compliance below 40%.
- ❖ Items relating to the description of review protocol, additional analyses and risk of bias showed the lowest compliance.
- ❖ ‘Hard-wiring’ of compliance through journal submission systems, as well as improved education, awareness and a cohesive strategy among all stakeholders is called for.

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# **CHAPTER 9**

## **SUPPORT FOR REPORTING GUIDELINES IN SURGICAL JOURNALS NEEDS IMPROVEMENT: A SYSTEMATIC REVIEW**



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A summary of the following chapter is published in the International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, contributing to writing and critically revising the manuscript in light of feedback. The author received assistance from medical students and junior doctors for data collection (IB, SR, SYL, MA and AJF) and was supervised by Professor Dennis Orgill. They were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 9.1 BACKGROUND

Medical knowledge is growing at a phenomenal rate, doubling every 3.5 years.<sup>1,2</sup> In an era of evidence-based medicine (EBM), health research can have a significant impact on the care of patients and potentially drive up quality and outcomes.<sup>3</sup> However, the reporting of health research can be poor, even where reporting guidelines exist.<sup>4,5,6,7,8,9</sup> Clinicians need complete, clear and transparent information to make sense of research and to integrate relevant findings into their EBM practice.

The same goes for policy makers setting agendas for future research or deciding where to allocate funds and for other researchers or those doing systematic reviews wanting to

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1. Agha RA, Barai I, Rajmohan S, Lee S, Anwar MO, Fowler AJ, Orgill DP and Altman DG. Support for reporting guidelines in surgical journals needs improvement: A systematic review. International Journal of Surgery 2017;45:14-17.

incorporate the research into their own work. Since the publication of the first CONSORT statement in 1996, there has been a huge increase in the publication of reporting guidelines.<sup>10</sup> The EQUATOR Network – an umbrella organization for developers of reporting guidelines – lists 319 in its database at the time of writing.<sup>11</sup> Prior work by the author, has demonstrated the deficiencies in reporting quality of Randomised controlled trials (RCTs) in Plastic Surgery<sup>12</sup> but also in other surgical specialties including Trauma<sup>13</sup>, urology, vascular, orthopaedic, hepatic, gastrointestinal and cardiovascular.<sup>14</sup>

The reporting of any study should be complete, clear and transparent. This is important for advancing the practice of medicine with whilst allowing for proper scrutiny and critical appraisal. Better reported studies are more easily incorporated during evidence synthesis for systematic reviews. Ultimately, such evidence is impacting everything from bedside treatment decisions to public policy – so it's important we get it right as a key part of improving quality and reducing waste in research.<sup>15</sup>

## **9.2 AIMS AND OBJECTIVES**

The objective of this study was to analyse the frequency and strength of recommendation for such reporting guidelines within surgical journals. Whilst there have been studies looking at the mention of individual guidelines like CONSORT, Preferred reporting items for systematic reviews and meta-analyses (PRISMA) or Standards for Reporting Diagnostic Accuracy (STARD), to the author's knowledge, this is the most comprehensive, assessing all available reporting guidelines within GFAs of surgical journals specifically.<sup>16,17,18</sup>

### 9.3 METHODS

The 198 surgical journals listed within the Surgery category of the Thomson Reuters Journal Citation Reports for 2014 were included.<sup>19</sup> The online GFA of each journal was searched by two groups independently (IB/MOA and SR/SL) in July-August 2015. Both teams had been given training on reporting guidelines in a small group as part of a two-hour session on research and critical appraisal. They were given detailed data extraction instructions by email with the lead author (RA) providing a worked example in the database. Two complete sets of results were then compared for discrepancies; any which could not be easily resolved were then referred to a more senior author (AJF). Inter-rater agreement between teams was calculated using Cohen's Kappa Statistic.<sup>20</sup> The following data were extracted:

- ❖ Strength of recommendation to use any reporting guidelines – split broadly into advised and required (the actual words used were documented).
- ❖ Which guidelines were mentioned. If only one to three guidelines were mentioned (e.g. only CONSORT compliance was mentioned) this would be classed as advising or requiring “some” guidelines, but if all relevant guidelines for the journals content were mentioned (typically CONSORT, STROBE, PRISMA, STARD as a minimum), then this would be “all relevant guidelines”
- ❖ Whether any extensions of a particular guideline were mentioned.

All data were extracted and populated into a Microsoft Excel® 2011 database (Microsoft, Redmond, WA, USA). No funding was received for this work.

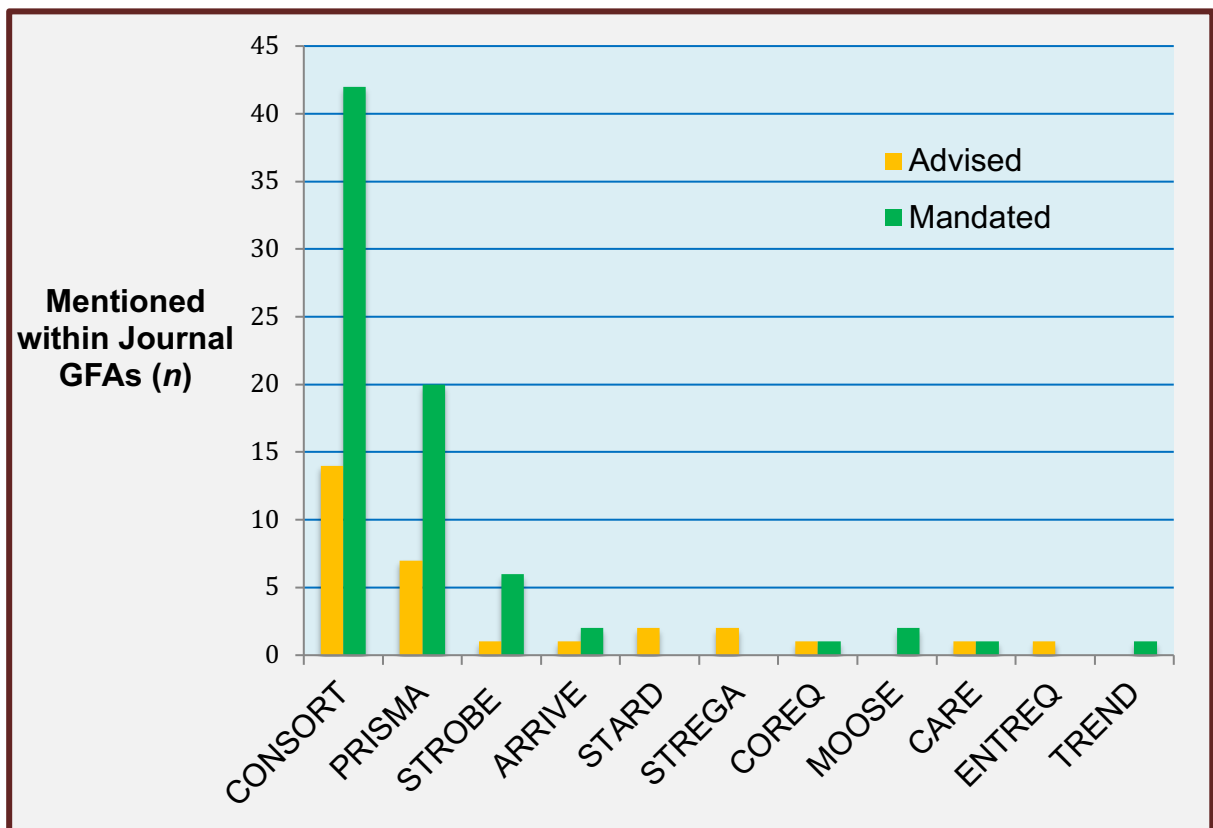
## 9.4 RESULTS

Of the 198 surgical journals included, five had changed their name and the list contained both the old and new names, hence there were 193 surgical journals in total. These had a median impact factor of 1.526 (range 0.047 to 8.327), with a median of 145 articles published per journal (range 29-659), with 34,036 articles published in total over the two-year period 2012-2013. The majority of journals (62.2%) did not mention reporting guidelines at all within their GFA. Cohen's *Kappa* was 0.67 when analysing whether guidelines were mentioned at all, implying moderate agreement. There was a mismatch in the data extracted on 71 of the 193 journals during the first phase of data extraction. Following discussion between the two independent teams, only 14 journals ultimately needed referral to a more senior author for adjudication.

Table 9.1 below looks at the journals who constitute the 37.8% (73/193) fraction, to assess the strength of the recommendation for adherence to reporting guidelines:

<b>TABLE 9.1. RECOMMENDATIONS RELATING TO REPORTING GUIDELINES WITHIN JOURNAL GFAS</b>	
<b>Instructions</b>	<b>Frequency % (n)</b>
Advised use of some guidelines	17.8% (13/73)
Required use of some guidelines	53.4% (39/73)
Advised some and mandated others	11.0% (8/73)
Advised use of all guidelines	4.1% (3/73)
Required use of all guidelines	13.7% (10/73)

Typical words used for those advising usage were “suggest”, “recommend”, and “encouraged”, whereas for those requiring their use typical words were “must” and “should”. Of the 73 journals advising or requiring use of reporting guidelines, 43.8% (32/73) required the submission of a completed guideline checklist and 11.0% (8/73) mentioned using extensions to at least one guideline. Figure 1 below shows the frequency with which different reporting guidelines were either advised or required. CONSORT is clearly the most frequently mentioned followed by PRISMA.



**Figure 9.1:** A bar chart showing the frequency with which various reporting guidelines are mentioned within journal GFAs.

No journal GFA stated that the authors should use all relevant reporting guidelines for their work and place a link to the Equator website where such guidelines are housed (<http://www.equator-network.org>).

## 9.5 DISCUSSION

The results show that the majority (62%) of surgical journals are not mentioning reporting guidelines with their guide for authors. Of the 38% who mention reporting guidelines only 14% actually require the use of all reporting guidelines relevant to their field and the types of articles they accept. Given that the majority of surgical research studies are observational by design, the author was surprised to note that only seven journals explicitly mentioned the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.<sup>21</sup> CONSORT and PRISMA were the most frequently mentioned which may reflect their earlier publication and better recognition amongst journals.

Whilst journals may mention reporting guidelines within their GFAs, the level of adherence to these and checking by editors and peer-reviewers will be variable between journals and within journals. Indeed, a recent systematic review assessing completeness of reporting in relation to the statement made within the GFA proved inconclusive.<sup>22</sup> An earlier Cochrane systematic review focusing on randomised controlled trials and CONSORT was conducted by Turner et al. It found that 25 of 27 outcomes assessing completeness of reporting favored CONSORT-endorsing journals over non-endorsers, of which five were statistically significant.<sup>23</sup>

Smidt et al showed that since the publication of the STARD statement, the quality of reporting of diagnostic studies improved slightly over time, more so in those journals adopting the STARD statement.<sup>17</sup> Cobo et al performed a masked randomised controlled trial assessing the effect of reporting guidelines on the peer-review process.<sup>24</sup> They compared conventional peer-review to conventional review with an additional review looking for missing items from reporting guidelines. They saw an improvement in manuscript quality in favour of the additional review group. In addition, more papers with the additional reviews improved from baseline (43% vs 20%) compared to the conventional review alone.<sup>24</sup>

The results are broadly consistent with previous studies of reporting guidelines in surgical journal GFAs. Kunath et al studied the endorsement of reporting guidelines amongst uro-nephrological journals indexed in the Journal Citation Reports 2009.<sup>25</sup> They found that 25.5% mentioned at least one reporting guideline (compared with 37.8% in this study), with CONSORT the most frequently cited. However, other reporting guidelines were mentioned by <6% of the journals, compared with 25% in this cohort (49/193). Smith et al analysed how endorsement of PRISMA and CONSORT reporting guidelines in 134 surgical journals in journal citation reports changed from 2011 to 2014.<sup>16</sup> They found an increase from 30% to 42% for CONSORT and from 10% to 19% for PRISMA. This sample had 25% for CONSORT and 14% for PRISMA. These more recent lower figures may represent the analysis of a larger cohort of 193 journals.

Publication is the final stage of research, and researchers have a duty to provide a complete, accurate and transparent account. When boiled down, Austin Bradford Hill's timeless questions, why did you start, what did you do, what did you find and what does it

mean, are still relevant today.<sup>26</sup> Reporting guidelines are a tool for authors, allowing them to develop the structure of their article, providing the details on what to include and helping them to realise the article's true potential.

## **9.6 STRENGTHS AND LIMITATIONS**

One of the key strengths of this research is the comprehensive analysis of all surgical journals listed in the surgery category for the Thomson Reuters impact factor index. This allows a 'birds-eye' across a wide range of surgical. Of course, there are newer journals not included in this index, but it does give a foundation for a reasonable analysis.

A limitation of this work is its cross-sectional nature and the degree to which authors read journal GFAs. In addition, there may be discordance between the number of guidelines mentioned, the strength of their recommendation and the true extent of the implementation of such guidelines in practice. Implementation in the published papers after all is what counts the most. In terms of the strength of the recommendation, we took the precise language used to be important. So was something "advised", "recommended" or did the journal say "must-comply with" or "is mandatory" in the GFA. However, the strength of the recommendation may not necessarily tally precisely with the degree of editorial and reviewer support for reporting guidelines in any particular journal. So, the correlation may not necessarily be direct when discussing the path to implementation in the final published paper.

## 9.7 IMPLICATIONS FOR FUTURE RESEARCH

The National Library of Medicine is now actively promoting the use of reporting guidelines and the International Committee of Medical Journal Editors (ICMJE) encourages all journals to monitor reporting standards and collect associated reporting guideline checklists in the process of submission.<sup>27,28</sup> It does seem reasonable and logical that a journal intent on raising the reporting quality of manuscripts it publishes, would include a strong and clear statement requiring their use within its GFA and front-load enforcement in the submission process rather than later on in peer-review.

If the guideline is included with the paper, it is then amenable to scrutiny by the peer-reviewers and editor. A before and after study of such a measure is indeed the subject of chapter 10. Indeed, many journals are taking such steps with the simultaneous publication of a position statement amongst 30+ rehabilitation journals and some surgical journals are taking robust positions too.<sup>29,30,31</sup> Future research to determine the prevalence and impact on reporting quality of journal GFA statements is required. It would be useful to repeat this study in five years to see how the situation has changed amongst surgical journals given the rising awareness of such issues.

## 9.8 SUMMARY

The key findings of this chapter can be summarised as follows

- ❖ The use of reporting guidelines within the guide for authors of major surgical journals needs improvement.
- ❖ Authors, reviewers and editors should work to ensure that research is reported in line with the relevant reporting guidelines.
- ❖ Adherence should be front-loaded and hard-wired within journal submission systems.
- ❖ This will allow peer-reviewers to focus on what's present, not what's missing, raising the level of scholarly discourse between authors and the scientific community and reducing frustration amongst readers.

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# **CHAPTER 10**

**IMPACT OF THE MANDATORY  
IMPLEMENTATION OF REPORTING  
GUIDELINES ON REPORTING  
QUALITY IN A SURGICAL JOURNAL:  
A BEFORE AND AFTER STUDY**



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A summary of the following chapter is published in the International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and critically revising it, in light of feedback. The author received assistance from eight medical students for data collection in two independent teams (AF, CL, KW, RC, HS, DJ, CC and BG). They were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months. Training on the project was provided at this meeting by presenting the project verbally and discussing any questions that arose (please also see section 10.7: implications for future research).

## 10.1 BACKGROUND

Journals are an important conduit for the publication of research. However, the reporting quality of research has been shown to be lacking. Previous studies of surgical randomised controlled trials (RCTs) have shown that approximately half of the mandatory items for inclusion were omitted and this was consistent when looking at ophthalmic surgery and plastic surgery.<sup>1-3</sup> Reporting quality has similarly been shown to be lacking in observational studies<sup>4</sup> and in systematic reviews in plastic surgery.<sup>5</sup> This deficiency has also been shown to exist in medical studies.<sup>6,7</sup>

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<sup>1</sup>. Agha R, Fowler A, Limb C, Whitehurst K, Coe R, Sagoo H, Jafree D, Chandrakumar C and Gundogan B. *Impact of the Mandatory Implementation of Reporting Guidelines on Reporting Quality in a Surgical Journal: A Before and After Study*. International Journal of Surgery 2016;30:169-72.

Poor reporting quality undermines proper critical appraisal of research. Readers need complete, clear and transparent information to assess research fully. Endorsing reporting guidelines is an important first step. A Cochrane systematic review showed some benefit to this, 25 outcomes improved with a Consolidated Standards of Reporting Trials (CONSORT) endorsement, with five being statistically significant.<sup>8</sup> However, the review concluded by saying that more robust mechanisms are needed to enhance compliance.

## **10.2 AIMS AND OBJECTIVES**

To determine if the reporting quality of observational studies, RCTs and systematic reviews could be improved, by mandating compliance with the relevant reporting guideline during the submission process to a single surgical journal.

## **10.3 METHODS**

The policy above was implemented in the International Journal of Surgery (IJS), in March 2013 (in practice the practical implementation took from March to August 2013). This involved asking all authors submitting observational studies, RCTs and systematic reviews to submit a completed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, CONSORT or a Preferred Reporting of Items of Systematic Reviews and Meta-Analyses (PRISMA) checklist respectively along with their paper, making it available to the editor and peer-reviewers.<sup>9-11</sup> Articles were analysed in three distinct periods, one before, one during transition and one after implementation of the policy:

Period 1(pre-implementation): July - Dec 2012

Period 2(peri-implementation): July – Dec 2013

Period 3(post-implementation): July - Dec 2014

During this period, article abstracts were assessed issue by issue at [www.journal-surgery.com](http://www.journal-surgery.com) to assess for eligibility. Where there was doubt, the full text of the article was downloaded. Observational studies were selected by two independent teams (KW/RC/CC and HS/CL/DJ) and populated to a pre-formatted Excel database. Each article was assigned a number and then scored according to the 22 items of the STROBE Statement by two teams acting independently (and a similar process for CONSORT and PRISMA). Each item was given a single mark. Where an item was subdivided into three or four parts, then each part was given the appropriate weighting i.e. 0.33 and 0.25 respectively. Where items were not applicable, they were extracted from the denominator to ensure the overall score was a fair reflection of compliance.

Both article eligibility and scoring disagreements were referred to author AJF for dispute resolution if they could not be resolved by discussion beforehand between the two teams. The periods pre and post implementation were compared to assess for any statistically significant difference using either a t-test or the appropriate non-parametric test depending on the distribution of the data. Cohens kappa was calculated to determine inter-rater reliability.

## 10.4 RESULTS

Results for each guideline are given in turn below. Following initial marking, it was noted that there was very poor concordance between teams (Cohens Kappa = 0.45), and so all papers were re-marked by AJF. All points were then discussed between AJF and a member of the original marking team until agreement was reached on a final score.

### STROBE

The number of articles in each period and median compliance with the STROBE Statement is shown below in table 10.1:

<b>TABLE 10.1. NUMBER OF STUDIES, MEDIAN AND RANGE OF COMPLIANCE WITH STROBE STATEMENT PER PERIOD ASSESSED.</b>			
<b>Period</b>	<b>Number of Observational Studies</b>	<b>Median Compliance</b>	<b>Range of compliance</b>
1	25	68.4%	44% - 88%
2	77	67.2%	46% - 84%
3	50	76.5%	54% - 97%
<b>Increase from period 1 to 3 = 13%</b>			

The 13% increase in STROBE compliance from period 1 to 3 was statistically significant as shown by the two-sample homoscedastic t-test comparing period 1 and 3 ( $p=0.00018$ ). This test was performed after performing a normality test (mean absolute deviation to standard deviation ratio) and confirming a Gaussian distribution. The items which improved are listed below (table 10.2):

**TABLE 10.2. TOP FIVE IMPROVED ITEMS IN STROBE CHECKLIST**

Item	Description	Percentage increase in compliance
12e	Statistical Methods - describe any sensitivity analyses	300%
6	Participants - for matched studies, give matching criteria and number of exposed and unexposed	103%
3	Bias - Describe any efforts to address potential sources of bias	83%
14c	Descriptive data - Cohort study—summarise follow-up time (e.g., average and total amount)	81%
11	Quantitative variables - Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	77%

## CONSORT

There were no RCTs found in period 1 (table 10.3) and the most improved items from the CONSORT checklist are shown in table 10.4:

**TABLE 10.3. NUMBER OF RCTS, MEDIAN AND RANGE OF COMPLIANCE WITH CONSORT STATEMENT PER PERIOD ASSESSED**

Period	Number of RCTs	Median Compliance	Range of compliance
1	0	N/a	N/a
2	3	50%	36-50%
3	10	70%	54-82%
<b>Percentage increase from period 2 to 3 = 40%</b>			

**TABLE 10.4. TOP FIVE IMPROVED ITEMS IN CONSORT CHECKLIST**

Item	Description	Percentage increase in compliance
8a	Sequence generation - method used to generate the random allocation sequence	200%
16	Numbers analysed - for each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	170%
13b	Participant flow - for each group, losses and exclusions after randomisation, together with reasons	140%
11a	Blinding - If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	140%
9	Allocation concealment - mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	65%

## PRISMA

PRISMA compliance results for systematic review and meta-analyses are shown in table 10.5 below with the top five improved items shown in table 10.6:

**TABLE 10.5. NUMBER OF STUDIES, MEDIAN AND RANGE OF COMPLIANCE WITH PRISMA STATEMENT PER PERIOD ASSESSED**

Period	Number of Systematic Reviews	Median Compliance	Range of compliance
1	4	48%	15%-78%
2	10	72%	63%-89%
3	14	76%	48%-96%
<b>Percentage increase from period 1 to 3 = 58%</b>			

<b>TABLE 10.6. TOP FIVE IMPROVED ITEMS IN PRISMA CHECKLIST</b>		
<b>Item</b>	<b>Description</b>	<b>Percentage increase in compliance</b>
20	Results of individual studies - for all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	243%
21	Synthesis of results - present results of each meta-analysis done, including confidence intervals and measures of consistency.	157%
23	Additional analysis - give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression)	157%
14	Synthesis of results - describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	157%
12	Risk of bias in individual studies - describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	129%

## 10.5 DISCUSSION

The results show that overall guideline compliance following implementation of the policy increased for observational studies by 13% (68% to 77%,  $p=0.00018$ ), for RCTs by 40% (50%-70%) as well as for systematic reviews by 58% (48%-76%). The items that improved the most were those providing greater details on study design, outcome definitions and measurement, how quantitative variables were handled during the analyses and discussing limitations and detailing potential sources of bias. The results also show that there is some time needed for adjustment of a journal's processes, editors and peer-reviewers to these changes, and hence no significant change was evident during the peri-implementation period (period 2).

An estimated US\$240 billion is spent annually on health research worldwide.<sup>12</sup> More than 15 million researchers authored over 25 million scientific papers between 1996 and 2011.<sup>13</sup> This enormous investment necessitates a focus on quality and transparency. Unfortunately, it is also estimated that 85% of research resources are wasted.<sup>12</sup> In recent times, transparency has become a major part of the healthcare research discourse. The principle of 'exposing problems to the sun' is a good one – open access, open science, open data and reporting guidelines have all been born from this rubric. Complete, clear and transparent reports aid critical appraisal and reproducibility, essential if other surgeons are to take on board a change to their clinical practice.

Poor reporting remains a fundamental problem within healthcare research.<sup>7</sup> The focus on solutions to these longstanding problems is important. Researchers, funders, editors, peer-reviewers and readers must recognise this problem and advocate robust and sustainable ways of enhancing reporting quality. Some journals do recommend adherence with

reporting guidelines in their guide for authors (GFA). However, the author's own research in this area, has shown that 62% of the 198 surgical journals within the Journal Citation Report 2014 made no mention of reporting guidelines within their GFA (see chapter 9).<sup>14</sup> Only 5% mandated one or more reporting guidelines, most commonly the Consolidated Standards of Reporting Trials (CONSORT) for randomised controlled trials (RCTs).<sup>14</sup>

Despite recognition and updating of their GFA, author compliance is not guaranteed. Indeed, a recent systematic review assessing completeness of reporting in relation to the statement made within the GFA proved inconclusive.<sup>15</sup> Smidt et al showed that since the publication of the STARD statement, the quality of reporting of diagnostic studies improved slightly over time, more so in those journals adopted the STARD statement.<sup>16</sup> Cobo et al performed a masked randomised controlled trial (RCT) assessing the effect of reporting guidelines on the peer-review process.<sup>17</sup> They compared conventional peer-review to conventional review with an additional review looking for missing items from reporting guidelines. They saw an improvement in manuscript quality in favor of the additional review group. In addition, more papers with the additional reviews improved from baseline compared to the conventional review alone (43% vs 20%).

More robust mechanisms are needed and this is where mandating the submission of a completed reporting guideline checklist can be useful. Authors need to identify the page number upon which they have fulfilled each criterion and editors and peer-reviewers can cross-check their compliance. The results show the utility of this measure.

## 10.6 STRENGTHS AND LIMITATIONS

A limitation of this work is that, there was no one specifically assigned to rigorously check compliance with the checklist. This was due to time constraints within the journal editorial process and concerns over such a measure's sustainability in the long term. This is reflected within the results, with compliance rising to 76.5% rather than 100%. The implementation was a pragmatic rather than being rigid and creating inertia, becoming resource intensive and costly. It is worth noting that once the checklist is submitted with the article, it stays with it through its journey i.e. it is included in the combined portable format document (PDF). This PDF is what is sent to editors and peer-reviewers, so they too can scrutinise the checklist against the manuscript. This process as well necessitates education and guidelines amongst the reviewers and editors. The standard reviewer guidance does include a point about whether any relevant reporting guidelines have been complied with, although again, this could be ignored, just like journal GFAs.

The low number of articles (13) in the RCT group is a limitation and there were none in the first period at all. This makes the analysis for RCTs more difficult. Whilst there is a trend for improvement, one would exercise caution in the interpretation given low numbers mean bias is likely to play a bigger role. Further study of RCTs over longer periods would be useful to 'shine more light' on them. A further limitation is the initial discrepancies of marking, which required re-marking. As a result, the author has implemented training for future research projects to ensure all researchers are up to a standardised level. Finally, over the period 2011-13, the IJS had a change in impact factor as follows:

2011 – 1.293

2012 – 1.436

2013 – 1.650

The impact factors are published in June of the subsequent year, therefore they fall into the published period 2012-14. Whilst the rise in impact factor could lead to better reported studies being submitted, the author has previously shown no link between reporting quality and impact factor, so this link isn't well supported.<sup>1,3</sup> The use of the Journal Impact Factors as a tool by which to assess a journal's quality is not without significant and longstanding criticism.<sup>18</sup> For instance, lack of normalisation makes comparisons difficult between fields, their potential for manipulation, the length of the citation window, what is deemed a citable item and the fact that they don't necessarily relate to actual usage or social discussion of an article.<sup>18</sup> Impact factors of course are a form of journal-level metric. Article level metrics are increasingly important since a highly cited article could be published in a journal with a relatively low impact factor.<sup>18</sup>

## **10.7 IMPLICATIONS FOR FURTHER RESEARCH**

It is hoped that compliance would continue to rise as these processes bed down further within the journal's workflow, and this could be an area for further investigation. How will compliance be in subsequent years? What is the trend like? Does it plateau and if so at what point? What is needed to gain further improvements? It would also be reasonable, given the large range of study types published, to assess the impact of the policy on other study types as well.

A key learning point for the author on this project, has been around how to better train and support medical students getting involved in such research. The use of verbal face to face communication at an introductory meeting is helpful. It stimulates engagement and allows

for rapid discussion and responses from the author. However, detailed written instructions and a frequently asked questions (FAQs) document should also be developed as reference and support material (see chapter 14 for further discussion of this point under section 14.3: what are the implications for future research).

## **10.8 SUMMARY**

The key findings of this chapter can be summarised as follows:

- ❖ Implementing a policy mandating the submission of a completed STROBE, CONSORT and PRISMA checklist for the relevant article types, can increase compliance with these guidelines.
- ❖ Median compliance with STROBE increased by 12% (n=152), with CONSORT by 40% (n=13) and with PRISMA by 58% (n=28).
- ❖ The author advocates this measure for other journals and for other study types.

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# **CHAPTER 11**

## **DEVELOPMENT OF THE SCARE GUIDELINE FOR REPORTING SURGICAL CASE REPORTS**



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A summary of the following chapter has been published in International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback. The author had assistance from medical students/junior doctors (AJF, AS, IB and SR) in data acquisition and was supervised by Professor Dennis Orgill. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 11.1 BACKGROUND

Case reports have been popular within the medical literature since the time of Hippocrates.<sup>1</sup> With the rise of evidence-based medicine (EBM) and their designation as level five evidence their importance has decreased as focus has shifted to higher levels of evidence, such as randomised controlled trials (RCTs). Such studies minimize the bias that's inherent in looking at a single patient or even a series of them, and are hence able to answer research questions with less inherent bias and more reliably – if conducted well. Some even feared their extinction due to low citation rates, negative effects on journal impact factor and restricted page budgets.<sup>2,3</sup> As a result, many journals stopped publishing

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<sup>1</sup>. Agha RA, Fowler AJ, Saetta A, Barai I, Rajmohan S, Orgill DP and the SCARE Group. *The SCARE Guideline: Consensus-based surgical case report guidelines*. International Journal of Surgery 2016;34:180-186.

case reports altogether.<sup>2,4</sup>

The rise of open access and electronic publishing has revived the humble case report, with the launch of new journals dedicated to publishing them.<sup>4</sup> In 2015, International Journal of Surgery (IJS) Case Reports ([www.casereports.com](http://www.casereports.com)) became the largest publisher of surgical case reports globally according to Scopus® ([www.scopus.com](http://www.scopus.com)).

Vandenbrouke has discussed the contribution of case reports to medical progress: *“they permit discovery of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine.”*<sup>5</sup>

Case reports have specific relevance within the surgical literature. The IDEAL recommendations call for structured case reports for reporting a “first-in-man” study – i.e. the first time a new surgical technique is used, in stage 1 of their framework.<sup>6,7</sup> This has been exemplified in recent times by case reports of facial transplantation and other innovative techniques.<sup>8</sup>

The Case Report or CARE Guidelines were developed in 2013 to provide a framework that supports transparency and accuracy in the publication of case reports and the reporting of information from patient encounters.<sup>9</sup> They have been adopted by multiple journals and compliance with them has been mandatory at IJS Case Reports. However, they are not tailored to surgery. In this author’s experience, the corollary is that peer-

reviewers often focus on what's missing, rather than what's actually present within the manuscript. The experience of over 3,000 case reports informs us that surgical case reports have specific reporting needs that need to be recognised in an adapted reporting guideline based on CARE. The objective of this research is to conduct a Delphi consensus exercise amongst experienced case report reviewers and editors to develop the Surgical CAse REport (SCARE) Guidelines.

## 11.2 METHODS - DEVELOPING THE SCARE GUIDELINE

A research protocol was published *a priori*.<sup>10</sup> In summary, the existing CARE guidelines were used as a starting point, together with a DELPHI consensus exercise approach using Moher et al's guidance on developing reporting guidelines.<sup>11</sup> A survey was issued using Google Forms (<https://www.google.co.uk/forms/about>). This asked participants in round one, how each item of the CARE guidelines should be changed, as well as an opportunity to provide free text feedback for any issues that were not addressed. Following analysis of this information from round 1, the 13 items of the CARE guidelines were adjusted as indicated by the participants.

In a subsequent round, participants were first informed of the results of the first round by email correspondence and the complete set of results on Google Forms. They were then asked to rate their level of agreement with the revised items and any additional items that were suggested using a nine-point Likert scale and methodology as proposed by the GRADE group.<sup>12,13</sup> In this scale, 1 to 3 signifies an outcome of limited importance, 4 to 6 important but not critical and 7 to 9 critical. If 70% or more of respondents scored an item 7 to 9 and fewer than 15% scored it 1 to 3, then that item proceeded into the reporting

guideline.<sup>12</sup> Similarly, consensus that an outcome should not be included was 70% or more scoring it 1 to 3 and 15% or less scoring it 7 to 9. The entire process was conducted electronically and there were no pre-determined number of Delphi rounds.

### **11.3 PARTICIPANT SELECTION**

Surgeons and others with significant experience in reviewing or editing case reports were selected. They were drawn from the reviewer pool of IJS Case Reports (the top 150 by number of reviews performed in the database of reviewers were invited) as well as those who have written on the topic of case reports or case series in the past or specific individuals who were recommended by Professor Doug Altman, who pioneered the CONSORT guideline.

## 11.4 RESULTS

In total, 59 participants agreed to the invitation to participate in this study, representing 21 countries. and all ten surgical specialties as well as allied specialties including; dermatology, pathology, oncology, clinical pharmacology, acute care surgery, with many participants also occupying positions on journal editorial boards.<sup>14</sup> This is summarised in the table 11.1 below:

<b>Table 11.1. CHARACTERISTICS OF STUDY PARTICIPANTS</b>	
<b>(It should be noted, that where a single individual has multiple specialty interests/expertise, it has been shown on its own line as a standalone combination)</b>	
<b>Specialties (<i>n</i>)</b>	<b>Geographic Distribution (<i>n</i>)</b>
<b>(alphabetical order)</b>	<b>(alphabetical order)</b>
1. Acute Care Surgery (1)	❖ Argentina (1)
2. Breast Surgery (2)	❖ Australia (1)
3. Breast Surgery/Plastic Surgery/Vascular Surgery (1)	❖ Barbados (1)
4. Cardiac Surgery (1)	❖ Brazil (1)
5. Cardiothoracic Surgery (1)	❖ Canada (3)
6. Chiropractor (1)	❖ China (1)
7. Clinical Pharmacology (1)	❖ Egypt (1)
8. Clinical Pharmacology/Dermatology/Internal Medicine (1)	❖ Germany (3)
9. Colorectal Surgery (3)	❖ India (7)
10. Colorectal Surgery/Hepatopancreaticobiliary (HPB) Surgery/Upper GI Surgery (1)	❖ Iran (1)
	❖ Ireland (1)
	❖ Israel (1)
	❖ Italy (3)
	❖ Japan (1)

11. Dentistry (3)	❖ Malaysia (1)
12. Dermatology (2)	❖ Pakistan (2)
13. Emergency Medicine (1)	❖ Saudi Arabia (1)
14. Former editor of a major journal (1)	❖ Singapore (1)
15. General Surgery (11)	❖ Turkey (1)
16. Head and Neck Surgical Oncology (1)	❖ United Kingdom (15)
17. HPB (3)	❖ USA (12)
18. Neurosurgery (1)	
19. Oncology (1)	
20. Orthopaedic Surgery (3)	
21. Otolaryngology (1)	
22. Paediatric Surgery (2)	
23. Pathology (1)	
24. Plastic Surgery (3)	
25. Transplant Surgery/Urology (1)	
26. Upper GI (3)	
27. Upper GI/Colorectal Surgery (1)	
28. Upper GI/Transplant (1)	
29. Urology (5)	
30. Vascular (1)	

A pilot study was done prior to round 1 to check the participants understanding of the questions. This involved 15/59 (25%) participants completing the survey prior to it going out to the remainder of the group. The only change made following this, was to include a field for name, so that the author could see who has actually completed the survey and therefore who needed to be reminded. There was no evidence of misinterpretation or confusion with the survey. In round 1, there was a 64% (38/59) response rate. The consensus view together with participant responses are integrated into table 11.2 below.

<b>TABLE 11.2. CARE GUIDELINES AND ROUND 1 RESPONSES</b>			
<b>Topic</b>	<b>Item</b>	<b>Checklist item description</b>	<b>Responses (<i>n</i>=38)</b>
<b>Title</b>	<b>1</b>	The words “case report” should be in the title	No Change 92% (35/38)
<b>Key Words</b>	<b>2</b>	2 to 5 key words that identify areas	No Change 87% (33/38)
<b>Abstract</b>	<b>3a</b>	Introduction—What is unique about this case? What does it add to the medical literature?	No Change 92% (35/38)
	<b>3b</b>	The main symptoms of the patient and the important clinical findings	
	<b>3c</b>	The main diagnoses, therapeutics interventions, and outcomes	
	<b>3d</b>	Conclusion—What are the main “take-away” lessons from this case?	
<b>Introduction</b>	<b>4</b>	One or two paragraphs summarizing why this case is unique or educational with references	No Change 89% (34/38)
<b>Patient Information</b>	<b>5a</b>	De-identified demographic information and other patient specific information	No major change 92% (35/38) but specifically add patient age, gender, ethnicity, occupation and hand dominance if relevant. Add drug history.
	<b>5b</b>	Main concerns and symptoms of the patient	
	<b>5c</b>	Medical, family, and psychosocial history including relevant genetic information (also see timeline)	
	<b>5d</b>	Relevant past interventions and their outcomes	
<b>Clinical Findings</b>	<b>6</b>	Describe the relevant physical examination (PE) and other significant clinical findings	No Change 89% (34/38)
<b>Timeline</b>	<b>7</b>	Important information from the patient’s history organized as a timeline	No Change 79% (30/38) “No need for timeline” “delay from presentation to surgery should be reported”
<b>Diagnostic</b>	<b>8a</b>	Diagnostic methods (such as PE,	No Change 89% (34/38)

<b>Assessment</b>		laboratory testing, imaging, surveys)	Spell out “PE” (i.e. physical exam). Add histopathology and radiological images.
	<b>8b</b>	Diagnostic challenges (such as access, financial, or cultural)	
	<b>8c</b>	Diagnostic reasoning including other diagnoses considered	
	<b>8d</b>	Prognostic characteristics (such as staging in oncology) where applicable	
<b>Therapeutic Intervention</b>	<b>9a</b>	Types of intervention (such as pharmacologic, surgical, preventive, self-care)	Changes 53% (20/38) “What time periods” “Postoperative surgical stay.”
	<b>9b</b>	Administration of intervention (such as dosage, strength, duration)	“Need to stress patient reported outcome measures” “Describe concurrent treatments (antibiotics, analgesics, nil-per-os, etc.)”
	<b>9c</b>	Changes in intervention (with rationale)	“What was done, when it was done, and how it was done. Focus on the decision making process in case of intervention” “Surgical technique and used materials” “1. particular surgical tools or need for equipment 2. the level of difficulty of the surgery. 3. anticipated learning curve. 4. similarity to other procedures (may be too obvious to be worth mentioning). 5. For e.g. (cutaneous) laser surgery dosing, i.e. number of treatments and settings of the laser, information that informs the setting e.g. skin type. 6. anticipated complications and

			<p>caution.</p> <p>7. backup teams, can it be done ambulatory?</p> <p>8. information about post surgery care, post-surgery disability, specialty needs, and special wound care needs facilitate replication”</p> <p>“Types of intervention (non-operative, operative, minimally invasive, endovascular, endoscopic, preventive)”</p> <p>“Why was that specific operation chosen? Is it an innovative operation? (Explain rationale and peculiar technical aspects). Are new devices used? (Describe them). Were there any unexpected outcomes?(Unpredicted histology, very rare intraoperative surgical complications).”</p>
<b>Follow-up and Outcomes</b>	<b>10a</b>	Clinician and patient-assessed outcomes (when appropriate)	<p>Changes 71% (27/38)</p> <p>“Future surveillance requirements - e.g. EVAR”</p> <p>“Some items like blood loss, operative time, wound complications, re-exploration/revision surgery, 30-day post-op morbidity may need to be specified.”</p> <p>“How were complications prevented, diagnosed and managed.”</p>
	<b>10b</b>	Important follow-up diagnostic and other test results	
	<b>10c</b>	Intervention adherence and tolerability (How was this assessed?)	
	<b>10d</b>	Adverse and unanticipated events	

<b>Discussion</b>	<b>11a</b>	Discussion of the strengths and limitations in your approach to this case	No change 87% (33/38) “Contraindications for the procedure” “Any new hypothesis generating findings?” “Potential patient risk and possible complication if new description of surgical technique or implant.”
	<b>11b</b>	Discussion of the relevant medical literature	
	<b>11c</b>	The rationale for conclusions (including assessment of possible causes)	
	<b>11d</b>	The primary “take-away” lessons of this case report	
<b>Patient Perspective</b>	<b>12</b>	When appropriate the patient should share their perspective on the treatments they received	No change 89% (34/38)
<b>Informed Consent</b>	<b>13</b>	Did the patient give informed consent? Please provide if requested	No change 97% (37/38)
<b>Additional items</b>		Acknowledgement section; competing interests; ethics committee or institutional review board approval where appropriate. The setting in which the case was done: academic, community or private practice setting? Limitations of the case report Patient optimization pre-op Any radiological figures or pathological sections, intraoperative findings photos, endoscopic images.	Changes 47% (18/38) but no specific comments given.

The guideline was adjusted with incorporation of recommended changes. Round 2 commenced after all 59 participants in the study were provided feedback on the results of round 1, via email correspondence and summary results shown on Google Forms to which participants were provided a hyperlink. There was an 83% (49/59) response rate in round 2. All items were approved by the participants with Likert scores 7-9 awarded by >70% of respondents, apart from item 12 – which had 63% (table 11.3). Given that this is in the

original guideline and is optional i.e. “*when appropriate*”, it has carried over to the SCARE guideline.

<b>TABLE 11.3. DELPHI ROUND 2 RESPONSES – ITEMS INCLUDED HERE CONSTITUTE THE FINAL SCARE GUIDELINE</b>			
<b>Topic</b>	<b>Item</b>	<b>Checklist item description</b>	<b><i>n</i>=49, Scores 7-9</b>
<b>Title</b>	<b>1</b>	The words “case report” and the area of focus should appear in the title (e.g. presentation, diagnosis, surgical	94% (46/49)
<b>Key Words</b>	<b>2</b>	3 to 6 key words that identify areas covered in this case report (include "case report" as one of	78% (38/49)
<b>Abstract</b>	<b>3a</b>	Introduction—What is unique or educational about the case? What does it add to the surgical literature? Why is this important?	98% (48/49)
	<b>3b</b>	The patient's main concerns and important clinical findings.	
	<b>3c</b>	The main diagnoses, therapeutics interventions, and outcomes.	
	<b>3d</b>	Conclusion — what are the “take-away” lessons from this case?	
<b>Introduction</b>	<b>4</b>	A summary of why this case is unique or educational with reference to the relevant surgical literature and current standard of care (with references, 1-2 paragraphs). Nature of the institution in which the patient was managed; academic, community or private practice setting?	88% (43/49)
<b>Patient Information</b>	<b>5a</b>	De-identified demographic and other patient specific information including age, sex,	90% (44/49)

		ethnicity, occupation and other useful pertinent information e.g. BMI and hand dominance.	
	<b>5b</b>	Presentation including presenting complaint and symptoms of the patient as well as the mode of presentation e.g. brought in by ambulance or walked into Emergency room or referred by family physician.	
	<b>5c</b>	Past medical and surgical history and relevant outcomes from interventions	
	<b>5d</b>	Drug history, family history including any relevant genetic information, and psychosocial history including smoking status and where relevant accommodation type, walking aids, etc.	
<b>Clinical Findings</b>	<b>6</b>	Describe the relevant physical examination and other significant clinical findings (include clinical photographs where relevant and where consent has been given).	98% (48/49)
<b>Timeline</b>	<b>7</b>	Inclusion of data which allows readers to establish the sequence and order of events in the patient's history and presentation (using a table or figure if this helps). Delay from presentation to intervention should be reported.	90% (44/49)
<b>Diagnostic Assessment</b>	<b>8a</b>	Diagnostic methods (physical exam, laboratory testing, radiological imaging, histopathology etc).	94% (46/49)
	<b>8b</b>	Diagnostic challenges (access, financial, cultural).	
	<b>8c</b>	Diagnostic reasoning including other diagnoses considered	
	<b>8d</b>	Prognostic characteristics when applicable (e.g. tumour staging). Include relevant radiological or	

		histopathological images in this section (the latter may sometimes be better placed in section 9).	
<b>Therapeutic Intervention</b>	<b>9a</b>	Pre-intervention considerations e.g. Patient optimisation: measures taken prior to surgery or other intervention e.g. treating hypothermia/hypovolaemia/hypotension in a burns patient, ICU care for sepsis, dealing with anticoagulation/other medications, etc	92% (45/49)
	<b>9b</b>	Types of intervention(s) deployed and reasoning behind treatment offered (pharmacologic, surgical, physiotherapy, psychological, preventive) and concurrent treatments (antibiotics, analgesia, anti-emetics, nil by mouth, VTE prophylaxis, etc). Medical devices should have manufacturer and model specifically mentioned.	
	<b>9c</b>	Peri-intervention considerations - administration of intervention (what, where, when and how was it done, including for surgery; anaesthesia, patient position, use of tourniquet and other relevant equipment, prep used, sutures, devices, surgical stage (1 or 2 stage, etc). Pharmacological therapies should include formulation, dosage, strength, route, duration, etc).	
	<b>9d</b>	Who performed the procedure - operator experience (position on the learning curve for the technique if established, specialisation and prior relevant training).	
	<b>9e</b>	Any changes in the interventions with rationale. Include intra-operative photographs and/or video or relevant histopathology in this section. Degree of novelty for a surgical technique/device should be mentioned e.g. "first in-human".	
	<b>9f</b>	Post-intervention considerations e.g. post-operative	

		instructions and place of care.	
<b>Follow-up and Outcomes</b>	<b>10a</b>	Clinician assessed and patient-reported outcomes (when appropriate) should be stated with inclusion of the time periods at which assessed. Relevant photographs/radiological images should be provided e.g. 12 month follow-up.	94% (46/49)
	<b>10b</b>	Important follow-up measures - diagnostic and other test results. Future surveillance requirements - e.g. imaging surveillance of endovascular aneurysm repair (EVAR) or clinical exam/ultrasound of regional lymph nodes for skin cancer.	
	<b>10c</b>	Where relevant - intervention adherence and tolerability (how was this assessed).	
	<b>10d</b>	Complications and adverse or unanticipated events. Described in detail and ideally categorised in accordance with the Clavien-Dindo Classification. How they were prevented, diagnosed and managed. Blood loss, operative time, wound complications, re-exploration/revision surgery, 30-day post-op and long-term morbidity/mortality may need to be specified.	
<b>Discussion</b>	<b>11a</b>	Strengths, weaknesses and limitations in your approach to this case. For new techniques or implants - contraindications and alternatives, potential risks and possible complications if applied to a larger population. If relevant, has the case been reported to the relevant national agency or pharmaceutical company (e.g. an adverse reaction to a device).	98% (48/49)
	<b>11b</b>	Discussion of the relevant literature, implications for clinical practice guidelines and any relevant hypothesis generation.	
	<b>11c</b>	The rationale for your conclusions.	

	<b>11d</b>	The primary “take-away” lessons from this case report.	
<b>Patient Perspective</b>	<b>12</b>	When appropriate the patient should share their perspective on the treatments they received.	63% (31/49)
<b>Informed Consent</b>	<b>13</b>	Did the patient give informed consent for publication? Please provide if requested by the journal/editor. If not given by the patient, explain why e.g. death of patient and consent provided by next of kin or if patient/family untraceable then document efforts to trace them and who within the hospital is acting as a guarantor of the case report.	80% (39/49)
<b>Additional Information</b>	<b>14</b>	Conflicts of Interest, sources of funding, institutional review board or ethical committee approval where required/appropriate.	84% (41/49)

## 11.5 THE SCARE GUIDELINE

Table 11.3 constitutes the SCARE guideline, and this is provided again in an appendix together with a column in which the author can state the page number on which the criterion was achieved. All authors submitting case reports should also submit a completed SCARE checklist (see appendix) with their manuscript and also state explicitly in their report that they have complied with the SCARE guideline which they can cite. The guideline represents the minimum of what should be reported, and authors are encouraged to provide additional details they deem relevant to the understanding of the case.

## 11.6 ENDORSEMENT

The SCARE guideline has been endorsed by IJS Case Reports, which publishes more surgical case reports than any other journal according to SCOPUS®. It has also been endorsed by Annals of Medicine and Surgery and IJS Open, IJS Oncology and IJS Short Reports (all part of IJS Publishing Group Ltd). The author hopes that more journals would endorse the guideline in due course.

## 11.7 STRENGTHS AND LIMITATIONS

The Delphi technique was named after the ancient Greek oracle, who was able to predict the future.<sup>15</sup> Its original purpose was to “obtain the most reliable consensus of opinion of a group of experts ... by a series of intensive questionnaires interspersed with controlled opinion feedback”.<sup>16</sup> Its purpose is the collection and aggregation of opinion for complex decision making, in the context of uncertainty, conflicting evidence or a lack of ‘hard’ evidence in a particular area.<sup>17</sup> It was initially used by the military to estimate the probable effects of massive atomic bombing.<sup>15</sup> Many sectors now deploy it from economics, finance, commerce, town planning and healthcare. Core features are; a number of questionnaire rounds, the feedback of responses to the group and the opportunity for participants to modify their responses in the next round until consensus is reached.<sup>18</sup>

There are a number of criticisms of the Delphi technique. Some have argued that its “designed to force consensus” rather than allow participants a free hand to make their own choices.<sup>19</sup> Details can obviously be hidden in simple numerical or statistical summaries

that are presented to the group after a round. Consensus may not necessarily be reached where a clear bimodal distribution exists, as participants may simply remain in their ‘ideological camp’ rather than cross-over to the other side, in what would be a significant shift in their opinion.<sup>20</sup> Another criticism is that the Delphi technique doesn’t consider reliability measurements and scientific validation of the findings, ultimately, we are still organising a series of opinions.<sup>21</sup> Reproducibility and external validity can also a weakness. Different panels with questions being asked slightly differently can produce very different results.<sup>15</sup>

There are a number of alternatives to the Delphi technique. One example, is the nominal group technique (NGT), developed by Delbecq and Van de Ven.<sup>22</sup> This is a structured face-to-face group interaction, where participants are empowered with an opportunity to have their voices heard and opinions considered by all. It has four key stages; silent generation, round robin, clarification and voting (ranking or rating).<sup>23</sup> This technique however, would have necessitated a face-to-face interaction, which the author knew would not logistically or financially plausible with 59 participants from 21 countries. The same problem therefore exists for other structured face-to-face meetings like the Rand UCLA Appropriateness Method, where all information and items remain ‘on the table’ until the end, which can make the exercise unwieldy.<sup>24</sup> Whereas the Delphi technique does allow for a large number of people who don’t normally meet, to ‘come together’ from diverse locations and backgrounds. Areas of expertise can be made anonymous easily in an online environment. This prevents the group being dominated by those with big personalities or reputations, which is a higher risk in face-to-face meetings and techniques like NGT and the Rand UCLA Appropriateness Method.<sup>25</sup>

Some techniques are not suited to the development of reporting guidelines. For instance,

the analytic hierarchy process (AHP) developed by Thomas Saaty, where participants deconstruct a problem into a hierarchy of numerous component problems, each of which can be analysed independently.<sup>26</sup> Each participant then makes judgements in terms of meaning and relative importance which are then converted into a value. AHP has had diverse applications from reducing the impact of climate change to faculty selection at university to conflict resolution and even proposed as a way forward for the Israeli-Palestinian conflict.<sup>27,28,29,30</sup>

Another option would be a simple questionnaire without feedback to the participants, a key part of the Delphi technique. This process of feedback however, is important and a key mechanism for those with divergent views to generate cohesion. It engenders group ownership and allows for individuals to be swayed by others and reappraise their views in the light of the responses of the group as a whole. If people simply complete a survey and don't know how others answered, it's more difficult to move the process forward towards consensus. The author does feel that Google Forms, lends itself well to conducting Delphi consensus exercises, with it being freely available, having a clearly presented user interface to construct a survey and good usability for those completing it as well as clear feedback mechanisms to participants.

## 11.8 SUMMARY

The key points of this chapter can be summarised as follows:

- ❖ The SCARE guideline is a consensus-based guideline following two DELPHI rounds amongst a multidisciplinary and expert group in the area of surgery and case reports.
- ❖ The author aims for broad dissemination and adoption amongst surgeons and surgical journals.
- ❖ Future work will focus on feedback from the community as well as studies of its implementation to help inform a future revision of these guidelines.

## 11.9 SCARE GROUP PARTICIPANTS

The following people contributed to the SCARE Guideline: Raafat Affi, Cairo University, Raha Al-Ahmadi, King Faisal Specialist Hospital and Research Centre, Joerg Albrecht, John H. Stroger Jr. Hospital of Cook County, Abdulrahman Alsawadi, Colchester Hospital University NHS Foundation Trust, Jeffrey Aronson, Radcliffe Infirmary, Oxford, M. Hammad Ather, Aga Khan University, Mohammad Bashashati, Texas Tech University Health Sciences Center, Somprakas Basu, Banarus Hindu University, Patrick Bradley, Nottingham University Hospitals, Mushtaq Chalkoo, Hyderpora, Ben Challacombe, Guy's and St Thomas' NHS Foundation Trust, Trent Cross, James Cook University, Laura Derbyshire, North West Deanery, Naheed Farooq, Central Manchester University Hospital Foundation Trust, Jerome Hoffman, University of California Los Angeles, Huseyin Kadioglu, Bezmialem Vakif University, Veeru Kasivisvanathan, University College London, Boris Kirshtein, Soroka University Medical Center, Roberto Klappenbach, Simplemente Evita Hospital, Daniel Laskin, Virginia Commonwealth University, Diana Miguel, University Hospital Jena, James Milburn, Queens Medical Centre, Seyed Reza Mousavi, Shohada Medical Center Tajrish, Oliver Muensterer, University Medicine Mainz, James Ngu, Changi General Hospital, Iain Nixon, East Kent University Hospitals, Ashraf Noureldin, Cumberland Royal Infirmary, Benjamin Perakath, Dr. Gray's Hospital, Nicholas Raison, King's College London, Kandiah Raveendran, Fatimah Hospital, Timothy Sullivan, Minneapolis Heart Institute, Achilleas Thoma, McMaster University, Mangesh Thorat, Wolfson Institute of Preventative Medicine, Queen Mary University of London, Michele Valmasoni, Università di Padova, Samuele Massarut, Centro di Riferimento Oncologico Aviano Italy, Anil D'cruz, Tata Memorial Hospital, Baskaran Vasudevan, MIOT Hospitals, Salvatore Giordano, Turku University Hospital, Gaurav Roy, Medanta-The Medicity, Donagh Healy, University Hospital Waterford, David Machado-Aranda, University of Michigan, Bryan Carroll, Eastern Virginia Medical School and David Rosin, University of West Indies.

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# **CHAPTER 12**

## **THE METHODOLOGICAL AND REPORTING QUALITY OF CASE SERIES IN SURGERY NEEDS IMPROVEMENT: A SYSTEMATIC REVIEW**



**BALLIOL**  
**COLLEGE**  
UNIVERSITY OF OXFORD

A summary of the following chapter has been published in the British Journal of Surgery.<sup>1</sup> The author was involved in concept and design, data acquisition, interpretation and analysis, writing the paper and its critical revision in light of feedback. The author received assistance in the area of data acquisition from six medical students (AF, SL, BG, KW, HS and KJLJ) and was supervised by Professor Dennis Orgill. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

## 12.1 BACKGROUND

A case series is an uncontrolled study that either samples participants with both a specific intervention (exposure) and a specific outcome, or samples participants with a specific outcome of interest regardless of their exposure status.<sup>1</sup> A series sampled only on exposure is a cohort study.<sup>1</sup> Reports of case series are commonly a retrospective review of a ‘string’ of patients with a unifying feature - be that exposure (including treatment) or outcome, or both. There has also been significant confusion between case series and a single group cohort study.<sup>2</sup> Case series are frequent within the healthcare literature but are also present within social sciences and the humanities.<sup>1</sup> As with case reports, their value has been debated.<sup>3,4</sup> In the age of evidence-based medicine (EBM), with the randomised controlled

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<sup>1</sup> Agha R, Fowler A, Lee S, Gundogan B, Whitehurst K, Sagoo H, Jeong KJL, Altman D and Orgill D. *A Systematic Review of the Methodological and Reporting Quality of Case Series in Surgery*. British Journal of Surgery 2016;103(10):1253-8.

trial (RCT) as the criterion standard to show the efficacy of a particular treatment, what is their role?

The use of a case series in the recognition of a new disease was exemplified in 1999 by the epidemic of West Nile encephalitis in New York.<sup>5</sup> Historically, case series were important in identifying the impact of maternal drinking on pregnancy outcome and the role of vitamin C in preventing scurvy.<sup>6,7</sup> More recently, a study by Albrecht et al of case series published in *The Lancet* found that a high proportion led to follow-up trials and that they were useful in establishing an early evidence base for treatments of rare diseases in which trials would not be feasible.<sup>8</sup> For some specialties, establishing control groups may be difficult, such as in accident and emergency medicine. In the social sciences, many social psychology studies have been case series, for example Yale psychologist Stanley Milgram's seminal work on obedience to authority figures.<sup>9</sup>

In a 2005 report, Dalziel et al found that case series were used in 30% of Health Technology Assessments (HTA) used in the provision and suitability of care.<sup>10</sup> Poor reporting in the case series included in their study, however, severely constrained their analysis and investigation of the hypothesis that findings in case series may be affected by methodological characteristics.<sup>10</sup> Readers need complete, transparent information in all reports of research. Poor reporting of case series undermines critical appraisal, assessment of external validity and whether, for instance, a surgeon should change their practice.

No standardised reporting criteria have been developed within a robust methodological framework for case series. The aim of this work was to close this gap and produce the basis for a reporting guideline for case series that is methodologically robust, easy to use and accepted internationally across a broad range of specialties and disciplines. Following

guidance on guideline development, the early steps in this process require an analysis of previous literature to identify previous guidance (if any) and to analyse relevant evidence on the quality of reporting of published research articles within the domain of interest.<sup>11</sup> This phase of the study involves a systematic review of the reporting quality of published surgical case series.

## **12.2 AIMS AND OBJECTIVES**

In this chapter, the author reports a systematic review of the reporting quality within recently published surgical case series.

## **12.3 METHODS**

This systematic review was conducted according to the recommendations outlined in the Cochrane Handbook version 5.1.0 for Systematic Reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>12,13</sup> A protocol was developed and registered on the National Institute of Health Research (NIHR) – PROSPERO database (CRD42015016145). There were no deviations from the protocol during the conduct of this research.<sup>14</sup>

### **Criteria for selecting studies**

The following search criteria were devised to locate studies specifically pertaining to the reporting quality of case series within surgery and to inform the development of recommendations for reporting such studies.

### **Types of studies/material**

Research articles and systematic reviews which highlight reporting issues within case series.

### **Types of participants**

Human participants undergoing surgery.

### **Types of interventions**

Any surgical intervention.

### **Types of comparator**

Typically, case series will have no comparator or control group. Nothing was specified here within the search criteria.

### **Outcomes**

Specified reporting deficiencies identified within the articles relating to case series and categorised under the following headings:

1. Failure to use standardised definitions (e.g. for outcomes and complications).
2. Missing or selective data (e.g. failing to document loss to follow-up and omitting cases or only presenting certain important variables and not others).
3. Lack of transparency or incomplete reporting (e.g. failure to describe the patient population, intervention or outcomes in sufficient detail).
4. Whether alternative study designs were considered

5. Other issues (any other reporting deficiencies of note that did not come under items 1-4 above).

## **Search methods for identification of studies**

### **Electronic Searches**

The following electronic databases were searched from their inception to 5<sup>th</sup> November 2014: MEDLINE, EMBASE, Cochrane Methods Register and Science Citation Index restricted to the English language. In addition, as part of the 'grey' literature search, the Conference Proceedings Citation Index was also searched.

### **Search terms and keywords**

The search strategy was developed through consultation with an information specialist based at the Bodleian Library, University of Oxford. Its aim was to locate papers related specifically to the reporting quality of case series (table 12.1). The search was performed on 5<sup>th</sup> November 2014 from inception of the database to this date. This search utilised English language keywords combined with Boolean logical operators. The search was restricted to the English Language and tailored to the idiosyncrasies of each database. An example of a search strategy for the MEDLINE database is shown in Table 12.1.

<b>TABLE 12.1. Search strategy for the MEDLINE database</b>		
<b>#</b>	<b>Searches</b>	<b>Results</b>
1	case series.mp.	39714
2	"series of cases".mp.	2580
3	"series of case reports".mp.	547
4	1 or 2 or 3	42346
5	Research Design/st [Standards]	9548
6	Research design/ and Quality Control/	1034
7	Research design/ and "Reproducibility of Results"/	6230
8	Research design/ and Data interpretation, Statistical/	4912
9	*Research design/	24740
10	(quality adj5 (reporting or criteria or characteristic? or feature? or standard? or aspect?)).ti,ab.	29385
11	(reporting adj5 (selection or recruit* or eligibility or study size or study design? or outcome?)).ti,ab.	4466
12	(reporting adj5 ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti,ab.	153
13	(reporting adj5 (missing data or missing value* or incomplete data or incomplete value*)).ti,ab.	64
14	(methodolog* adj5 (reporting or criteria or characteristic? or feature? or standard? or aspect? or quality)).ti,ab.	19999
15	(reporting adj2 (scor* or system*)).ti,ab.	6476
16	strobe.ti,ab.	560
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	91558
18	4 and 17	591
19	(case series adj5 (methodologic* or reporting)).ti,ab.	171
20	(case series adj5 (quality or bias or heterogen* or rigor* or rigour* or robust* or generalisab* or valid*)).ti,ab.	181
21	(case series adj5 (missing data or missing value* or incomplete data or incomplete value*)).ti,ab.	0
22	(case series adj5 ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti,ab.	6

23	(case series and (methodologic* or reporting)).ti.	14
24	(case series and (quality or bias or heterogen* or rigor* or rigour* or robust* or generalisab*)).ti.	38
25	(case series and (missing data or missing value* or incomplete data or incomplete value*)).ti.	0
26	(case series and ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti.	6
27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	873
28	limit 27 to English language	842

### Identification and selection of articles

Studies identified by the electronic search strategy were listed. Results including citation, title and abstracts were populated into Microsoft Excel® Database (Microsoft, Redmond, WA, USA) and duplicates removed. Titles and abstracts were screened independently by two teams of authors (SL/KJLJ and BG/HS/KW) for issues relating to the reporting quality of case series.

Articles selected after title and abstract screening had their full text downloaded and a further assessment was made of eligibility. Once articles were selected for inclusion, data extraction took place. Any conflicts in either the eligibility of articles or the data extracted from them, not resolvable between the two teams were referred to a single senior author (RA) for resolution, selected on the basis of recent experience with multiple other published systematic reviews.

### **Data extraction and management**

Data was extracted independently by two teams of authors using a standardised data extraction form. Disagreements were resolved by discussion. Where resolution was not achieved, the same senior author as in the preceding section made a final decision. Data were then entered into a Microsoft Excel ® 2011 database (Microsoft, Redmond, WA, USA).

### **Data Synthesis and statistical analysis**

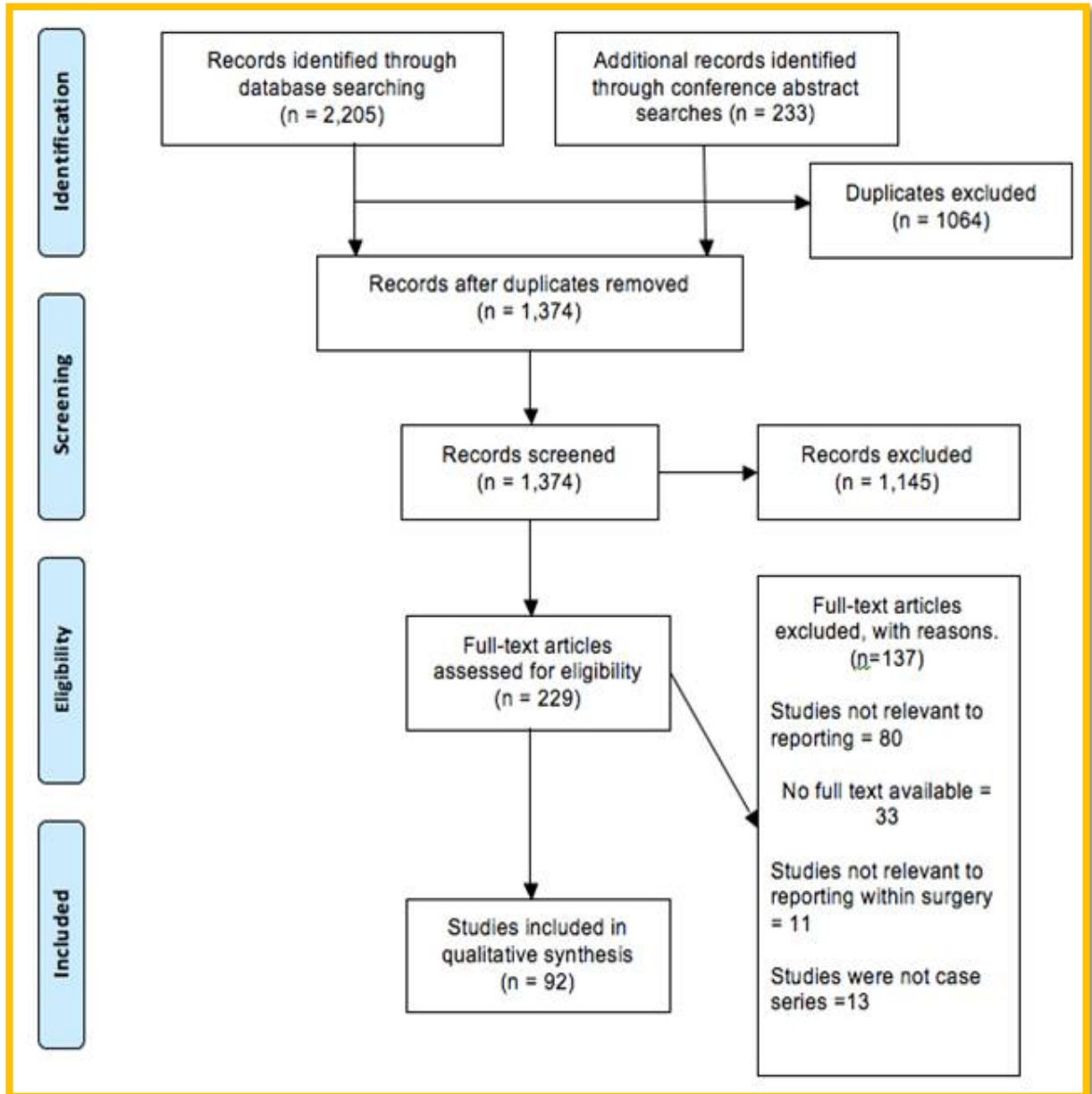
Outcomes were tabulated, with descriptive statistics used to determine frequently missing types of data within reports of case series.

### **Subgroup Analysis**

A sensitivity analysis was performed whereby results from those studies whose primary aim was to assess the methodological and reporting quality of multiple case series (such as a research paper assessing reporting quality of case series), was looked at separately from those articles which simply mentioned an issue ‘in passing’ in their discussion (such as a single case series or a systematic review related to a particular clinical condition/treatment).

## 12.4 RESULTS

The searches identified 1,374 records. Through the process of screening and eligibility assessments 92 articles, published over the period 1990 to 2014, were selected for inclusion (figure 12.1).



**Figure 12.1:** PRISMA flow diagram (adapted from Moher et al, 2010<sup>13</sup>).

Within the two independent reviewing teams there were discrepancies over whether 46 of the 229 papers (17%) should be included. Of these 46, there were 45 which were rejected and one was included in the final list to go forward into the qualitative synthesis. When it came to data extraction there were discrepancies over 105 of the 460 points (22.8%), that could not be resolved by discussion between the two teams and which were resolved as per protocol. Results are summarised in table 12.2.

<b>TABLE 12.2. SUMMARY OF RESULTS</b>					
<b>Type of Data</b>	<b>Failure to use standardised definitions</b>	<b>Missing or selective data</b>	<b>Lack of transparency or complete reporting</b>	<b>Were alternative study designs considered</b>	<b>Other issues</b>
<b>Articles (n=46)</b>	54% (25/46)	63% (29/46)	74% (34/46)	9% (4/46)	48% (22/46)
<b>Systematic Reviews (n=32)</b>	78% (25/32)	72% (23/32)	81% (26/32)	19% (6/32)	47% (15/32)
<b>Conferences (n=14)</b>	14% (2/14)	64% (9/14)	29% (4/14)	0% (0/14)	79% (11/14)
<b>Total (n=92)</b>	57% (52/92)	66% (61/92)	70% (64/92)	11% (10/92)	52% (48/92)

### Subgroup Analysis

There were three systematic reviews and eight articles where the aim was to specifically investigate the methodological and reporting quality of case series. The results are summarised in table 12.3.

<b>TABLE 12.3. SUMMARY OF SUBGROUP ANALYSIS</b>					
<b>Type of Data</b>	<b>Failure to use standardised definitions</b>	<b>Missing or selective Data</b>	<b>Lack of transparency or incomplete reporting</b>	<b>Were alternative study designs considered</b>	<b>Other issues</b>
<b>Articles (n=8)</b>	75% (6/8)	100% (8/8)	75% (6/8)	38% (3/8)	100% (8/8)
<b>Systematic Reviews (n=3)</b>	33% (1/3)	100% (3/3)	67% (2/3)	33% (1/3)	100% (3/3)
<b>Total (n=11)</b>	64% (7/11)	100% (11/11)	73% (8/11)	37% (4/11)	100% (11/11)

The main “other issues” identified in this cohort include failure to clearly define the patient population under investigation, selection bias, insufficient follow-up time, and need for validated outcomes (even if the ones used were well defined).

## 12.5 DISCUSSION

The results show that surgical case series suffer from significant methodological and reporting issues. These can essentially be broken down along the five main lines of enquiry anticipated with high percentage frequencies across all areas studied; failure to use standardised definitions, missing or selective data, lack of transparency or complete reporting, whether alternative study designs were considered and other issues. The other issues can be further segmented with sample size calculation, patient population definition, follow-up time length and whether outcomes are validated.

The value of case reports and case series has been questioned in the evidence-based medicine (EBM) era. Hoffman has stated that “more often than not”, new ideas from such work are not sustained on further research.<sup>15</sup> Part of the focus of EBM, is in finding the

‘best’ available research evidence to answer a given clinical question. The ‘best’ will have the least bias and is more likely to get us closer to the truth of a given clinical question. However, is the poor reputation of the surgical case series the ‘fault’ of the concept, rather than its methodological and reporting execution? This systematic review clearly shows that those assessing the quality of case series often highlight areas that could have been improved through better conduct and reporting within the construct of the case series design.

Problems with the reporting of surgical case series have been documented in a recent systematic review by the author on autologous fat grafting for breast reconstruction.<sup>16</sup> In this study, 25 of 31 included studies were case series. Failure to correctly define the patient population under investigation, their demographic details and previous treatments is important, yet 20% did not even mention the age of the participants and 48% did not mention whether the participants had been treated with radiotherapy, an important prognostic factor.

It has been noted elsewhere that there are few formal assessments of how often the conclusions based on cases and case series are actually correct.<sup>17</sup> This was highlighted in an investigation assessing side effects reports, where 35 of 47 anecdotal reports were qualified as “clearly correct”. Hence the predictive record of unstructured observations may be valuable.<sup>18</sup> Furthermore, two modeling exercises have shown that case reports are likely to pick up true associations, for either rare diseases or more common diseases with a high relative risk.<sup>19,20</sup> Indeed such types of association led to the detection of “flock-workers lung”.<sup>21</sup>

So, when should a case series be performed? Vandembroucke argued in defence of case reports and case series, and listed their potential roles as<sup>22</sup>; the recognition and description of new diseases, the detection of drug side effects (adverse or beneficial), study of the mechanisms of disease, medical education and audit, and the recognition of rare manifestations of disease.

For surgical case series specifically, the author advocates the following reasons: rare diseases or rare circumstances (e.g. emergencies), new diseases – their description, natural history and management, studying the mechanism of disease and studying the impact of new procedures, including the establishment of learning curves as well as hypothesis generation. In addition, late or delayed effects following surgical interventions, such as biliary malignancy after bilio-digestive anastomosis, could be collated into a case series.<sup>23</sup> Where a new technique or device has been conceived and requires development and assessment, then the IDEAL (Idea, Development, Exploration, Assessment and Long-term follow-up) framework is recommended.<sup>24</sup>

In the on-going drive to improve the evidence base for clinical practice, a number of tools have been developed to improve the quality of reporting research. For example, publication of CONSORT (Consolidated Reporting Standards of Randomised controlled Trials) has seen the quality of articles in some fields improve significantly.<sup>25,26</sup> The CONSORT statement has also been used to highlight and raise awareness of poor compliance in some fields.<sup>27,28,29,30,31</sup> The same is true of observational studies using the STROBE guideline (strengthening the reporting of observational studies in epidemiology).<sup>32</sup>

A wide variety of reporting guidelines are now available across different research study types, from case reports to systematic reviews, but case series are a notable exception.<sup>33,34</sup> Surgery has the additional complexity of learning curves. The surgical technique selected is not the sole factor affecting outcome. Patients need to be carefully selected, appropriately worked-up and optimised pre-operatively, the technique has to be meticulously implemented in an appropriate setting with the relevant safe anaesthesia and with an appropriate post-operative setting/regimen. The entire package of patient management has to be delineated and documented in case series in order to be reproducible by others.

## **12.6 STRENGTHS AND LIMITATIONS**

Strengths of this review include conduct by an author with significant interest and experience in this area of methodological and reporting quality.<sup>35,36,37,38,39</sup> Limitations include restriction to the English language, although it has been estimated 80–90% of papers in scientific journals are written in English.<sup>40</sup> No synonyms for “case series” were used, as the author was not aware of any. The potential to have missed relevant articles in the search or incorrectly scoring the articles was hopefully minimised by having two teams that independently selected and scored articles. The limitations of the Delphi technique as a method of developing consensus and the alternatives to it were discussed extensively in chapter 11 (section 11.7).

## 12.7 IMPLICATIONS FOR FUTURE RESEARCH

The author's focus will now shift towards developing a guideline for the conduct and reporting of a case series, named **PROCESS – Preferred Reporting Of CasE Series in Surgery** – and this initiative has been registered on the EQUATOR Network site – a repository for reporting guidelines.<sup>41</sup> This systematic review has now provided the initial items for an expert panel to consider through a Delphi consensus exercise.

## 12.8 SUMMARY

The key findings of this chapter can be summarised as follows:

- ❖ The methodological and reporting quality of surgical case series needs improvement.
- ❖ Deficiencies were noted in the following areas; failure to use standardised definitions, missing or selective data, lack of transparency or complete reporting and whether alternative study designs were considered.
- ❖ The data shows that clear guidelines for the conduct and reporting of a case series may be useful to those planning or conducting them.
- ❖ The next step will be to develop such a guideline (see chapter 13).

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# **CHAPTER 13**

## **DEVELOPMENT OF PREFERRED REPORTING OF CASE SERIES IN SURGERY: THE PROCESS GUIDELINE**



**BALLIOL  
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UNIVERSITY OF OXFORD

A summary of the following chapter has been published in International Journal of Surgery.<sup>1</sup> The author was responsible for concept and design, data acquisition, analysis and interpretation, writing the paper and revising it in light of feedback from others. The author had assistance from three others (AJF, SR and IB) in data acquisition and was supervised by Professor Dennis Orgill. The medical students were recruited from the Academic Surgical Collaborative (ASC, [www.surgicalcollaborative.com](http://www.surgicalcollaborative.com)), of which the author is founder and director. The process involved emailing the membership list a brief outline of the project, and appointing those that showed interest in the project in a response email and subsequent face to face follow-up meeting at the Garrod Building, Royal London Hospital in Whitechapel, where the ASC had meetings every two to three months.

### **13.1 BACKGROUND**

Case series are frequent within the surgical and wider healthcare literature but are also present within social sciences and the humanities.<sup>1</sup> Dekkers et al defined a case series as an uncontrolled study that either samples participants with both a specific intervention (exposure) and a specific outcome, or samples participants with a specific outcome of interest regardless of their exposure status.<sup>1</sup> A series sampled only on exposure is a cohort study. Reports of case series are commonly a retrospective review of a string of patients with a unifying feature - be that exposure (including treatment) or outcome, or both. There has also been significant confusion between case series and a single group cohort study.<sup>2</sup>

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<sup>1</sup>. Agha RA, Fowler AJ, Rajmohan S, Barai I, Orgill DP and the PROCESS Group. *The PROCESS Statement: Preferred Reporting of Case Series in Surgery*. International Journal of Surgery 2016;36(Pt A):319-323.

As with case reports, their value has been debated.<sup>3,4</sup> In the age of evidence-based medicine (EBM), with the randomised controlled trial as the criterion standard to show the efficacy of a particular treatment, what is their role? Level four evidence was still the most common study type in a bibliometric analysis of research published in 2013 in the specialties of plastic surgery, orthopaedic surgery, otolaryngology and neurosurgery with significant outputs in maxillofacial surgery (33%) and vascular surgery (15%).<sup>5</sup> The use of a case series in the recognition of a new disease was exemplified in 1999 by the epidemic of West Nile encephalitis in New York.<sup>6</sup> Historically, case series were important in identifying the impact of maternal drinking and pregnancy outcome and the role of vitamin C in preventing scurvy.<sup>7,8</sup> A single case series can lead to very significant change, from the widespread use of negative pressure dressings following a case series of 10 patients<sup>9</sup> to a 49 patient case series that led to a new classification system for haemangiomas and vascular malformations in 1982, that is still in use today.<sup>10</sup>

Albrecht et al studied reports of case series and found that a high proportion led to follow-up trials and that they were useful in establishing an early evidence base for new treatments of rare diseases in which trials would not be feasible.<sup>11</sup> For some specialties, establishing control groups may be difficult, such as in accident and emergency medicine or paediatric medicine or surgery. In the social sciences, many social psychology studies have been case series, for example Yale psychologist Stanley Milgram's seminal work on obedience to authority figures.<sup>12</sup>

In a 2005 report, Dalziel et al found that case series were used in 30% of Health Technology Assessments (HTA) used in the provision and suitability of care.<sup>13</sup> Poor reporting in the case series included in their study, however, severely constrained their

analysis and investigation of the hypothesis that findings in case series may be affected by methodological characteristics.<sup>13</sup> Readers need complete, transparent information in all reports of research. Poor reporting of case series undermines critical appraisal, assessment of external validity and whether, for instance, a surgeon should change their practice.

No standardised reporting criteria have been developed within a robust methodological framework for case series. The aim of the present study was to close this gap and produce a reporting guideline for case series that is methodologically robust, easy to use and accepted internationally across a broad range of specialties and disciplines. Following guidance on guideline development, the early steps in this process require an analysis of previous literature to identify previous guidance (if any) and to analyse relevant evidence on the quality of reporting of published research articles within the domain of interest.<sup>14</sup>

The author recently completed a systematic review on the reporting quality of case series in surgery over the period 1990-2014 (see chapter 12).<sup>15</sup> From 92 articles that met the inclusion criteria, methodological and reporting issues identified were: failure to use standardised definitions (57%), missing or selective data (66%), transparency or incomplete reporting (70%), whether alternate study designs were considered (11%) and other issues (52%) such as failure to clearly define the patient population under investigation, selection bias insufficient follow-up time, need for validated outcomes.

The SCARE Guidelines for Case Reports using a DELPHI Consensus exercise which have now been adopted by multiple journals.<sup>16</sup> Following this experience, the objective of this

research is to conduct a Delphi consensus exercise amongst experienced surgical case series reviewers and editors to develop the Preferred Reporting Of Case Series in Surgery (PROCESS) Guidelines.

## **13.2 METHODS - DEVELOPING THE PROCESS GUIDELINE**

A survey was issued using Google Forms (<https://www.google.co.uk/forms/about>) asking participants in round one to help define surgical case series and what items should be included in them. In a subsequent round, participants were asked to rate their level of agreement with the guideline items from round one as well as items from the SCARE guidelines and any additional items that were suggested using a nine-point Likert scale as proposed by the GRADE group.<sup>17</sup> In this scale 1 to 3 signifies an outcome of limited importance, 4 to 6 important but not critical and 7 to 9 critical. If 70% or more of respondents scored an item 7 to 9 and fewer than 15% scored it 1 to 3, then that item proceeded into the reporting guideline. Similarly, consensus that an outcome should not be included was 70% or more scoring it 1 to 3 and 15% or less scoring it 7 to 9. The entire process was conducted electronically and there were no pre-determined number of Delphi rounds.

## **13.3 PARTICIPANT SELECTION**

Surgeons and others with significant experience in reviewing or editing case reports were selected. They were drawn from the reviewer pool of IJS Case Reports (the top 150 by number of reviews performed in the database of reviewers were invited) as well as those who have written on the topic of case reports or case series in the past or specific

individuals who were recommended by Professor Doug Altman, who pioneered the CONSORT guideline.

### 13.4 RESULTS

In total 59 participants agreed to the invitation to participate in this study, representing 21 countries and all ten surgical specialties as well as allied specialties including; dermatology, pathology, oncology, clinical pharmacology, acute care surgery, with many participants also occupying positions on journal editorial boards.<sup>18</sup> This is summarised in the table 13.1 below:

<b>Table 13.1. CHARACTERISTICS OF STUDY PARTICIPANTS</b>	
<b>(It should be noted, that where a single individual has multiple specialty interests/expertise, it has been shown on its own line as a standalone combination)</b>	
<b>Specialties (<i>n</i>)</b>	<b>Geographic Distribution (<i>n</i>)</b>
<b>(alphabetical order)</b>	<b>(alphabetical order)</b>
1. Acute Care Surgery (1)	❖ Argentina (1)
2. Breast Surgery (2)	❖ Australia (1)
3. Breast Surgery/Plastic Surgery/Vascular Surgery (1)	❖ Barbados (1)
4. Cardiac Surgery (1)	❖ Brazil (1)
5. Cardiothoracic Surgery (1)	❖ Canada (3)
6. Chiropractor (1)	❖ China (1)
7. Clinical Pharmacology (1)	❖ Egypt (1)
8. Clinical Pharmacology/Dermatology/Internal Medicine (1)	❖ Germany (3)
	❖ India (7)
	❖ Iran (1)

9. Colorectal Surgery (3)	❖ Ireland (1)
10. Colorectal Surgery/Hepatopancreaticobiliary (HPB) Surgery/Upper GI Surgery (1)	❖ Israel (1)
11. Dentistry (3)	❖ Italy (3)
12. Dermatology (2)	❖ Japan (1)
13. Emergency Medicine (1)	❖ Malaysia (1)
14. Former editor of a major journal (1)	❖ Pakistan (2)
15. General Surgery (11)	❖ Saudi Arabia (1)
16. Head and Neck Surgical Oncology (1)	❖ Singapore (1)
17. HPB (3)	❖ Turkey (1)
18. Neurosurgery (1)	❖ United Kingdom (15)
19. Oncology (1)	❖ USA (12)
20. Orthopaedic Surgery (3)	
21. Otolaryngology (1)	
22. Paediatric Surgery (2)	
23. Pathology (1)	
24. Plastic Surgery (3)	
25. Transplant Surgery/Urology (1)	
26. Upper GI (3)	
27. Upper GI/Colorectal Surgery (1)	
28. Upper GI/Transplant (1)	
29. Urology (5)	
30. Vascular (1)	

In round 1, there was a 49% (29/59) response rate. The participant responses are integrated into table 13.2 below.

<b>Table 13.2. DELPHI Round 1 Responses</b>	
<b>QUESTION</b>	<b>RESPONSES (N=29)</b>
<i>We are defining a case series as follows: A case series is a descriptive study of an uncontrolled group of patients who are sampled on the basis of a specific exposure/intervention or a specific outcome of interest regardless of their exposure status</i>	62.1% agree (18/29) 37.9% disagree (11/29) Comments – should be mentioned they are observational studies and they may relate to a specific disease.
<i>How do you differentiate a case series from a cohort study? Should a Cohort study always have two or more groups? Other reasons?</i>	Both are observational studies but cohort studies are comparative and patients in them are always sampled on the basis of exposure, whereas case series may be sampled on the basis of; disease/exposure/intervention or a specific outcome of interest
<i>What are the important elements that should be reported in a case series?</i>	
<ul style="list-style-type: none"> <li>• <i>What is the unifying theme - common presentation, diagnosis, intervention, outcome, etc</i></li> </ul>	93% (27/29)
<ul style="list-style-type: none"> <li>• <i>Whether it is prospective or retrospective</i></li> </ul>	76% (22/29)
<ul style="list-style-type: none"> <li>• <i>Whether alternative study designs were considered e.g. cohort, RCT, etc</i></li> </ul>	31% (9/29)
<ul style="list-style-type: none"> <li>• <i>Whether alternative study designs were considered e.g. cohort, RCT, etc</i></li> </ul>	86% (25/29)
<ul style="list-style-type: none"> <li>• <i>Whether the cases are consecutive or not</i></li> </ul>	90% (26/29)
<ul style="list-style-type: none"> <li>• <i>Whether it is multi centre or single centre</i></li> </ul>	
<ul style="list-style-type: none"> <li>• <i>What the time interval over which cases were</i></li> </ul>	

<p><i>collected giving years and potentially months as well if collected over a short period of time</i></p> <ul style="list-style-type: none"> <li>• <i>Patient population should be detailed</i></li> <li>• <i>Patient selection should be described in detail</i></li> <li>• <i>Changes to the intervention during the course of the series should be detailed</i></li> <li>• <i>A comment on learning curves should be made for new techniques</i></li> <li>• <i>Loss to follow-up should be detailed e.g. % of sample lost to follow-up and reasons if known</i></li> <li>• <i>Other elements not already included in the SCARE checklist (please state)</i></li> </ul>	<p>90% (26/29)</p> <p>90% (26/29)</p> <p>83% (24/29)</p> <p>86% (25/29)</p> <p>72% (21/29)</p> <p>83% (24/29)</p> <p>28% (8/29)</p>
<p><i>Other than the items above and those in the SCARE checklist, please let us know if anything else should be reported in a case series?</i></p>	<p>Why cases were non-consecutive.</p> <p>State if patients were excluded.</p>

Following adjustment of the guideline with incorporation of recommended changes, round 2 commenced. There was an 81% (48/59) response rate. All guideline items were approved by the participants with Likert scores 7-9 awarded by >70% of respondents, apart from 4a - registration and ethics - state the research registry number in accordance with the declaration of Helsinki, which had scores of 7-9 from 65% of participants. However, as this item is part of the declaration of Helsinki, it cannot be removed or augmented.

<b>Table 13.3. DELPHI ROUND 2 RESPONSES TO DEFINITIONS</b>	
<b>QUESTION</b>	<b>RESPONSES (N=46) AND COMMENTS</b>
<i>From the first-round results, a case series is being defined as: "an observational study of an uncontrolled group of patients collected or sampled on the basis of a specific disease/exposure/intervention or a specific outcome of interest."</i>	96% (44/46)
<i>A Case Series must be differentiated from a Cohort Study so we have defined those to following the first round results. "A Cohort Study is a comparative study typically involving two or more groups of patients that are sampled only on the basis of a specific exposure or intervention." This definition is similar to that put forward by the Centre of Evidence Based Medicine at Oxford University: <a href="http://www.cebm.net/glossary/">http://www.cebm.net/glossary/</a>.</i>	76% (35/46)  A single group cohort may still be utilised e.g. for prognostic studies.

<b>TABLE 13.4. DELPHI ROUND 2 RESPONSES TO GUIDELINE ITEMS</b>			
<b>SECTION</b>	<b>ITEM</b>	<b>CHECKLIST DESCRIPTION</b>	<b>RESPONSES (N=48)  SCORES 7-9</b>
<b>TITLE</b>	1	The words “case series” and the area of focus should appear in the title (e.g. disease, exposure/intervention or outcome).	80% (37/46)
<b>ABSTRACT</b>	2a	<b>Introduction</b>  What is the unifying theme of the case series.	89% (41/46)
	2b	<b>Methods</b>  Describe what was done, how and when was it done and by whom.	
	2c	<b>Results</b>  What was found.	
	2d	<b>Conclusion</b>  What have we learned and what does it mean	
<b>INTRODUCTION</b>	3	Explain the scientific background and rationale for the case series. What is the unifying theme - common disease, exposure, intervention and outcome, etc. Why is this study needed?	96% (44/46)
<b>METHODS</b>	4a	<b>Registration and ethics</b>  State the research registry number in accordance with the declaration of Helsinki - "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject" (this can be	65% (30/46)

		obtained from; ResearchRegistry.com or ClinicalTrials.gov or ISRCTN). Even retrospective studies should be registered prior to submission. State whether ethical approval was needed and if so, what the relevant judgement reference from the IRB or local ethics committee was? If ethical approval was not needed, state why.	
	4b	<p><b>Study design</b></p> <p>State the study is a case series and whether prospective or retrospective in design, whether single or multi-centre and whether cases are consecutive or non-consecutive.</p>	91% (42/46)
	4c	<p><b>Setting</b></p> <p>Describe the setting(s) and nature of the institution in which the patient was managed; academic, community or private practice setting? Location(s), and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p>	87% (40/46)
	4d	<p><b>Participants</b></p> <p>Describe the relevant characteristics of the participants (comorbidities, tumour staging, smoking status, etc). State any eligibility (inclusion/exclusion) criteria and the sources and methods of selection of participants. Describe length and methods of follow-up.</p>	93% (43/46)
	4e	<p><b>Pre-intervention considerations</b></p> <p>e.g. Patient optimisation: measures taken prior to surgery or other intervention e.g. treating hypothermia/hypovolaemia/hypotension in burns</p>	80% (37/46)

		patients, ICU care for sepsis, dealing with anticoagulation/other medications and so on.	
4f	<b>Types of intervention(s) deployed</b>	To include reasoning behind treatment offered (pharmacological, surgical, physiotherapy, psychological, preventive) and concurrent treatments (antibiotics, analgesia, anti-emetics, nil by mouth, VTE prophylaxis, etc). Medical devices should have manufacturer and model specifically mentioned.	87% (40/46)
4g	<b>Peri-intervention considerations</b>	Administration of intervention (what, where, when and how was it done, including details for surgery; anaesthesia, patient position, use of tourniquet and other relevant equipment, preparation used, sutures, devices, surgical stage (1 or 2 stage, etc) and operative time. Pharmacological therapies should include formulation, dosage, strength, route and duration). Authors are encouraged to use figures, diagrams, photos, video and other multimedia to explain their intervention.	89% (41/46)
4h	<b>Who performed the procedure(s)</b>	Operator experience (position on the learning curve for the technique if established, specialisation and prior relevant training).	83% (38/46)
4i	<b>Quality control</b>	What measures were taken to reduce inter or intra-operator variation. What measures were taken to ensure quality and consistency in the delivery of the intervention e.g. independent	76% (35/46)

		observers, lymph node counts, etc	
	4j	<p><b>Post-intervention considerations</b></p> <p>e.g. post-operative instructions and place of care. Important follow-up measures - diagnostic and other test results. Future surveillance requirements - e.g. imaging surveillance of endovascular aneurysm repair (EVAR) or clinical exam/ultrasound of regional lymph nodes for skin cancer.</p>	89% (41/46)
<b>RESULTS</b>	5a	<p><b>Participants</b></p> <p>Report numbers involved and their characteristics (co-morbidities, tumour staging, smoking status, etc).</p>	96% (44/46)
	5b	<p><b>Changes</b></p> <p>Any changes in the interventions during the course of the case series (how has it evolved, been altered or tinkered with, what learning occurred, etc) together with rationale and a diagram if appropriate. Degree of novelty for a surgical technique/device should be mentioned and a comment on learning curves should be made for new techniques/devices.</p>	89% (41/46)
	5c	<p><b>Outcomes and follow-up</b></p> <p>Clinician assessed and patient-reported outcomes (when appropriate) should be stated with inclusion of the time periods at which assessed. Relevant photographs/radiological images should be provided e.g. 12-month follow-up.</p>	93% (43/46)
	5d	<p><b>Intervention adherence/compliance and tolerability</b></p>	91% (42/46)

		How was this assessed. Describe loss to follow-up (express as a percentage and a fraction) and any explanations for it.	
	5e	<p><b>Complications and adverse or unanticipated events</b></p> <p>Described in detail and ideally categorised in accordance with the Clavien-Dindo Classification. How they were prevented, mitigated, diagnosed and managed. Blood loss, wound complications, re-exploration/revision surgery, 30-day post-op and long-term morbidity/mortality may need to be specified.</p>	89% (41/46)
<b>DISCUSSION</b>	6a	<b>Summarise key results</b>	93% (43/46)
	6b	<p><b>Discussion of relevance</b></p> <p>Relevant literature, implications for clinical practice guidelines, how have the indications for a new technique/device been refined and how do outcomes compare with established therapies and the prevailing gold standard should one exist and any relevant hypothesis generation.</p>	91% (42/46)
	6c	<b>Strengths and limitations of the study</b>	93% (43/46)
	6d	<b>The rationale for any conclusions?</b>	96% (44/46)
<b>CONCLUSIONS</b>	7a	<b>State the key conclusions from the study</b>	93% (43/46)
	7b	<b>State what needs to be done next, further research with what study design.</b>	78% (36/46)
<b>ADDITIONAL INFORMATION</b>	8a	<b>State any conflicts of interest</b>	98% (45/46)
	8b	<b>State any sources of funding</b>	96% (44/46)

### **13.5 PROCESS GUIDELINE**

Table 13.4 constitutes the PROCESS guideline, and this is provided again in an appendix together with a column in which the author can state the page number on which the criterion was achieved. Authors should submit a completed PROCESS checklist with their manuscript and also state explicitly in their report that they have complied with the PROCESS guideline which they should cite in their paper. The guideline represents the minimum of what should be reported, and authors are encouraged to provide additional details that are relevant.

### **13.6 ENDORSEMENT**

The PROCESS guideline has been endorsed by the IJS, IJS Case Reports, IJS Open, Annals of Medicine and Surgery, IJS Oncology and IJS Short Reports.

### **13.7 STRENGTHS AND LIMITATIONS**

The strengths and limitations of the Delphi technique and our work in developing the PROCESS guideline are very similar to what was discussed in chapter 11.7 when discussing the SCARE guideline. The author won't repeat those arguments here but will discuss limitations again in thesis discussion in chapter 14. One additional strength however to note, is that participants from the SCARE guideline were re-invited to participate in PROCESS, so their familiarity with the process could be considered an added strength going into the PROCESS guideline development.

## **13.8 SUMMARY**

After the completion of two DELPHI rounds consensus was reached amongst a multidisciplinary and expert group in the area of surgery and case series. If used appropriately, the PROCESS guidelines will aid in raising the reporting quality of surgical case series. Authors, reviewers, editors, journals, publishers and the wider surgical and scholarly community are encouraged to adopt these. Feedback from the community as well as studies of its implementation to help inform a future revision of these guidelines are most welcome.

## **13.9 PROCESS GROUP PARTICIPANTS**

The following people contributed to the PROCESS Guideline: Raafat Afifi, Cairo University, Raha Alahmadi, King Faisal Specialist Hospital and Research Centre, Joerg Albrecht, John H. Stroger Jr. Hospital of Cook County, Abdulrahman Alsawadi, Colchester Hospital University NHS Foundation Trust, Jeffrey Aronson, Radcliffe Infirmary, Oxford, M. Hammad Ather, Aga Khan University, Mohammad Bashashati, Texas Tech University Health Sciences Center, Somprakas Basu, Banarus Hindu University, Patrick Bradley, Nottingham University Hospitals, Mushtaq Chalkoo, Hyderpora, Ben Challacombe, Guy's and St Thomas' NHS Foundation Trust, Trent Cross, James Cook University, Laura Derbyshire, North West Deanery, Naheed Farooq, Central Manchester University Hospital Foundation Trust, Jerome Hoffman, University of California Los Angeles, Huseyin Kadioglu, Bezmialem Vakif University, Veeru Kasivisvanathan, University College London, Boris Kirshtein, Soroka University Medical Center, Roberto Klappenbach, Simplemente Evita Hospital, Daniel Laskin, Virginia

Commonwealth University, Diana Miguel, University Hospital Jena, James Milburn, Queens Medical Centre, Oliver Muensterer, University Medicine Mainz, James Ngu, Changi General Hospital, Iain Nixon, East Kent University Hospitals, Ashraf Noureldin, Cumberland Royal Infirmary, Benjamin Perakath, Dr. Gray's Hospital, Nicholas Raison, King's College London, Kandiah Raveendran, Fatimah Hospital, Timothy Sullivan, Minneapolis Heart Institute, Achilleas Thoma, McMaster University, Mangesh Thorat, Wolfson Institute of Preventative Medicine, Queen Mary University of London, Andy Petroianu, Federal University of Minas Gerais, Ashwini Rao, Manpal College of Dental Sciences Mangalore, Michele Valmasoni, Università di Padova, Samuele Massarut, Centro di Riferimento Oncologico Aviano Italy, Anil D'cruz, Tata Memorial Hospital, Baskaran Vasudevan, MIOT Hospitals, Salvatore Giordano, Turku University Hospital, Donagh Healy, University Hospital Waterford, David Machado-Aranda, University of Michigan , Frederick H. Millham, Newton-Wellesley Hospital, Bryan Carroll, Eastern Virginia Medical School, Indraneilm Mukherjee, Florida Hospital Tampa, Peter McCulloch, University of Oxford, Yasuhiko Sugawara, Japanese Red Cross Hospital and David Rosin, University of West Indies.

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# CHAPTER 14

# DISCUSSION AND CONCLUSION



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*“Surgical research or comic opera: questions but few answers.”*

Richard Horton

## **PRELUDE TO THE DISCUSSION**

This chapter does not aim to repeat the detailed discussions of individual studies in their relevant chapters. Instead, the author aims to summarise what was found in the thesis, what it means and what the implications are for the future.

### **14.1 WHAT THIS THESIS HAS DEMONSTRATED**

This thesis set out with three hypotheses:

1. Study registration, use of protocols and reporting quality is poor in the Plastic Surgery literature.
2. Study registration can be improved by the creation of a new global research registry.
3. Reporting quality can be improved by the mandatory implementation of reporting guidelines in a journal.

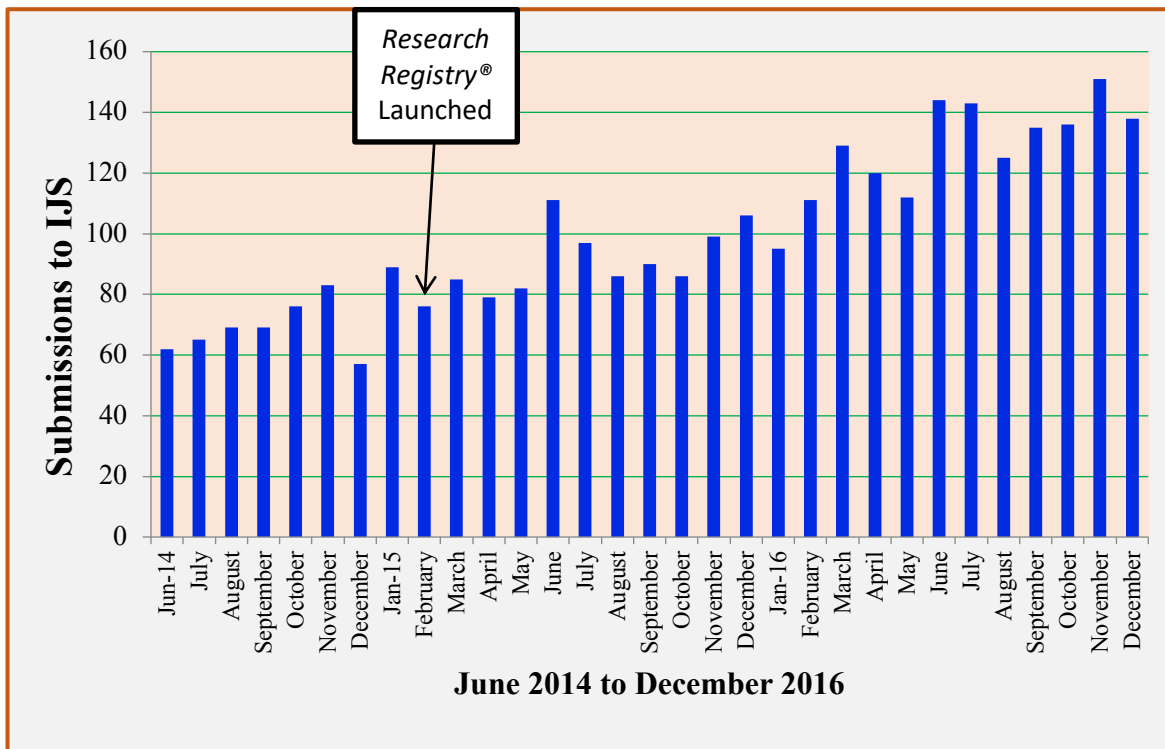
In the preceding chapters the author has provided evidence in support of these hypotheses. Chapter 4 demonstrated how only 4% of 595 recent research articles in plastic surgery had a protocol registered and only 0.5% published their protocol in a peer-reviewed journal. Just 33.3% of the RCTs were registered. The act of registration helps reduce reporting and publishing biases within the literature and these low rates are despite the DoH, Royal Colleges, United Kingdom General Medical Council (GMC), the U.S. Food and Drug Administration (FDA) and the International Committee of Medical Journal Editors (ICMJE)

mandating that clinical trials should be registered.<sup>1,2,3,4</sup> Indeed, in the case of the DoH 2013: “every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.”<sup>5</sup> The car registration plate metaphor shown in figure 2.7 is a powerful one. The language of the DoH changed in 2013 but prior to this, it was only clinical trials that had to be registered. The confusion that can stem from this position is clear, authors could say that are not conducting a clinical trial but a prospective or retrospective cohort study or a case series or any number of study designs which don’t carry the badge of a clinical trial. Why should ethical principles be circumvented in this way? The DoH 2013 is now clear – every research study.

So, what is the solution to the challenging problem of poor research registration? The author proposed a new global research registry, which would thus allow for the testing of the second hypothesis. Could it increase study registration? Following launch, chapter 5 analysed the first 500 registrations of the registry. These were all studies that were previously unregistered. The authors were attempting to submit to the International Journal of Surgery (IJS) but the submission process requires proof that the research has been registered, such as the trial registration number or unique identifying number (UIN), that only registries can provide once registration has taken place. Hence, authors were forced to register in order submit their work. It didn’t stop the flow of submissions with registrations for the first 500 studies coming from 57 countries and these studies included 1.77 million patients.

An important differentiator of the *Research Registry*® is that registration is instant. Hence authors are not waiting for days or even weeks to get the UIN. Making it easier for authors

to do the ‘right thing’, thinking of customer service principles and utilising their motivation to publish as a driver for the process was key. Once the registry was launched, all research studies involving human participants that were published in the IJS, had been registered prior to submission. There was also no perceivable impact of submissions to the journal (figure 14.1):



**Figure 14.1:** A graph of submissions to IJS over the period June 2014 to December 2016.

In chapter 6, the author analysed barriers to registration amongst 149 of the registrants who participated in the survey. It demonstrated how 45% of the participants registered their study at the time of journal submission, in order comply with the journal’s submission criteria. This percentage was much higher at the start of the registry, but as knowledge of its existence grows, people are registering more prospectively. The study also showed how 47.5% of participants found out about the *Research Registry* at the time of submission to

the IJS via the online author gateway. In addition, the *Research Registry* was the second most well-known registry in the group, with 41% aware of it (61/149), behind *ClinicalTrials.gov* with 62% (93/149). Given the 15-year head start of *ClinicalTrials.gov*, launching in 2000, this is not a bad start for a new global research registry amongst the cohort surveyed. It also shows the relatively poor penetration in this cohort of the other registries. This again shows how journals and registries can work together to increase awareness of this important step, which should be completed much earlier in the process, indeed prior to recruitment of the first patient in accordance with the Declaration of Helsinki.<sup>5</sup> Key barriers to registration were lack of awareness of the need to register and lack of time. The results showed how users want a registry that is simple, easy to use, fast and free.

The *Research Registry* has continued to develop. At the time of writing, it had registered over 3,000 studies, from over 100 countries, including over 10 million patients ([www.researchregistry.com](http://www.researchregistry.com)). It has become recognised by the Health Research Authority (HRA),<sup>6</sup> with 5% of certain types of HRA affiliated clinical trials being registered at the *Research Registry* (see appendix VII-X). Quality control, audit and curation have been maintained and enhanced. The breadth of studies and registrants continues to develop as word of mouth around the registry develops. Examples include; Help for Heroes (researchregistry1966), GSK Performance Lab (researchregistry1932), Public Health England (researchregistry1963), a Major International Multicentre Study including University of Oxford (researchregistry1986) and sports performance recovery garments for rugby players (researchregistry1932) as well as the traditional surgical base from which it started. Researchers are now ‘voting with their mouse’ for a registry that suits them better and deals with many of the barriers to registration.

Chapter 7 showed how reporting quality of recent observational studies in the field was poor. The mean compliance was 12 out of 22 mandatory items of the STROBE 2007 statement amongst 94 articles published in 2013. The top five most commonly missed items were; identifying the study design in the title/abstract (30% compliance), describing the setting, locations, relevant dates and periods of recruitment, exposure, follow-up and data collection (24%), any efforts made to address potential sources of bias (24%), numbers of individuals at each stage of the study (20%) and discussing the limitations of the work (40%). Similarly, chapter 8 demonstrated poor reporting quality amongst 79 systematic reviews published in 2013-14. They had a median PRISMA 2009 score of 16 out of 27. It was poorest for items related to the use of review protocol (5% compliance) and presentation of data on risk of bias of each study (18%).

Despite the guidelines being published 4-6 years prior to the relevant papers, plenty of time for authors to know of their existence and to utilise them, compliance was poor. Both studies essentially found that those writing them didn't go into the details of what happened and how they attempted to minimise or address bias. A study by Solomon et al. of all general surgical RCTs in 1990 found that the lowest quality trials, were those that had a surgeon as the principal author, which assessed an actual surgical procedure (as opposed to a drug being used in surgical patients) and which were published in a surgical journal.<sup>7</sup> Is it something about the surgical 'mind-set' that predisposes to poor reporting quality? Or is it a lack of formal research training? The answer is likely multifactorial and beyond the scope of this thesis but suffice to say, an effect does exist, and robust countermeasures are needed.

Surgical journals are ‘guilty’ of this too, proceeding to publish articles that were non-compliant despite editorial and peer-review. Indeed, chapter 9 showed how 62% of 193 surgical journals didn’t mention reporting guidelines at all within their guide for authors. Hence support for guidelines may only be lukewarm. Endorsing reporting guidelines may well be relevant. A Cochrane systematic review focusing on randomised controlled trials and CONSORT found that 25 of 27 outcomes assessing completeness of reporting, favoured CONSORT-endorsing journals over non-endorsers, of which five were statistically significant.<sup>8</sup>

So, what is the solution? Chapter 10, showed how the mandatory implementation of reporting guidelines in a single surgical journal can enhance reporting quality, when assessed in a before and after study. Compliance with STROBE increased 12% (n=152), with CONSORT it increased 40% (n=13) and with PRISMA it increased 58% (n=28). Other journals now need to take heed and strongly consider adopting such practices.

This thesis has proposed and explored successful solutions to two of the most challenging ‘Rubik’s Cubes’ in scholarly publishing and healthcare – poor research registration and poor reporting quality – longstanding, pervasive and resistant problems that have plagued the surgical and wider healthcare literature, leading to quotations like the one at the start of this chapter.

The solutions have involved utilising a stalwart of scholarly publishing that only recently celebrated its 350<sup>th</sup> birthday – the humble scientific journal.<sup>9</sup> The journal, its officers (editors, peer-reviewers, etc.) and its policies have acted as an important gatekeeper, ensuring things get done, be it registration or compliance with reporting guidelines. This is analogous to gatekeepers at certain establishments who ensure only people wearing certain

clothing e.g. a suit and tie get in, the person with jeans and trainers is turned away. Research registration and compliance with reporting guidelines is the ‘dress code’, its wearing the ‘right jacket’ for a scientific paper.

Once past the policy/electronic gateway gatekeeper, there are internal gatekeepers, the editors and peer-reviewers who are the ‘guardians’ of the scholarly literature. They too must ensure that the ‘dress code’ is adhered too. Front-loading these policies to the ‘front gate’ or the author gateway, preventing non-compliant papers getting into the journal’s ecosystem is paramount to reducing entropy. Gradually people learn what the dress code is and are better prepared in the future.

## 14.2. ACHIEVING OBJECTIVES SET FOR THIS THESIS

This thesis also had 10 objectives which are listed below together with the chapter in which they were achieved in this thesis (table 14.1).

<b>TABLE 14.1: OBJECTIVES AND THEIR ACHIEVEMENT WITHIN THE THESIS</b>		
<b>Objective No</b>	<b>Objective Description</b>	<b>Achieved within thesis</b>
<b>1</b>	To determine the levels of evidence in the recent Plastic Surgery literature, to compare with other surgical specialties and assess trends over time.	Chapter 3
<b>2</b>	To determine the rates of study registration and protocol publication in the Plastic Surgery literature.	Chapter 4
<b>3</b>	To build and implement a new global research registry to boost study registration prior to journal submission.	Chapter 5
<b>4</b>	To determine the barriers to research registration.	Chapter 6
<b>5</b>	To determine the reporting quality of observational studies in Plastic Surgery.	Chapter 7
<b>6</b>	To determine the reporting quality of systematic reviews in Plastic Surgery.	Chapter 8
<b>7</b>	To determine the existing support for reporting guidelines within surgical journals.	Chapter 9
<b>8</b>	Assess the impact of the mandatory implementation of reporting guidelines in a surgical journal.	Chapter 10
<b>9</b>	To develop a reporting guideline for surgical case reports.	Chapter 11
<b>10</b>	To develop a reporting guideline for surgical case series.	Chapter 12 and 13

The SCARE and PROCESS reporting guidelines were published in October and December 2016 respectively. They have already had a significant impact, according to Google Scholar (<https://scholar.google.com>), the SCARE guideline has been cited over 700 times and the PROCESS guideline has been cited over 100 times at the time of writing. Dedicated websites have been set-up at [www.scareguideline.com](http://www.scareguideline.com) and [www.processguideline.com](http://www.processguideline.com) and growing numbers of journals are endorsing and using them. The author hopes broader uptake amongst surgical journals will ultimately help drive reporting quality forward for these study types. The limitations of the individual studies were discussed within the relevant chapters.

### **14.3 LIMITATIONS AND IMPLICATIONS FOR FUTURE RESEARCH**

In each chapter of this thesis, limitations have been discussed for the relevant studies. In this section, the author wishes to discuss limitations that cross-cut the thesis and also detail potential solutions. The studies contained within this thesis represent a systematic and, in some cases, first-time look at a number of areas that constitute an EBM “state of the union” as far as the specialty of Plastic Surgery is concerned. This work is a veritable ‘stake in the ground’, providing a benchmark for future comparison. Indeed, such repetition would be useful. Are plastic surgeons responding to the EBM drive initiated by specialty associations? How are levels of evidence changing five years after the results shown in chapter 3? Is research registration and protocol publication increasing? If so how does that impact on the quality of the subsequent research but methodological and reporting quality? Are reporting guidelines being adopted more consistently by authors and by the journals

themselves? Will journal submission processes and workflows incorporate mandatory reporting guideline submission? These are all exciting questions for the future and the author has aimed to provide sufficient methodological details in each chapter to allow for such repetition.

In chapter 3 the levels of evidence work has some important limitations that are worth highlighting. Assessing the three highest impact factor journals with the specialty, ignores the fact that a significant amount of content is published in other journals (both specialty ones with lower impact factors and more general journals with higher impact factors). However, this is true for all these specialties. It is also more complex to do such a search and select and ‘pidgeon-hole’ articles that serve as ‘representatives’ for the specialty. High quality large RCTs in such journals may incorporate multiple specialties in different treatment arms and so again deciding where such articles go is more complex. Hence the methodology is easy to repeat in a few years. An alternative approach would be to conduct the search using Medical Subject Heading (MeSH) for the different specialties. This may be better at capturing higher impact articles published outside of the selected journals in more broad scope surgical and medical journals.

Very high impact journals tend to publish RCTs, systematic reviews of RCTs and large database-based analyses which drive their citations and hence impact factor. They don’t necessarily represent what the ‘bread and butter’ of a specialty is achieving. The top three specialty journals can act as a useful barometer for assessing the direction of travel within the specialty. Indeed, many of them are journals for the specialty association representing large national and international groups within the specialty. Some journals, such as JBJS

have formed their own dedicated case reports journals. Hence the number of case reports published in the main journal drop significantly. This would tend to result in proportionally higher LOE within these journals specifically.

The other limitation of our approach was to select journals on the basis of impact factors. The use of the Journal Impact Factors as a tool by which to assess a journal's quality is not without significant and longstanding criticism.<sup>18</sup> For instance, lack of normalisation makes comparisons difficult between fields, their potential for manipulation, the length of the citation window, what is deemed a citable item and the fact that they don't necessarily relate to actual usage of an article or its subsequent social media discussion and influence.<sup>18</sup> Impact factors of course are a form of journal-level metric. Article level metrics are increasingly important since a highly cited article could be published in a journal with a relatively low impact factor.

Part of the legacy of this research work includes the setting up of the *Research Registry*® ([www.researchregistry.com](http://www.researchregistry.com)). Whilst the authors information technology skills are subjectively at a reasonably good level, they have developed quite significantly from this work. The *Research Registry*® now has over 3,000 registrations. Hence, a follow-on study to the one assessing the first 500 registrations in this thesis would be welcome and is indeed planned – titled RR3,000. It would assess the impact of the registry, assessing both activity and quality metrics in a similar fashion to the RR500 study.

The section Editor's Choice on the home page of the registry illustrates just how diverse the registrations have become. From initially being focussed on surgery, to now including medicine, anaesthesia, critical care, sports performance, public health, mental health and even genomics with the registration of the Scottish Participation in the Genomics England 100,000 Genomes Project.<sup>10,11</sup> This growth and development has been most welcome and truly humbling. It does bring with it a responsibility to ensure the registry remains on a stable footing going forward as so many researchers have put their faith in the platform.

The quality measure utilised five points for auditing the registry data for quality (table 5.1). This is as opposed to using the 24-item WHO data set which the primary registries use for audit purposes.<sup>12</sup> This is an important limitation since it doesn't include as large a set of items and is a less comprehensive measure of the completeness of registration. Going forward the 24-item set would need to be used for audit purposes. The registry would need to acquire funding and administrative assistance to help it move along a more resource intensive audit path. In addition, the potential to allow its data to be contributed to the WHO platform is there and needs to be explored further.

The RR3,000 study will also help examine the state of the registry, the diversity of registration it is achieving and how it is making progress in these aforementioned aspects of quality as well as quantity of registrations. A user survey could also be carried out periodically to better understand barriers to registration and how the registry could be improved. Boosting the response rate for such surveys is important, given a 16.1% response rate was achieved in the survey in chapter 6.

Developing strategies that try to engage more with researchers is called for. Perhaps an ongoing study, whereby participants register and are immediately sent a survey to complete or it could be done on a rolling basis, month by month. These results could then be summed over the course of a year to give the results for that year. Using specialist mailing software like MailChimp and confirming email addresses would be useful methodological changes that could improve our response, rate as well following the principles of good survey design, such as piloting, simple layout, being concise, etc.<sup>13</sup>

The work done with reporting guidelines showed that particular items are more poorly reported than others. Table 7.4 (STROBE compliance) and table 8.1 (PRISMA compliance) showed common themes in what was least well reported. In particular these were items that related to; risk of bias, efforts to reduce potential sources of bias, handling of missing data and discussing the limitations of the study. This consistency across observational studies and systematic reviews is significant and gives us an important insight into what can go wrong most frequently when surgeons report research.

Author education as well as increasing the robustness of peer-review to deal with these frequently missed items would be important steps forward for our literature and the progress of research quality. Better support amongst journals for reporting guidelines and their mandatory implementation would also help. Chapter 10 showed that real benefits are there to be gained when reporting guidelines are weaved into the ‘fabric’ of a journal’s submission, workflow and peer-review process. Over time, reviewers and editors will

gradually become more accustomed to them and accept them as an important tool which should be used by authors prior to submission, so the editors and reviewers can focus on what's present, not what's missing.

The development of the SCARE and PROCESS guidelines using the DELPHI technique was discussed in chapters 11 and 13 respectively. The strengths, weaknesses, limitations and alternatives to the Delphi technique were discussed in detail in chapter 11. In summary the criticisms centre on forcing consensus rather than allowing it to more naturally form, variations in outcomes based on how the questions are posed, concerns over scientific validation (organising a series of opinions, rather than using logic), problems of dealing with bimodal distributions, reproducibility and external validity.<sup>14</sup> A range of alternatives were discussed in chapter 11 but they either suffer from being over complicated, being face-to-face where big personalities can dominate or not having a mechanism for fostering consensus in a disparate group. The Delphi technique is now well established for reporting guidelines development and the key process of giving feedback after each round does help foster consensus and this was reflected in the SCARE and PROCESS guideline development.

The impact of the SCARE and PROCESS guidelines on the completeness and transparency of reporting will be an interesting area for future study. A before and after study examining the impact of the guideline on the completeness of reporting would be useful. Such research would also show which areas are better dealt with by authors and which areas continue to be poorly reported. Why they would continue to be poorly reported is also an interesting

question. Targeted interventions towards addressing those specific areas could then be developed.

In chapter 2, the nature of surgical innovation was discussed in detail and how it differs from drug development. Significant steps have been taken in recent years to provide a more structured framework for surgical innovation development. The IDEAL Framework represents a significant development in this area.<sup>15</sup> The framework follows the natural history of surgical innovation and defines the appropriate study to be performed at each step of the pathway:

<b>TABLE 14.2 THE IDEAL FRAMEWORK</b>				
<b>Stage 1 IDEA</b>	<b>Stage 2a DEVELOPMENT</b>	<b>Stage 2b EXPLORATION</b>	<b>Stage 3 ASSESSMENT</b>	<b>Stage 4 LONG TERM MONITORING</b>
Initial report  Innovation may be planned, accidental or forced  Focus on explanation and description	“Tinkering”  (rapid iterative modification of technique and indications)  Small experience from one centre  Focus on technical details and feasibility	Technique now more stable  Replication by others  Focus on adverse effects and potential benefits  Learning curves important  Definition and quality parameters developed	Gaining wide acceptance  Considered as possible replacement for current treatment  Comparison against current best practice (RCT if possible)	Monitoring late and rare problems, changes in use & quality of surgical performance

The IDEAL Framework seems logical and provides a more structured way for developing surgical innovation. It's an integrated step-wise pathway, analogous to the pharmaceutical pathway outlined in chapter 2 where an innovation starts with toxicity studies to small groups to eventually having an RCT.<sup>15</sup> In surgery, there is a 'huge gap' between the first experience (typically a case report) and an RCT with many innovations never crossing that gap. As a result, innovation proceeds in a more haphazard, trial and error way, with less stringent governance, less regulatory oversight and potentially exposing patients to unnecessary risks.<sup>16</sup> The framework provides that 'road-map' to an RCT or other definitive study, providing surgical innovators with clear direction as to what the key question is at each stage.

Importantly, IDEAL is showing increasing signs of uptake within the surgical community. A practical guide to using the framework has been published.<sup>17</sup> There are now increasing numbers of publications utilising IDEAL, including a recent one from Plastic Surgeons examining decision modelling for breast reconstruction in the earliest stages of the IDEAL framework.<sup>18</sup> This is most encouraging, as are; the numerous publications housed in the library of the IDEAL website, the framework paper has now been cited over 550 times, the opening of the China IDEAL Centre and growing attendance at the IDEAL Conferences.<sup>19,20</sup> However, there is still a long way go to raise awareness and usage. Research using the IDEAL framework for new innovation should be encouraged but this will require more collaboration, so surgeons researching and leading the development of a particular innovation, can work in concert and make progress together.

In chapter 2, the author discussed Potter et al's survey of breast reconstruction surgeons.<sup>21</sup> They concluded by underscoring the need to help surgeons understand evidence, equipoise and bias and stated that investment into education and infrastructure for RCTs would be needed. Developing such postgraduate education programmes to help surgeons become comfortable with equipoise, understand evidence better and move towards more high quality RCTs is a major challenge. However, the rise of trainee research collaboratives (TRCs) is an important step in this direction. Jamjoom et al showed that the 24 TRCs they examined, had a portfolio of 80 projects, 16% of which were RCTs.<sup>22</sup> Examples include the ROSSINI trial, from the West Midlands Research Collaborative (with 104 citations thus far) and more recently, the NINJA study, a pilot RCT from the Reconstructive Surgery Trials Network (RSTN).<sup>23,24</sup>

This is most encouraging. Indeed, the author is part of this movement by setting up the Academic Surgical Collaborative (ASC) in 2014.<sup>25</sup> Incidentally, the growth and development of TRCs, may well help the uptake of IDEAL, since stages within the IDEAL framework (e.g. stage 2b) require collaboration between groups working with the same innovation, developing and sharing data and learning from their shared experiences as they build the conditions necessary for a definitive study which should be multi-centre to show external validity.<sup>15</sup>

This was an important step forward in conducting the research contained in this thesis. The author felt it was important to have data collected independently, as this would increase the validity of the work and reduce the potential conflict of interest or accusation that the data had been 'massaged' in any way to fit the hypotheses made at the start of the thesis. These

medical students were members of the ASC. The author had been working informally with medical students in years prior, developing research projects and attractive motivating people who were interested in getting involved. So, it made sense to formalise this into a trainee research collaborative, develop a website, management team, roster of projects and so on. Whilst the involvement of motivated and energetic medical students was welcome, there are a number of key learning points the author would like to reflect on.

When discussing things face to face and answering questions about a project when they are first introduced, is relatively straightforward. Such verbal face-to-face communication stimulates engagement and allows for rapid discussion and responses from the author. However, it's what happens afterwards that's often a route cause of frustration and problems. People can forget instructions, team members can become unwell, have exams, go on holiday, stop answering emails and momentum in a project can be lost and fragmentation and stagnation can set in. Hence, a key learning point has been around how to better support students during these projects.

Communication skills are vital, and the authors have been in sharp development. Conventionally one thinks of someone with great communication skills as being a great orator, clear, concise with good diction. However, it was the written communication which was lacking in early projects. Having detailed written instructions, a research protocol (with all the details that journal editors often ask us to remove) and a frequently asked questions (FAQs) document, should also be developed for all such project in the future.

This helps to support the medical students away from face-to-face meetings. Group dynamics are important too as some medical students could feel afraid to ask questions to the group by email, for fear of embarrassment. When questions have been posed, the author has noted that others were also thinking the same but were afraid to ask. Indeed, there are many issues which arise with one person or sub-group, that the wider group could benefit from or if they simply forget a particular operational detail discussed sometimes months previously.

How can we better train and support medical students getting involved in such research? Technology may well be able to help group working and this is an area of rapid development. Developing a research skills training programme has now become an important aspect of the ASC's future and the author is taking steps towards such development. A cadre of more knowledgeable ASC members getting involved in research going forward will lead to better quality of research and help inspire more medical students to get involved.

#### **14.4 WHAT ARE THE IMPLICATIONS FOR CLINICAL PRACTICE: MOVING EVIDENCE-BASED PLASTIC SURGERY FORWARD**

Choudhry et al's systematic review showed that clinical performance can deteriorate over time, after initially peaking in the years after graduation.<sup>26</sup> Indeed, they observed a 0.5% increase in mortality for every year since the treating physician had graduated from medical school, despite controlling for a patient's probability of death, hospital location and practice environment, physician specialty, board certification, and the volume of patients seen. They

postulated that older physicians may be less likely to update their “toolkits”, less likely to adopt new therapies and less receptive to new clinical guidelines and standards.<sup>26</sup>

A commitment to lifelong learning and keeping up to date must be integral to the foundations of ethical professional practice. Governments also want enduring, sustainable, evidence-based policies towards disease prevention and management that integrates scientific and clinical evidence with health economics and consumer research.<sup>27</sup> More cost-effectiveness studies are needed to ensure the dimension of cost can be considered given limited resources and therefore the need to prioritise.

The future the author hopes will include mandatory adherence by authors to reporting guidelines, including the ones developed during this doctorate, with enforcement by peer-reviewers, editors and journal submission systems and publishers. The Declaration of Helsinki now mandates, that all research is registered prior to recruitment of the first subject.<sup>28</sup> The launch of the *Research Registry*®, developed as part of this doctorate will be, the author hopes, a step in the right direction.

The author encourages Plastic Surgeons to register their work prospectively and submit their protocol for peer-review, hence opening it up to peer-review and a wider discussion, feedback and potentially a ‘course-correction’, such as refining the research question or a methodological enhancement. Thus, preventing wasted time, funding and cynicism. Authors and journals need to publish negative studies to prevent repetition, allow for learning and to prevent “back to the future” studies.

A system to transparently report complications (like the yellow card system for drugs) without fear of legal ramifications is needed. Above all, this all means greater effort, less haste and a stronger focus on the quality of research, implementation in clinical practice, collaboration and a multicentre approach. Future work will focus on utilisation, compliance with and impact of this work.

A pathway for the development of high quality research is given in figure 14.2:



**Figure 14.2:** A pathway for developing higher quality research projects.

## 14.5 THE BROADER PICTURE

Over 2500 years ago, Hippocrates declared, that the physician needed to “*rely on actual evidence rather than on conclusions resulting solely from reasoning, because arguments in the form of idle words are erroneous and can be easily refuted*”.<sup>29</sup>

Healthcare today is far more complex than at Hippocrates' time and doctors have to be able to justify their treatment decisions robustly. Pooling expertise through multidisciplinary teams has shown significant benefits for patient outcomes and for dealing with increasingly complex patients and diverse therapeutic modalities that no one physician or surgeon can master.<sup>30</sup>

Medical knowledge is growing at a phenomenal rate, postulated to be doubling every 18 months.<sup>31</sup> Each year, 800 new primary care guidelines are added and more than 2,000 new research papers are added to MEDLINE each day, this is a considerable challenge.<sup>32</sup>

Glasziou has argued<sup>31</sup>:

*“The search engine is now as essential as the stethoscope ... a 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system. The medical curriculum should reflect this importance of changing information for today's practitioner – the necessary skills must be taught and assessed with the same rigour as the physical examination.”*

Physicians and surgeons now find themselves in a perfect storm – stretched clinically dealing with a high turnover of patients of increasing complexity and information overload. Strong leadership and educational reform is now required.<sup>33</sup> Critically appraising research is difficult. Findings should be interpreted cautiously, and one should look for multiple high-quality studies showing a similar effect or a high quality systematic review of such evidence. Changing clinical practice should be based on robust evidence, appropriately interpreted and with patient safety of utmost concern. New interventions should be developed in EBM-rich pathways like IDEAL (idea, development, exploration and long-term follow-up).<sup>34</sup> Recent guidance has been provided on adopting new aesthetic surgical

innovations as well.<sup>35</sup>

EBM is not just the right thing to do by the patient, as its use will likely result in the best outcomes, but it is a clear and present answer (at least in part) to the perfect storm. The first published cost-effectiveness study of EBM clinical pathways in 2010, found that costs were 35% lower for those patients on-pathway rather than off, with no difference in overall survival.<sup>36</sup> EBM education is clearly needed to deal with the problems and the pressures of 21<sup>st</sup> century healthcare. Such skills must complement the traditional focus on craft skills to enable the modern-day Plastic Surgeon to consistently deliver high quality care.

## 14.6 CONCLUSION

There is a perfect storm developing in 21<sup>st</sup> century healthcare. Rising complexity and patient expectations in the context of fiscal restraint pose enormous challenges. EBM may be the best-kept secret in dealing with the ‘storm’. Such an approach, preferences management pathways that deliver better outcomes and often at less relative overall cost to society more broadly.

EBM in the field of Plastic Surgery has a long way to go. Study registration, protocol use and reporting quality are poor in plastic surgery. Potential solutions to these long-standing and difficult problems have been developed and explored within this thesis. These include the development of the *Research Registry*® and the mandatory implementation of reporting guidelines, with both measures front-loaded within a gatekeeper framework for journals.

It is now for Plastic Surgeons and the wider surgical community to pick up the gauntlet. Only then can we robustly defend against Richard Horton's assertions. Patients and the public need to be reassured of the existing compact with surgeons and that surgical research is no "comic opera." As a community, we increasingly must hold ourselves to the highest standards, to push forward high-quality research, evidence based surgical practice and the best outcomes for our patients and society at large.

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# APPENDIX I



ELSEVIER



## The methodological quality of randomized controlled trials in plastic surgery needs improvement: A systematic review

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Received 11 May 2012; accepted 7 November 2012

### KEYWORDS

Randomised controlled trials; Methodological quality; Linde Internal Validity Scale; Bias

**Summary** *Background:* Our objective was to assess the methodological quality of randomized controlled trials (RCTs) in Plastic Surgery.

*Methods:* An information specialist searched MEDLINE for the period of 1 January 2009 to 30 June 2011 for the MESH heading "Surgery, Plastic" with limitations for English language, human studies and randomized controlled trials. Results were manually searched for RCTs involving surgical techniques. The papers were then scored with the authors' seven point extended version of the Linde Internal Validity Scale (ELIVS). Secondary scoring was then performed and discrepancies resolved by consensus.

*Results:* 57 papers met the inclusion criteria. The median ELIVS score was 3.0 with a range of 1.0–6.5. Compliance was poorest with use of intention to treat analysis (4%), blinding of patients (23%) and the handling and reporting of patient withdrawals (25%). There was no statistically significant correlation between journal ELIVS score and 2010 impact factor or number of authors (Spearman rho 0.10 and 0.27 respectively). Multicentre trials had a higher average ELIVS score than single centre ones (3.6 vs 2.7) although this did not reach significance. There was no correlation between the volume of RCTs performed in a particular country and methodological quality.

*Conclusion:* The methodological quality of RCTs in Plastic Surgery needs improvement.

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## Background

Randomized controlled trials (RCTs) are the best way of determining the cause and effect relationship between interventions and outcomes. However, poor quality RCTs contain irremediable bias.<sup>1,2</sup> The purpose of the current study is to systematically review the methodological quality of recent surgical RCTs in Plastic Surgery.

## Methods

### Search methods

An information specialist based at a plastic surgery unit (Queen Victoria Hospital) searched MEDLINE from 1 January 2009 to 30 June 2011 for the Medical Subject Headings (MESH is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed) heading "Surgery, Plastic" with the 'explode' function activated and limitations set for English language, human studies and randomized controlled trials. Results were then manually searched by two of us (EE and CFC) for relevant RCTs involving surgical techniques. Papers involving purely pharmacological therapies in all arms, cost analyses, study protocols, interim or non-randomized studies, short communications and RCTs involving virtual or simulated procedures were excluded.

### Scoring

Primary scoring of the RCTs was done by EE. These scores were then validated and checked by CFC and any disagreements were resolved by consensus. An extended version of the Linde Internal Validity Scale<sup>3</sup> (see Table 1) was used to score the RCT's methodological quality:

The LIVS builds on the Jadad score,<sup>4</sup> is simple, easy to remember and has been used on numerous occasions<sup>5,6</sup> for the assessment of methodological quality. Our extension is to supplement the standard LIVS with allocation concealment to form an extended version (ELIVS).

Potential correlations between ELIVS score and 2010 impact factor, number of authors, single vs multicentre study, year of publication and country of corresponding author were assessed. Spearman rho was calculated using SPSS version 20.

## Results

From an initial set of 254 papers retrieved from MEDLINE, 63 were selected following a manual search and assessment of the abstract. Subsequent to complete download of all 63 papers, six were excluded for being a study protocol, purely pharmacological or theoretical, retrospective or an interim study. This resulted in 57 RCTs which met the inclusion criteria (seven were multicentre), published across 28 journals. All RCTs compared treatment interventions and none related to diagnosis (Figure 1).

During the scoring process, out of 399 items, there were 31 initial disagreements ( $\kappa = 0.86$ ) between primary and secondary scorers and these were resolved through discussion. The median ELIVS score was 3.0 (range 1.0–6.5, interquartile range 2.5). There was no significant trend in improvement of median ELIVS scores (see Table 2) (Table 3):

### ELIVS score and impact factor

There was no correlation between ELIVS score and impact factor (Spearman rho correlation = 0.10,  $p = 0.295$ ), see Figure 2 below:

**Table 1** Extended Linde Internal Validity Scale items (items 7i and 7ii were worth 0.5 points each).

Item	Description	Further detail
1	Treatment allocation	Was it randomized?
2	Randomization method	The method of randomization was described in the paper, and that method was appropriate
3	Allocation concealment	Steps taken to conceal the allocation sequence was detailed and this was sufficient
4	Post-randomization baseline comparison	Usually in a table. Showing both groups are similar postrandomization for all known prognostically important factors
5	Patients blinded	The method of blinding was described, and it was appropriate
6	Evaluators blinded	The method of blinding was described, and it was appropriate
7i	Handling and reporting of withdrawals	Full accounting for all patients who entered the trial
7ii	Intention to intention treat analysis	A per-protocol analysis could be provided in addition as part of a sensitivity analysis

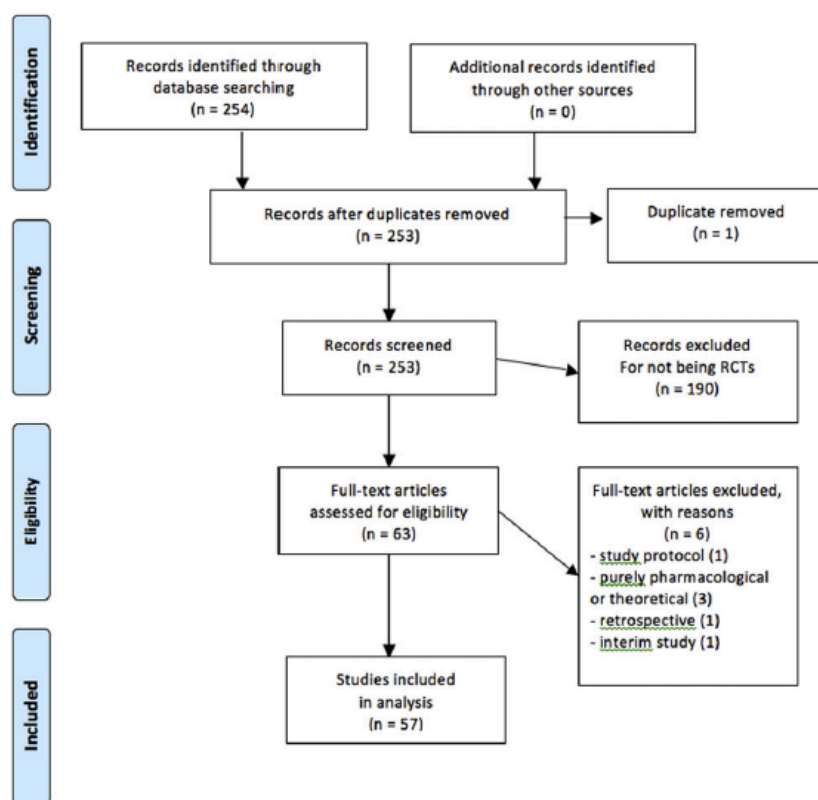


Figure 1 PRISMA flow diagram, illustrating how papers were selected (adapted from Moher et al., 2009).<sup>7</sup>

### ELIVS score and number of authors

There was no correlation between ELIVS score and number of authors per study (Spearman rho correlation = 0.27,  $p = 0.114$ ), see Figure 3 below:

### Single centre vs multicentre

Multicentre trials ( $n = 7$ ) had greater mean ELIVS scores than single centre trials ( $n = 50$ ) but this was not statistically significant ( $p = 0.66$  on Chi-squared test).

Table 2 Summary statistics for the ELIVS scores for 2009–2011.

Year	Number of RCTs	Median ELIVS score	Interquartile range	Range
2009	26	3.0	2.0–4.9	1.0–6.5
2010	21	3.0	2.0–4.0	1.0–6.5
2011 <sup>a</sup>	10	3.5	3.0–3.5	2.0–6.5

<sup>a</sup> To 30 June only.

### Discussion

Over the last decade there have been increasing calls for the adoption of an evidence-based medicine (EBM) approach within surgery and this trend includes plastic surgery. The evidence base in plastic surgery is still dominated by case series with higher levels of evidence and RCTs in particular being encouraged.<sup>8–15</sup> A review by Chang et al.<sup>16</sup> of 1419 manuscripts published in aesthetic plastic surgery journals over 10 years, found that only 3.2% were randomized.

In prior research,<sup>17</sup> we looked at 164 surgical RCTs over a three year period, across six surgical specialties, involving approximately 20,000 patients. We found the reporting quality to be poor with an average CONSORT score of 11.2 out of 22. Previous reviews of surgical RCTs have shown that in 20%, the conclusions were not supported by the data.<sup>18</sup> Furthermore, the lowest quality RCTs were those that involved a surgical technique, were published in a surgical journal, or where a surgeon was the principal author.<sup>19</sup>

The lowest scoring item in our study was use of an intention to treat analysis (ITT, only 4%). This is consistent with other surgical specialties where less than half of all RCTs in a previous series reported ITT.<sup>17</sup> This involves analysing participants in the groups they were initially

**Table 3** Compliance with individual items of the ELIVS score.

ELIVS scores in detail		
Criteria	Abbreviated description	Compliance <i>n</i> = 57
1	Treatment allocation	100%
2	Randomization method	37%
3	Allocation concealment	32%
4	Post-randomization baseline comparison	65%
5	Patients blinded	25%
6	Evaluators blinded	44%
7i	Handling and reporting of withdrawals	25%
7ii	Intention to treat analysis	4%

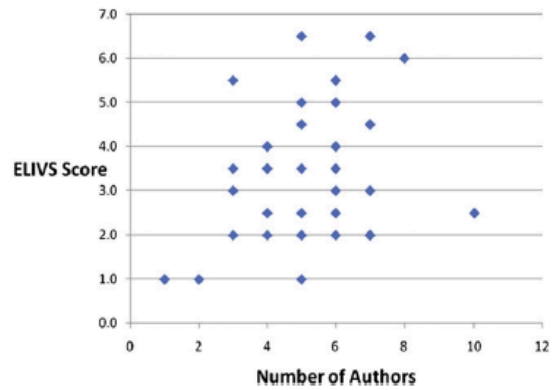


Figure 3 ELIVS score vs number of authors.

assigned; despite cross-over, withdrawal, loss to follow-up, poor compliance or response to treatment. The alternative is a per-protocol analysis where participants are analysed in accordance with the treatments which they actually received. ITT may seem counterintuitive to surgeons. However, ITT helps maintain the fidelity of randomization. Omitting ITT may compromise the balance of prognostic factors and hidden confounders between the two groups. Therefore, bias can be introduced if ITT is not utilized. Another advantage of an ITT analysis is that it forces clarity with respect to protocol deviation, non-compliance, withdrawals and cross-overs.<sup>20</sup> ITT analysis may reliably suggest what will happen in 'real life' outside the 'bubble' of trial conditions as it incorporates the choices that patients make. A per-protocol analysis can be done in addition to ITT as part of a sensitivity analysis which could help provide useful information on therapeutic efficacy and patient selection.

Several studies have found plastic surgery RCTs to need improvement in methodological quality. McCarthy et al.<sup>21</sup> analysed level 1 studies in five plastic surgery journals from 1978 to 2009. They found that 39% reported randomization technique, 15.5% performed a power analysis and 20% were not blinded. Velga et al.<sup>22</sup> analysed 96 RCTs in

plastic surgery published 2004–8 and found that 29% appropriately described allocation concealment, a percentage not significantly different than the 32% in our review ( $p = 0.89$  Yates corrected Chi square test).

Allocation concealment is an important step towards true randomization and hence was included in our ELIVS score. It aims to prevent individuals in charge of allocating patients and treatments to introduce bias. Studies have shown how trial allocation concealment details are often unclear or inadequate.<sup>23</sup> Other work has shown how this is associated with a 20–30% exaggeration of the treatment effect compared with trials of the same interventions with adequate concealment.<sup>1,2,24–28</sup> Momeni et al.<sup>29</sup> analysed 172 RCTs from three plastic surgical journals during 1990–2005 and found that only 34% were double blinded, 12% reported on their allocation concealment and 37% described participant drop-outs. It should be noted that the CONSORT 2010 statement doesn't specifically advocate the terms; single, double or triple blinded, rather who was blinded after assignment to interventions (for example participants, care providers and assessors) and how exactly.<sup>30</sup>

Taghinia et al.<sup>31</sup> analysed 163 RCTs performed over a 20 year period and found an average Jadad score of 2.3. They also determined that RCTs with higher methodological quality had higher reporting quality as well (as measured using CONSORT). The same correlation has been determined by others.<sup>24,32–35</sup> Ayeni et al. looked at 463 RCTs published between 1990 and 2010 in nine plastic surgery journals. They found only 19% performed a priori power analysis or sample size calculation, although there was evidence this was improving (Table 4).<sup>36</sup>

One of the limitations of our study, is that authors may have omitted details around these seven fundamental principles of an RCT. We feel that crucial markers of quality should be stated explicitly in the paper and the team of authors, peer-reviewers, and editors should recognize this in the final version of the accepted paper. Another limitation was our analysing papers by publication date rather than the submission date, since publication lag times for journals varies. Other limitations of our study include restriction to the English language and searching only MEDLINE.

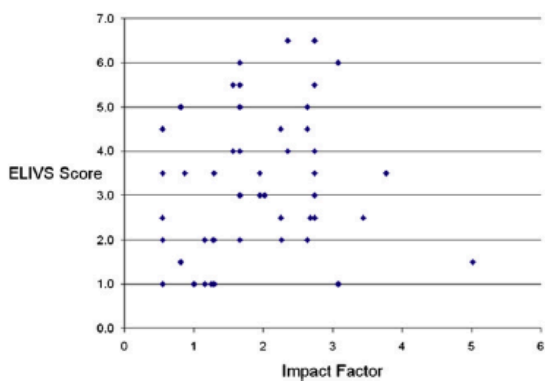


Figure 2 ELIVS score vs impact factor.

**Table 4** A summary of the key findings from previous studies.

Study	Number of studies and years searched	Key findings
Veiga et al., 2011	96, 2004–8	29% appropriately described allocation concealment
McCarthy et al., 2010	309, 1978–2009	39% reported their randomization technique, 15.5% performed a power analysis and 20% were not blinded at all
Momeni et al., 2008	172, 1990–2005	34% were double blinded, 12% reported on their allocation concealment and 37% described participant drop-outs
Taghinia et al., 2008	163, 1986–2006	An average Jadad score of 2.3. RCTs with higher methodological quality had higher reporting quality as well (as measured using CONSORT)
Ayeni et al., 2012	463, 1990–2010	19% performed a priori power analysis or sample size calculation

## Recommendations

1. Editors and peer-reviewers need to ensure that RCTs missing key quality criteria are not published.
2. A trial methodologist or biostatistician should be involved in the planning and analysis phases of an RCT. This is more likely to ensure robust methodology, a pre-trial power calculation (preventing type II errors) and proper statistical analysis of the results.
3. Researchers should define clear research questions with clear, well-defined primary and secondary outcomes and should utilize an intention to treat analysis.
4. Reporting guidelines like CONSORT should be used for RCTs and PRISMA for systematic reviews and meta-analyses.

## Conclusion

RCTs in Plastic Surgery have increased steadily over the last two decades. However, RCTs methodological and reporting quality still requires improvement. We highlight the low use of intention to treat analyses and allocation concealment, which have become recognized as key markers of quality and bias minimization.

## Ethical approval

Our research did not require approval from an ethics committee or informed patient consent.

## Funding

None received.

## Conflicts of interest

None.

## Acknowledgements

The authors would like to thank Patricia Rey, Information Specialist at Queen Victoria Hospital NHS Foundation Trust for her guidance and meticulous search of the literature to retrieve the initial set of papers.

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# APPENDIX II

## Randomised controlled trials in plastic surgery: a systematic review of reporting quality

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Received: 31 May 2013 / Accepted: 9 September 2013 / Published online: 30 October 2013  
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### Abstract

**Background** We recently conducted a systematic review of the methodological quality of randomised controlled trials (RCTs) in plastic surgery. In accordance with convention, we are here separately reporting a systematic review of the reporting quality of the same RCTs.

**Methods** MEDLINE® and the Cochrane Database of Systematic Reviews were searched by an information specialist from 1 January 2009 to 30 June 2011 for the MESH heading ‘Surgery, Plastic’. Limitations were entered for English language, human studies and randomised controlled trials. Manual searching for RCTs involving surgical techniques was performed within the results. Scoring of the eligible papers was performed against the 23-item CONSORT Statement checklist.

Independent secondary scoring was then performed and discrepancies resolved through consensus.

**Results** Fifty-seven papers met the inclusion criteria. The median CONSORT score was 11.5 out of 23 items (range 5.3–21.0). Items where compliance was poorest included intervention/comparator details (7 %), randomisation implementation (11 %) and blinding (26 %). Journal 2010 impact factor or number of authors did not significantly correlate with CONSORT score (Spearman  $\rho=0.25$  and  $0.12$ , respectively). Only 61 % declared conflicts of interest, 75 % permission from an ethics review committee, 47 % declared sources of funding and 16 % stated a trial registry number. There was no correlation between the volume of RCTs performed in a particular country and reporting quality.

**Conclusions** The reporting quality of RCTs in plastic surgery needs improvement. Better education, awareness amongst all stakeholders and hard-wiring compliance through electronic journal submission systems could be the way forward. We call for the international plastic surgical community to work together on these long-standing problems.

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**Keywords** Randomised controlled trials · Research methodology · Reporting quality · Consort · Levels of evidence

### Introduction

Randomised controlled trials (RCTs) represent the criterion standard in evaluating healthcare interventions. However, RCTs can yield biased results if they lack methodological rigour [1], especially where surgical techniques are involved [2]. Readers need complete, clear and transparent information in order to assess a trial accurately. Unfortunately, many trials fail to

provide critical information in published reports [3–5]. Inadequately reported RCTs are associated with bias in estimating the effectiveness of interventions and with poor methodology [6–12].

The Consolidated Standards of Reporting Trials statement was originally developed in 1996 [13] to aid reporting of RCTs, and an extension for non-pharmacological interventions (CONSORT NPT) was published in 2008 [14]. It consists of a 23-item checklist and flow diagram.

Our team have previously assessed the methodological quality of recent RCTs in plastic surgery, concluding that it requires improvement [15]. However, although flaws in methodology limit the validity and generalizability of study results, without accurate reporting, shortcomings in study design and implementation can be compounded and become difficult to accurately assess. Studies looking at methodological quality are usually separate from reporting quality [16]. Given this previous work, the purpose of this new study is to systematically review the reporting quality of recent RCTs in plastic surgery using CONSORT NPT criteria. This new work will allow the plastic surgical community to take stock of where reporting quality has been in recent years.

## Material and methods

### Search methods

The search technique was the same as used for this team's previous work assessing the methodological quality of plastic surgery RCTs [15]. An information specialist (trained in database searching by NHS Evidence, who conducts approximately 100 searches per year and is the staff trainer) based at the lead authors Plastic Surgery Unit searched MEDLINE® and the Cochrane Database of Systematic Reviews from 1 January 2009 to 30 June 2011 for the Medical Subject Headings (MESH is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed) 'Surgery, Plastic' or 'Reconstructive Surgical Procedures' with 'or' used as a Boolean operator and with the 'explode' function activated. We chose this time period since the CONSORT NPT statement was only published in 2008 and hence it would be unfair to hold RCTs prior to this period to a standard that did not exist at the time of writing. Limitations were set for the English language, human studies and randomised controlled trials.

Results were then manually searched by four of us (ED, MS, CFC and EE) for relevant RCTs involving surgical techniques. Papers involving purely pharmacological therapies in all arms, cost analyses, study protocols, interim or non-randomised studies, short communications and RCTs involving virtual or simulated procedures were excluded.

### Scoring

The papers were then scored by one of three primary scorers (ED, MS, EE) against the 23-item CONSORT NPT checklist with each item being given an equal weighting. Items 4 and 11 were subdivided into four and three sub-parts, respectively; a full point was only gained if all sub-parts were fulfilled; otherwise, the appropriate fraction was awarded. The resulting mark out of 23 was termed the 'CONSORT score'. Following this initial round of scoring (ED scored 2009, MS scored 2010 and 2011), all papers were then re-scored by a single secondary scorer (CFC). Discrepancies were then resolved by consensus (between ED, MS and CFC), and if that could not be reached, they were referred to the lead author (RA) for a final judgement. Evaluators were not blinded to the country of origin of the authors.

Compliance with individual items of the statement was analysed (by summing the number of articles fulfilling that item divided by the total number of included articles) as well as the relationship between CONSORT score and year of publication, geographical origin (for the RCT), the number authors and the ISI 2010 impact factor for the journals in which the RCTs were published. These additional correlates were chosen to give information about whether improvements are occurring over time and whether volume and perceived markers of RCT quality (like impact factor of the journal in which it is published) correlate with actual reporting quality as defined by CONSORT.

### Secondary analyses

In addition to the CONSORT score, papers were assessed for whether they fulfilled seven additional criteria referred to in the CONSORT NPT and whether they mention conflicts of interest, sources of finding, a trial registry number and ethical approval.

### Statistical analysis

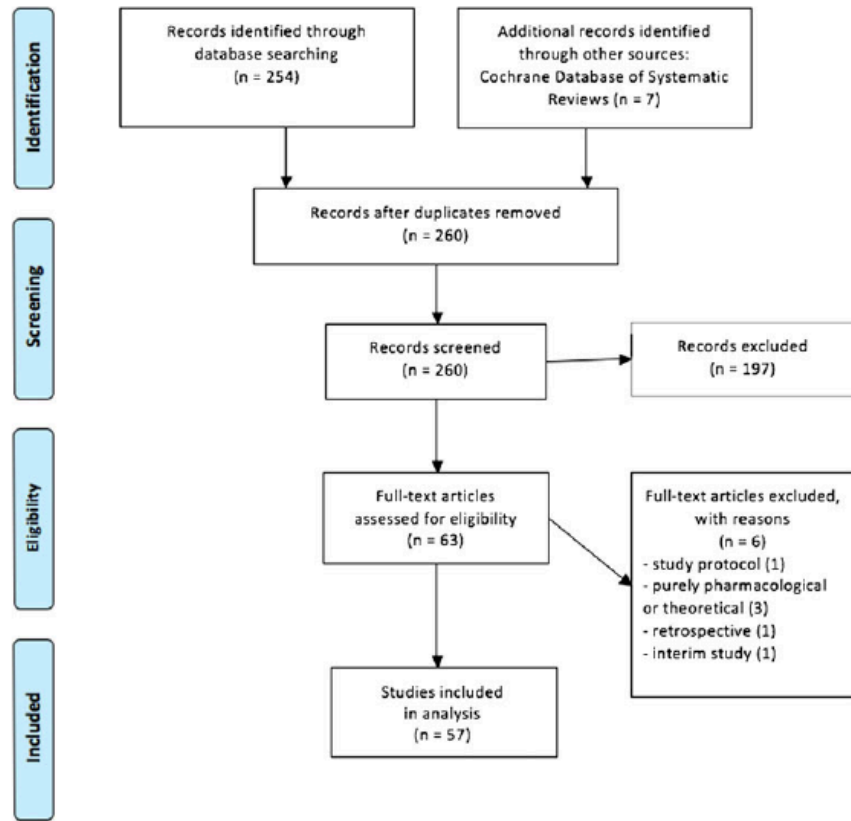
In line with previous work [15], inter-rater agreement was assessed using the Kappa score. Data were analysed using non-parametric descriptors such as median, and correlations were calculated using Spearman rho, using SPSS version 20.

## Results

The search history was as follows:

1. MEDLINE; exp SURGERY, PLASTIC/; 25,698 results
2. MEDLINE; exp RECONSTRUCTIVE SURGICAL PROCEDURES/; 52,999 results
3. MEDLINE; 1 OR 2; 76,741 results

**Fig. 1** PRISMA flow diagram, illustrating how papers were selected (adapted from Moher et al. [17])



4. MEDLINE; 3 [Limit to: Publication Year 2009–2011 and English Language]; 11,395 results
5. MEDLINE; 4 [Limit to: (Publication Types Randomized Controlled Trial) and Publication Year 2009–2011 and English Language]; 254 results

From the initial set of 254 papers retrieved from MEDLINE, 63 were selected following a manual search and abstract assessment by the authors (ED, MS, CFC). Subsequent to complete download of all 63 papers, six were excluded for being a study protocol, purely pharmacological or theoretical, retrospective or an interim study. This resulted in 57 RCTs which met the inclusion criteria (seven were multicentre), published across 28 journals. All RCTs compared treatment interventions and none related to diagnosis. No further relevant trials were found in the Cochrane Database of Systematic Reviews (Fig. 1).

The median CONSORT score was 11.5 out of 23 items (range 4.5–21.0) with a Kappa score 0.80. There was a slight trend for improvement over the 3-year period, on average 1.5 CONSORT points per year (Speaman rho 0.999) (see Table 1).

**Compliance with individual items of the CONSORT**

Compliance was highly variable for the different CONSORT items. This is shown in Fig. 2. Compliance was the poorest for items related to intervention/comparator details (7 %), randomisation implementation (11 %) and blinding (26 %), as shown in Table 2.

**Compliance with additional criteria**

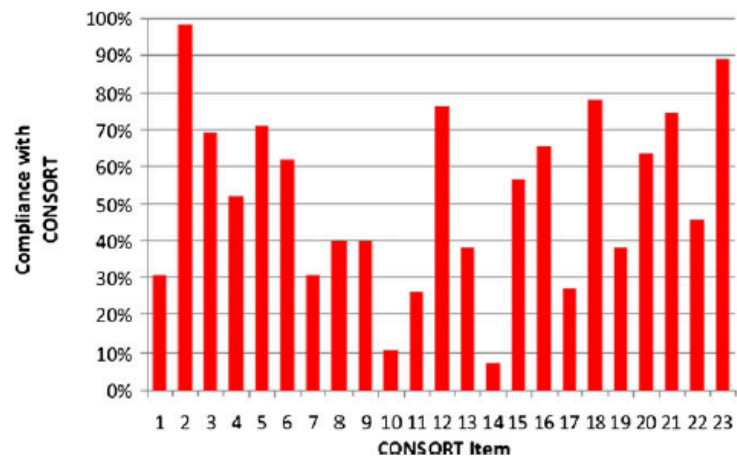
There was poor fulfilment of additional criteria and only 61 % declared conflicts of interest, 75 % permission

**Table 1** Summary statistics for CONSORT scores per year

Year	Number of RCTs	Median CONSORT score	Range
2009	26	9.9	4.5–17.3
2010	21	11.5	5.3–21.0
2011 <sup>a</sup>	10	12.9	9.0–15.0

<sup>a</sup>To 30 June 2011 only

**Fig. 2** Compliance of the 57 RCTs with the individual items of the CONSORT statement



**Table 2** Compliance of RCTs with individual items of the CONSORT statement (ranked in order of increasing fulfilment)

Criteria	Abbreviated description	Compliance (%)
New item (23)	Details of the experimental treatment and comparator as they were implemented	7
10	Who generated the allocation sequence, who enrolled participants and who assigned participants to their groups	11
11	Whether or not participants, those administering the interventions and those assessing the outcomes were blinded to group assignment	26
16	Number of participants (denominator) in each group included in each analysis and whether analysis was by 'intention-to-treat'	27
1	How participants were allocated to interventions—is it mentioned in the title	31
7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	31
13	Flow of participants through each stage (a diagram is strongly recommended)	38
18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory	38
8	Method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification)	40
9	Method used to implement the random allocation sequence, clarifying whether the sequence was concealed until interventions were assigned	40
21	Generalizability (external validity) of the trial findings	45
4	Precise details of the interventions intended for each group and how and when they were actually administered	52
14	Dates defining the periods of recruitment and follow-up	56
6	Clearly defined primary and secondary outcome measures	62
19	All important adverse events or side effects in each intervention group	64
15	Baseline demographic and clinical characteristics of each group	65
3	Eligibility criteria for participants and the settings and locations where the data were collected	69
5	Specific objectives and hypotheses	71
20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision	75
12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	76
17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision	78
22	General interpretation of the results in the context of current evidence	89
2	Scientific background and explanation of rationale	98

Consort table adapted from Moher et al. [7]

**Table 3** Compliance of RCTs with additional criteria

Additional criteria	Compliance (%)
AD1—eligibility criteria for care providers	7
AD2—details on the centres' volume	5
AD3—number of care providers performing the treatment in each group	38
AD4—number of participants treated by each care provider	31
AD5—details on patients' expectancies or preference for the treatments at baseline	2
AD6—baseline data of care providers	0
AD7—details on care providers' compliance with the planned procedure	4
Ethical approval	75
Sources of funding	47
Trial registry number	16
Conflicts of interest	61

from an ethics review committee, 47 % declared sources of funding and just 16 % stated a trial registry number (Table 3).

**CONSORT score and number of authors**

There was no correlation between number of authors and CONSORT score (Spearman rho=0.12, see Fig. 3).

**CONSORT score and impact factor**

There was no correlation between journal impact factor and CONSORT score (Spearman rho=0.26, see Fig. 4).

**Geographical distribution of RCTs and CONSORT compliance**

There was no correlation between the volume of RCTs conducted in a particular country and CONSORT score (Fig. 5).

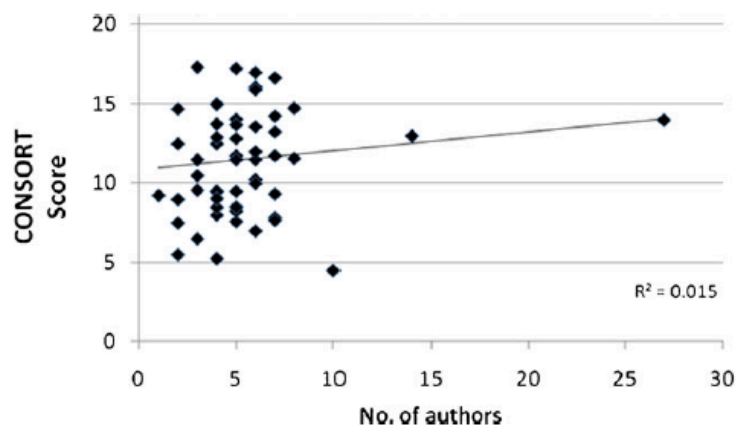
**Discussion**

Over the last decade, there have been increasing calls for utilising an evidence-based medicine approach within surgery [18, 19]. However, the evidence base in plastic surgery is still dominated by case series, and calls for higher levels of evidence (including RCTs) are gathering pace [20, 21]. Poor reporting 'short circuits' proper critical appraisal prevents inclusion in systematic reviews and meta-analyses, and resulting clinical judgements could be misleading and potentially dangerous.

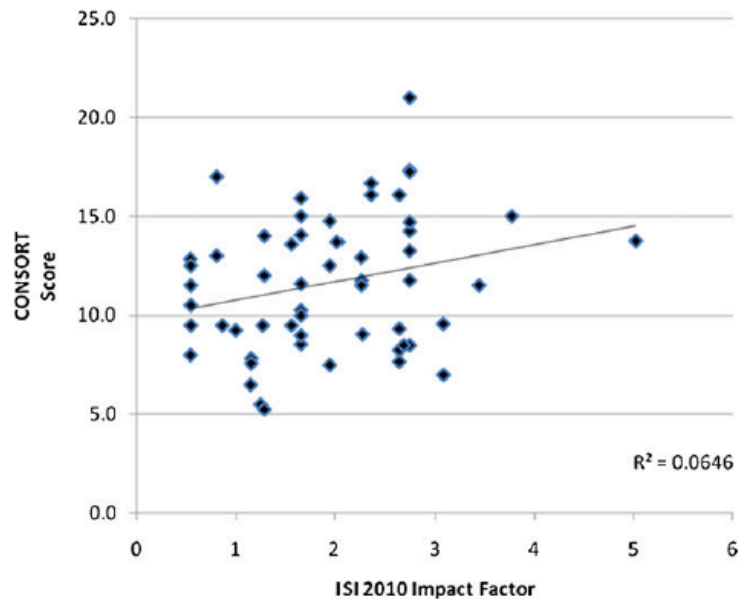
Previous reviews of surgical RCTs have shown that, in 20 %, the conclusions were not justified by the data [22]. Solomon et al. found that the lowest quality RCTs were those that involved a surgical technique, were published in a surgical journal and where a surgeon was the principal author [23].

Research in the field of RCT reporting quality has pointed to the consistent absence of the same key quality data: sample size calculations, randomisation sequence generation method and implementation, post-randomisation verification of balance in known confounders, allocation concealment, blinding, intention-to-treat analysis and participant flow charts. Our study is the first to assess the compliance of recent RCTs in plastic surgery with the CONSORT NPT criteria, and the results support this pattern of poor compliance with a low median CONSORT score of 11.5. This is similar to the CONSORT scores (out of 22) found in earlier work by one of us (RAA), with 11.1 for Urological RCTs, 10.3 for cardiac surgery, 10.9 for general surgery, 11.9 for hepatobiliary, 10.8 for orthopaedic and 12.0 for vascular surgery [19]. Furthermore, the additional CONSORT NPT criteria were severely lacking (Table 3). Whilst they are not core criteria, the authors recognise them as important for RCTs of interventions. Poor reporting has also been linked with poor methodology as shown by Taghnia et al. [24] and others [8–12].

**Fig. 3** CONSORT score against number of authors



**Fig. 4** CONSORT score against ISI 2010 impact factor

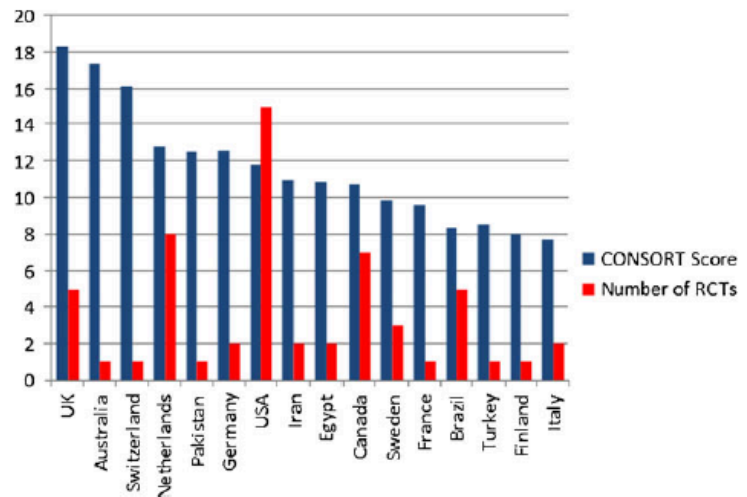


Studies with more authors have been correlated with higher citation levels [25]. One would anticipate that more authors on a study would lead to better reporting quality; however, our research did not support this, consistent with earlier work [19]. There was also no correlation between CONSORT score and the impact factor of the journal in which the RCT was published, again consistent with earlier work by one of us (RA) [19]. The impact factor is heralded by many plastic surgeons and editors [26] as the reflection of increasing journal and article quality. Yet successive studies are now showing that it has no bearing on the quality of reporting of one of the highest levels of evidence—the RCT. Sinha et al. [27] identified the

top three ranked surgical journals by impact factor and found that, of 42 RCTs analysed, only 40 % had a Jadad score  $\geq 3$  and there was no significant difference between CONSORT-endorsing and non-endorsing journals. Our data showed no link between volume of RCTs from a particular geographic region and CONSORT score. This suggests that the problems of poor reporting are indeed global and not confined to a few select countries.

Within plastic surgery specifically, several studies have found that RCTs need improvement in reporting quality. McCarthy et al. [28] analysed level 1 studies in five plastic surgery journals from 1978 to 2009. They found that only

**Fig. 5** A bar chart of CONSORT score and number of RCTs against country



39 % reported randomisation technique. In their analysis of 96 RCTs in plastic surgery published between 2004 and 2008, Veiga et al. [29] found that 29 % appropriately described allocation concealment. Momeni et al. [30] analysed 172 RCTs from three plastic surgical journals during 1990–2005 and found that only 12 % reported on their allocation concealment and 37 % described participant dropouts. Karri looked at 133 RCTs published across three plastic surgery journals from 1980 to 2004 [31]. Sample size calculation was only reported in 12.8 % of trials, randomisation methodology in 29.3 %, allocation concealment in 18.8 %, blinding of investigator/assessment in 51.9 % and study limitations in only 33.8 % trials. Veiga Filho et al. in 2005 examined 34 RCTs in plastic surgery and concluded that they were overall of low quality with 59 % scoring two points or less on a Jadad score [32]. In addition, they concluded that the process of randomisation in the studies was appropriately designed and conducted but that authors did not report it. Follow-up work by the same group in 2011 concluded that RCT quality as measured by Jadad criteria had ‘significantly increased’ [29].

In 2005, the International Committee of Medical Journal Editors implemented a policy [33] that required registration of all clinical trials prior to enrolment of the first patient (part of the aim being a reduction in publication bias from the non-publication of negative studies). In 2007, this became part of US regulatory requirement with section 801 of the Food and Drug Administration Amendments Act [34]. In 2008, trial registration became an ethical requirement with the updated Declaration of Helsinki mandating it [35]. Despite this, only 16 % of RCTs in our sample stated their trial registry. The low reporting of conflicts of interest, sources of funding and ethical approval is concerning; such information is pivotal scientific and scholarly transparency and integrity.

On the positive side, there was an upward trend in the median CONSORT score, rising three points over the 3-year period 2009–2011. However, since all the CONSORT items are mandatory for reporting, this increase is unlikely to be due to a serious appreciation and compliance with CONSORT specifically. It is more likely to be due to general improvements in reporting that may be occurring or simply random.

The limitations of our study include restriction to the English language, searching only MEDLINE® and analysing papers by publication date rather than submission date, since publication lag times for journals vary. The English language has increasingly become the lingua franca of science with an estimated 80–90 % of papers in scientific journals written in English [36]. This has been coupled with initiatives to offer translation services of key papers [37]. We feel that this strategy would still capture all the relevant papers. Whilst we did not blind our evaluators to the country of origin of the authors, we do not feel there was any inherent bias against a particular country and scores were recorded in a dispassionate manner.

Further work is needed to assess barriers to compliance with CONSORT amongst key stakeholders in the process: authors, journal reviewers and editors, funders, institutions and readers. Meticulous planning, involvement of a trial methodologist, biostatistician and compliance with CONSORT NPT in the eventual paper would be key for those conducting and reporting RCTs. Journal editors and peer reviewers as guardians of the scholarly literature have an important gatekeeper role here [38, 39].

We support previous calls for the better education of plastic surgeons at all levels in clinical research methods, evidence-based medicine and improved funding/support of plastic surgical RCTs. McCulloch et al. [40] have called for the deployment of alternative prospective designs, such as interrupted time series studies, to be used when randomised trials are not feasible—we support their call and indeed suggest that registry studies may be useful in some instances.

One solution is to hard-wire compliance with CONSORT by making the checklist a mandatory item for submission if a manuscript is submitted as an RCT. It can also be published as a supplementary item online allowing for greater transparency and scrutiny by readers. Such a policy was adopted by the *International Journal of Surgery* in January 2013 [41].

## Conclusion

The reporting quality of RCTs in plastic surgery requires improvement. Perceived surrogate markers of quality such as number of authors and impact factor of the journal had no relationship on CONSORT compliance. We suggest ways this could be improved including better education, awareness amongst all stakeholders and hard-wiring compliance through electronic journal submission systems.

**Acknowledgments** The authors would like to thank Patricia Rey, Information Specialist at Queen Victoria Hospital NHS Foundation for her guidance and meticulous search of the literature to retrieve the initial set of papers.

**Conflict of interest** RA is on the Editorial Board of the *International Journal of Surgery*.

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# APPENDIX III

**SEARCH STRATEGY FOR PRISMA COMPLIANCE STUDY****ELECTRONIC SEARCH STRATEGY OF MEDLINE DATABASE**

<b>Database: Ovid MEDLINE(R) &lt;1946 to January Week 3 2015&gt;</b>	
<b>Searched Date: 27<sup>th</sup> Jan 2015</b>	
1	Meta-Analysis as Topic/ (13819)
2	meta analy\$.tw. (59579)
3	metaanaly\$.tw. (1270)
4	Meta-Analysis/ (51709)
5	(systematic adj (review\$1 or overview\$1)).tw. (49880)
6	exp Review Literature as Topic/ (7754)
7	or/1-6 (116721)
8	cochrane.ab. (28347)
9	embase.ab. (27353)
10	(psychlit or psyclit).ab. (850)
11	(psychinfo or psycinfo).ab. (6585)
12	(cinahl or cinhal).ab. (9582)
13	science citation index.ab. (1893)
14	bids.ab. (344)
15	cancerlit.ab. (556)
16	or/8-15 (44146)
17	reference list\$.ab. (9222)
18	bibliograph\$.ab. (10980)
19	hand-search\$.ab. (3670)
20	relevant journals.ab. (679)
21	manual search\$.ab. (2207)
22	or/17-21 (23968)
23	selection criteria.ab. (19066)
24	data extraction.ab. (9201)
25	23 or 24 (26732)
26	Review/ (1906340)
27	25 and 26 (18988)

28	Comment/ (557875)
29	Letter/ (826756)
30	Editorial/ (346652)
31	animal/ (5358571)
32	human/ (13628325)
33	31 not (31 and 32) (3879559)
34	or/28-30,33 (5110454)
35	7 or 16 or 22 or 27 (142076)
36	35 not 34 (132965)
37	plastic & reconstructive surgery.jn. (25971)
38	(aesthetic plastic surgery or aesthetic surgery journal).jn. (3808)
39	"archives of facial plastic surgery".jn. (1013)
40	"journal of plastic reconstructive & aesthetic surgery jpras".jn. (4231)
41	"annals of plastic surgery".jn. (8895)
42	37 or 38 or 39 or 40 or 41 (43918)
43	limit 42 to yr="2013 - 2014" (3431)
44	36 and 43 (93)

## **ELECTRONIC SEARCH STRATEGY OF EMBASE DATABASE**

<b>Database: EMBASE &lt;1996 to 2015 Week 04&gt;</b>	
<b>Searched Date: 27<sup>th</sup> Jan 2015</b>	
1	exp Meta Analysis/ (82084)
2	((meta adj analy\$) or metaanalys\$.tw. (87424)
3	(systematic adj (review\$1 or overview\$1)).tw. (72907)
4	or/1-3 (161503)
5	cancerlit.ab. (633)
6	cochrane.ab. (39933)
7	embase.ab. (38573)
8	(psychlit or psychlit).ab. (928)
9	(psychinfo or psycinfo).ab. (9431)

10	(cinahl or cinhal).ab. (12208)
11	science citation index.ab. (2155)
12	bids.ab. (382)
13	or/5-12 (63014)
14	reference lists.ab. (10174)
15	bibliograph\$.ab. (12679)
16	hand-search\$.ab. (4803)
17	manual search\$.ab. (2797)
18	relevant journals.ab. (845)
19	or/14-18 (27970)
20	data extraction.ab. (11715)
21	selection criteria.ab. (18653)
22	20 or 21 (29221)
23	review.pt. (1547696)
24	22 and 23 (15657)
25	letter.pt. (571207)
26	editorial.pt. (372624)
27	animal/ (635468)
28	human/ (10153859)
29	27 not (27 and 28) (440219)
30	or/25-26,29 (1378174)
31	4 or 13 or 19 or 24 (194517)
32	31 not 30 (188319)
33	"plastic and reconstructive surgery".jn. (17025)
34	(aesthetic plastic surgery or aesthetic surgery journal).jn. (3652)
35	"archives of facial plastic surgery".jn. (411)
36	"journal of plastic reconstructive aesthetic surgery jpras".jn. (51)
37	"annals of plastic surgery".jn. (5475)
38	33 or 34 or 35 or 36 or 37 (26614)
39	limit 38 to yr="2013 - 2014" (2156)
40	32 and 39 (70)

# APPENDIX IV

## **A PROTOCOL FOR THE DEVELOPMENT OF REPORTING CRITERIA FOR SURGICAL CASE REPORTS: THE SCARE STATEMENT**

A summary of the following appendix is published in the International Journal of Surgery.<sup>1</sup> The author wrote the first draft and revised it in light of comments from the other authors.

### **INTRODUCTION**

Since the time of Hippocrates, case reports have been popular within the medical literature.<sup>1</sup> In recent decades however, their importance has decreased as focus has shifted to randomised controlled trials (RCTs). Such studies minimise the bias that's inherent in looking at a single patient or even a series of them, and are hence able to answer research questions more reliably. Indeed, some even feared their extinction due to low citation rates, negative effects on journal impact factor and restricted page budgets.<sup>2,3</sup> As a result, many journals stopped publishing case reports altogether.<sup>2,4</sup>

The rise of electronic publishing and open access models have led to a resurgence of the clinical case report. In 2008, the International Journal of Surgery (IJS) stopped accepting case reports for publication and in 2010 launched a journal specifically devoted to them – IJS Case Reports.<sup>4</sup> In 2015, IJS Case Reports became the largest publisher of surgical case reports globally according to the Scopus® indexing service.

Vandenbrouke outlined how case reports further medical progress: “*they permit discovery*

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<sup>1</sup> Agha R, Fowler AJ, Saetta A, Barai I, Rajmohan S, Orgill DP on behalf of the SCARE Steering Group and the Academic Surgical Collaborative. *A Protocol for the Development of Reporting Criteria for Surgical Case Reports: the SCARE Statement*. International Journal of Surgery 2016;27:187-189.

*of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine.”<sup>5</sup>*

Case reports have specific relevance within the surgical literature. The IDEAL recommendations call for structured case reports for reporting a “first-in-man” study – i.e. the first time a new surgical technique is used, in stage 1 of their framework.<sup>6,7</sup> This has been exemplified in recent times by case reports of facial transplantation and other innovative techniques.<sup>8</sup>

The Case Report or CARE Guidelines were developed in 2013 to provide a framework that supports transparency and accuracy in the publication of case reports and the reporting of information from patient encounters.<sup>9</sup> They have been adopted by multiple journals and compliance with them has been mandatory at the IJS Case Reports. However, they are not tailored to surgery.

The journal’s editors experience of over 3,000 case reports, informs us that surgical case reports have specific reporting needs that should be recognised in an adapted reporting guideline based on CARE. Some of these include; discussion around patient selection, the reporting of any pre-operative optimisation, where the surgeon performing the operation is on the learning curve (if established) or what their experience with the technique in question is, post-operative instructions and care, reporting complication rates and length of follow-up (supported by photos, scan results and multimedia as appropriate). The objective of this research is to conduct a Delphi consensus exercise amongst experienced

case report reviewers and editors to develop the Surgical CAse REport (SCARE) Guidelines.

## **METHODS**

We will start with the CARE statement as it stands. This underwent a three-phase consensus process consisting of a literature review and interviews, a face-to-face consensus meeting and post-meeting feedback, review, and pilot testing, followed by finalisation.

### **DELPHI PROCESS**

The Delphi questionnaire will be administered via SurveyMonkey® ([www.surveymonkey.com](http://www.surveymonkey.com)) and conducted using standard Delphi Methodology.<sup>10</sup> It is planned that the same questionnaire will be completed by all stakeholders throughout the process. The author will invite participants to recommend adaptations to the current items and suggest new ones. The ones suggested above will be included in this first round aimed at generated new items and adapting the current ones for surgery.

In each subsequent round, the participants will rate the importance of reporting each outcome on a nine-point Likert scale as proposed by the GRADE group.<sup>11</sup> In this scale 1 to 3 signifies an outcome of limited importance, 4 to 6 important but not critical and 7 to 9 critical. If 70% or more of respondents score an item 7 to 9 and fewer than 15% score it 1 to 3, then that item should proceed into the reporting guideline. Similarly, consensus that an outcome should not be included would be 70% or more scoring it 1 to 3 and 15% or less scoring it 7 to 9. Sequential rounds and questionnaire administration and completion

will take place until a final set of outcomes with agreed definitions are achieved. The entire process will be conducted electronically and there is no pre-determined number of Delphi rounds. The process will also be used to agree standard definitions for the outcomes.

## **PARTICIPANT SELECTION**

Surgeons and others with significant experience in reviewing case reports. They will be drawn from the reviewer pool of the IJS Case Reports. We will invite the top 150 reviewers (by number of case reports reviewed) who have collectively reviewed over 1,000 case reports for their input.

## **ETHICS AND DISSEMINATION**

No ethical approval is necessary since there is no direct patient input. The research will be published in a peer-reviewed journal. It will be disseminated electronically and in print. Journals publishing case reports within surgery will be encouraged to endorse the statement.

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# APPENDIX V

## SCARE CHECKLIST

SCARE CHECKLIST			
Topic	Item	Checklist item description	Page No.
Title	1	The words “case report” and the area of focus should appear in the title (e.g. presentation, diagnosis, surgical technique or device or outcome).	
Key Words	2	3 to 6 key words that identify areas covered in this case report (include "case report" as one of the keywords).	
Abstract	3a	Introduction—What is unique or educational about the case? What does it add to the surgical literature? Why is this important?	
	3b	The patient's main concerns and important clinical findings.	
	3c	The main diagnoses, therapeutics interventions, and outcomes.	
	3d	Conclusion — what are the “take-away” lessons from this case?	
Introduction	4	A summary of why this case is unique or educational with reference to the relevant surgical literature and current standard of care (with references, 1-2 paragraphs). Nature of the institution in which the patient was managed; academic, community or private practice setting?	
Patient Information	5a	De-identified demographic and other patient specific information including age, sex, ethnicity, occupation and other useful pertinent information e.g. BMI and hand dominance.	
	5b	Presentation including presenting complaint and symptoms of the patient as well as the mode of presentation e.g. brought in by ambulance or walked into Emergency room or referred by family physician.	
	5c	Past medical and surgical history and relevant outcomes from interventions	
	5d	Drug history, family history including any relevant genetic information, and psychosocial history including smoking status and where relevant accommodation type, walking aids, etc.	
Clinical Findings	6	Describe the relevant physical examination and other significant clinical findings (include clinical photographs where relevant and where consent has been given).	

<b>Timeline</b>	<b>7</b>	Inclusion of data which allows readers to establish the sequence and order of events in the patient's history and presentation (using a table or figure if this helps). Delay from presentation to intervention should be reported.
<b>Diagnostic Assessment</b>	<b>8a</b>	Diagnostic methods (physical exam, laboratory testing, radiological imaging, histopathology etc).
	<b>8b</b>	Diagnostic challenges (access, financial, cultural).
	<b>8c</b>	Diagnostic reasoning including other diagnoses considered
	<b>8d</b>	Prognostic characteristics when applicable (e.g. tumour staging). Include relevant radiological or histopathological images in this section (the latter may sometimes be better placed in section 9).
<b>Therapeutic Intervention</b>	<b>9a</b>	Pre-intervention considerations e.g. Patient optimisation: measures taken prior to surgery or other intervention e.g. treating hypothermia/hypovolaemia/hypotension in a burns patient, ICU care for sepsis, dealing with anticoagulation/other medications, etc
	<b>9b</b>	Types of intervention(s) deployed and reasoning behind treatment offered (pharmacologic, surgical, physiotherapy, psychological, preventive) and concurrent treatments (antibiotics, analgesia, anti-emetics, nil by mouth, VTE prophylaxis, etc). Medical devices should have manufacturer and model specifically mentioned.
	<b>9c</b>	Peri-intervention considerations - administration of intervention (what, where, when and how was it done, including for surgery; anaesthesia, patient position, use of tourniquet and other relevant equipment, prep used, sutures, devices, surgical stage (1 or 2 stage, etc). Pharmacological therapies should include formulation, dosage, strength, route, duration, etc).
	<b>9d</b>	Who performed the procedure - operator experience (position on the learning curve for the technique if established, specialisation and prior relevant training).
	<b>9e</b>	Any changes in the interventions with rationale. Include intra-operative photographs and/or video or relevant histopathology in this section. Degree of novelty for a surgical technique/device should be mentioned e.g. "first in-human".
	<b>9f</b>	Post-intervention considerations e.g. post-operative instructions and place of care.

<b>Follow-up and Outcomes</b>	<b>10a</b>	Clinician assessed and patient-reported outcomes (when appropriate) should be stated with inclusion of the time periods at which assessed. Relevant photographs/radiological images should be provided e.g. 12-month follow-up.
	<b>10b</b>	Important follow-up measures - diagnostic and other test results. Future surveillance requirements - e.g. imaging surveillance of endovascular aneurysm repair (EVAR) or clinical exam/ultrasound of regional lymph nodes for skin cancer.
	<b>10c</b>	Where relevant - intervention adherence and tolerability (how was this assessed).
	<b>10d</b>	Complications and adverse or unanticipated events. Described in detail and ideally categorised in accordance with the Clavien-Dindo Classification. How they were prevented, diagnosed and managed. Blood loss, operative time, wound complications, re-exploration/revision surgery, 30-day post-op and long-term morbidity/mortality may need to be specified.
<b>Discussion</b>	<b>11a</b>	Strengths, weaknesses and limitations in your approach to this case. For new techniques or implants - contraindications and alternatives, potential risks and possible complications if applied to a larger population. If relevant, has the case been reported to the relevant national agency or pharmaceutical company (e.g. an adverse reaction to a device).
	<b>11b</b>	Discussion of the relevant literature, implications for clinical practice guidelines and any relevant hypothesis generation.
	<b>11c</b>	The rationale for your conclusions.
	<b>11d</b>	The primary “take-away” lessons from this case report.
<b>Patient Perspective</b>	<b>12</b>	When appropriate the patient should share their perspective on the treatments they received.
<b>Informed Consent</b>	<b>13</b>	Did the patient give informed consent for publication? Please provide if requested by the journal/editor. If not given by the patient, explain why e.g. death of patient and consent provided by next of kin or if patient/family untraceable then document efforts to trace them and who within the hospital is acting as a guarantor of the case report.
<b>Additional Information</b>	<b>14</b>	Conflicts of Interest, sources of funding, institutional review board or ethical committee approval where required.

# APPENDIX VI

## **PROTOCOL FOR DEFICIENCIES WITHIN SURGICAL CASE SERIES: A SYSTEMATIC REVIEW**

A summary of this appendix is published in the British Medical Journal Open.<sup>1</sup> The author was involved in; concept and design, drafting of the paper and its critical revision in light of comments from co-authors.

### **ABSTRACT**

Case Series are an important and prevalent study type. Currently no guideline exists for their reporting and there is evidence of key data being missed from such reports. This represents a wasted opportunity to change practice and advance this field. Reporting guidelines have been shown to be efficacious in raising the bar for reporting quality. We propose to develop such a reporting guideline for case series using a well-established and methodologically robust technique. The first step in this process is a systematic review of literature relevant to the reporting deficiencies of case series. Here the author presents the protocol for such a review.

### **INTRODUCTION**

A case series is an uncontrolled study that samples participants with both a specific outcome and a specific intervention (exposure), or one that samples participants with a specific outcome of interest, regardless of their exposure status.<sup>1</sup> They are commonly a retrospective review of a string of interesting cases with a unifying feature - be that exposure, intervention, treatment or outcome. It is unclear whether the definition implies that the cases should be

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<sup>1</sup> Agha R, Fowler AJ, Lee SY, Gundogan B, Whitehurst K, Sagoo H, Jeong KJL, Altman DG and Orgill DP. *A Systematic Review Protocol for Reporting Deficiencies within Surgical Case Series*. BMJ Open 2015;5:e008007.

consecutive. They are frequent within the medical literature but are also present within social sciences and the humanities.<sup>1</sup> As with case reports, their value has been debated.<sup>2,3</sup> In the age of evidence-based medicine (EBM) and the randomised controlled trial (RCT) as the criterion standard to show the efficacy of a particular treatment, what is their role?

In the summer of 1999, the use of a case series in the recognition of a new disease was exemplified by the epidemic of West Nile encephalitis in New York.<sup>4</sup> Historically case series were important in identifying the impact of maternal drinking on pregnancy outcome and the role of vitamin C in preventing scurvy.<sup>5,6</sup> More recently, a study by Albrecht of case series published in the *Lancet* found that a high proportion went on to have follow-up trials and that they were useful in establishing an early evidence base for treatments of rare diseases in which trials would not be feasible.<sup>7</sup> For some specialties, establishing control groups may be difficult e.g. accident and emergency medicine. In the social sciences, many social psychology studies have been case series, for example Yale Psychologist Stanley Milgram's seminal work on obedience to authority figures.<sup>8</sup>

In a 2005 report, Dalziel et al, outlined that case series are used in 30% of Health Technology Assessments (HTA) - used in the provision and suitability of care.<sup>9</sup> However, poor reporting in the case series included in their study severely constrained their analysis and investigation of the hypothesis that findings in case series may be affected by methodological characteristics.<sup>9</sup> Currently, no standardised reporting criteria developed within a robust methodological framework exist for case series. In the on-going drive to improve the evidence base for clinical practice, a number of tools have been developed to improve the quality of reporting research. For example publication of CONSORT (Consolidated Reporting Standards of Randomised controlled Trials) has seen the quality of articles in some fields improve significantly.<sup>10,11</sup> The CONSORT statement has also been

used to highlight and raise awareness of poor compliance in some fields.<sup>12,13,14,15,16</sup> More recently our group has shown deficiency of observational studies in Plastic Surgery using the guideline STROBE (strengthening the reporting of observational studies in epidemiology).<sup>17</sup>

A wide variety of reporting guidelines are now available across different research study types, except for case series. Problems in the reporting of surgical case series in particular have been highlighted to us from our recent experience conducting a systematic review of autologous fat grafting for breast reconstruction.<sup>18</sup> In this study, 25 of the 31 included studies were case series, yet 20% did not mention the age of the participants and 48% did not mention whether the participants had been treated with radiotherapy, an important prognostic factor. Surgery has the additional complexity of learning curves. The technique selected is not the sole factor affecting outcome. Patients need to be carefully selected, appropriately worked-up and optimized pre-operatively, the technique has to be meticulously implemented in an appropriate setting and with an appropriate post-operative regimen.

Readers need complete, clear and transparent information and failure to provide this ‘short-circuits’ critical appraisal, assessment of external validity and whether, for instance, a surgeon should change their practice. The author aims to close this gap and help produce a reporting guideline for case series that is methodologically robust, easy to use and accepted internationally across a broad range of specialties and disciplines. According to Moher et al’s guidance on guideline development, the early steps in this process require an analysis of previous literature to identify previous guidance (if any) and to analyse relevant evidence on the quality of reporting of published research articles within the domain of interest.<sup>19</sup> Here we report our protocol for such a systematic review.

## **OBJECTIVE**

Conduct a systematic review on the reporting deficiencies within surgical case series.

## **METHODOLOGY**

This systematic review will be conducted according to the recommendations outlined in the Cochrane Handbook for reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>25</sup> The protocol has been registered at [www.researchregistry.com](http://www.researchregistry.com) with unique identifying number: reviewregistry3.

## **CRITERIA FOR SELECTING STUDIES:**

The following search criteria were specifically devised to locate studies specifically pertaining to the reporting quality of case series and to provide evidence for the objectives previously stated.

### **TYPES OF STUDIES/MATERIAL**

Research articles and systematic reviews which highlight reporting deficiencies in case series.

### **TYPES OF PARTICIPANTS**

Human participants undergoing surgery.

### **TYPES OF INTERVENTIONS**

Any surgical intervention.

### **TYPES OF COMPARATOR**

Typically, case series will have no comparator or control group. We did not specify anything here within our search criteria.

## OUTCOMES

Specified reporting deficiencies identified within the articles relating to case series.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

### ELECTRONIC SEARCHES

The following electronic databases will be searched from their inception to 5<sup>th</sup> November 2014: MEDLINE, EMBASE, Cochrane Methods Register, Science Citation Index and Conference Proceedings Citation Index.

### SEARCH TERMS AND KEYWORDS

The search strategy has been developed through consultation with an information specialist based at the Bodleian Library, University of Oxford. Its aim is to locate papers related specifically to the reporting quality of case series. This search will utilise the English language keywords combined with Boolean logical operators. The search will be restricted to the English Language and tailored to the idiosyncrasies of each individual aforementioned database. An example of a search strategy for the MEDLINE database is shown below:

<b>TABLE: SEARCH STRATEGY FOR THE MEDLINE DATABASE</b>		
<b>#</b>	<b>SEARCHES</b>	<b>RESULTS</b>
1	case series.mp.	39714
2	"series of cases".mp.	2580
3	"series of case reports".mp.	547
4	1 or 2 or 3	42346
5	Research Design/st [Standards]	9548
6	Research design/ and Quality Control/	1034
7	Research design/ and "Reproducibility of Results"/	6230

8	Research design/ and Data interpretation, Statistical/	4912
9	*Research design/	24740
10	(quality adj5 (reporting or criteria or characteristic? or feature? or standard? or aspect?)).ti,ab.	29385
11	(reporting adj5 (selection or recruit* or eligibility or study size or study design? or outcome?)).ti,ab.	4466
12	(reporting adj5 ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti,ab.	153
13	(reporting adj5 (missing data or missing value* or incomplete data or incomplete value*)).ti,ab.	64
14	(methodolog* adj5 (reporting or criteria or characteristic? or feature? or standard? or aspect? or quality)).ti,ab.	19999
15	(reporting adj2 (scor* or system*)).ti,ab.	6476
16	strobe.ti,ab.	560
17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	91558
18	4 and 17	591
19	(case series adj5 (methodologic* or reporting)).ti,ab.	171
20	(case series adj5 (quality or bias or heterogen* or rigor* or rigour* or robust* or generalisab* or valid*)).ti,ab.	181
21	(case series adj5 (missing data or missing value* or incomplete data or incomplete value*)).ti,ab.	0
22	(case series adj5 ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti,ab.	6
23	(case series and (methodologic* or reporting)).ti.	14
24	(case series and (quality or bias or heterogen* or rigor* or rigour* or robust* or generalisab*)).ti.	38
25	(case series and (missing data or missing value* or incomplete data or incomplete value*)).ti.	0
26	(case series and ((loss adj2 follow up) or dropout? or drop out? or attrition or retention)).ti.	6
27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	873
28	limit 27 to english language	842

## **IDENTIFICATION AND SELECTION OF ARTICLES**

Studies identified by the electronic search strategy will be listed. Results including citation, title and abstracts will be populated into Microsoft Excel® Database (Microsoft, Redmond, WA, USA) and duplicates removed. Titles and abstracts will be screened independently by two teams of authors (SL/KJ and BG/HS/KW) for issues relating to the reporting quality of case series. Any conflicts not resolvable between the two teams will be referred to the lead author (RA) for resolution. Articles selected after title and abstract screening will have full text downloaded and a further assessment made of eligibility. Once articles have been selected for inclusion, data extraction will take place.

## **DATA EXTRACTION AND MANAGEMENT**

Data will be extracted independently by two teams of authors (SL/KJ and BG/HS/KW) utilising standard extraction fields where relevant data for each study will be collated. The identified reporting quality issue was categorised under the headings of; failure to use standardised definitions, missing or selective data, transparency or complete reporting and other. We will also record whether the use of alternative study designs was considered. Any conflict of extraction will be resolved by discussion; where resolution isn't possible, the lead author (RA) will have final say. This data will then be entered into a Microsoft Excel® 2011 database (Microsoft, Redmond, WA, USA). Data collected will then be grouped into themes along which reporting deficiencies are occurring.

## **DATA SYNTHESIS AND STATISTICAL ANALYSIS**

Outcomes will be tabulated, with descriptive statistics performed as appropriate to determine frequently missing types of data within reports of case series.

## **SENSITIVITY ANALYSIS**

A sensitivity analysis will be performed whereby results from those studies whose primary aim was to assess the reporting quality of multiple case series will be looked at separately from those articles which may mention an issue in passing in their discussion.

## **DISSEMINATION**

The author hopes to disseminate the findings as widely as possible, irrespective of the results as they add to the wider corpora of information on this subject. The systematic review will be published in a peer-reviewed journal and will be presented at a wide range of national and international conferences.

## **CONCLUSION**

This systematic review will inform us as to what types of data are missing and how reporting could be improved. It is an important first step along the path towards a guideline for reporting case series.

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# APPENDIX VII

HRA Training | Glossary | Vacancies | Contact Us | A A A | Search the site

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**NHS**  
**Health Research Authority**

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- Our plans and projects
- Research Transparency
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- Collaboration and Development
- Replacing the Research Governance Framework

## Research Transparency

The HRA has reviewed this text to ensure greater consistency in the use of language in conveying standards that should be followed (ethical obligations or best practice) or must be followed (legal requirements) although readers are advised that the HRA holds both in high regard [19 August 2015].

**The HRA website material is a statement of the HRA understanding. Whilst the reader is encouraged to seek further clarification from the HRA in respect of any queries via the queries line, it will be for the reader to take their own legal advice as to what their legal duties are.**

The HRA has a specific duty to promote research transparency. Transparency of research is essential so that participants and patients are protected from unnecessary research and patients benefit from improved outcomes and care informed by high quality research. The HRA has signed up to [AllTrials](#), supports the Lancet's [REduce research Waste And Reward Diligence \(REWARD\) campaign](#) and is working with others to ensure greater transparency of health research. The AllTrials website provides information on global initiatives to ensure all trials are registered and reported.

Our [business plan](#) includes our plans to further promote transparency in health and social care research. Key elements are highlighted in the following sections.

### Trial registration

The [World Medical Association Declaration of Helsinki](#) states that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."; and the [International Committee of Medical Journal Editors \(ICMJE\)](#) considers clinical trials for publication only if registered in an appropriate registry.

Since September 2013, the registration of clinical trials has been a formal condition of Research Ethics Committee (REC) approval and in September 2015 we undertook our first annual [Audit Report](#)

The [Transparency, registration and publication](#) page of the Resources section of the HRA website set out the current HRA policy position.

### Useful links:

- The [EudraCT](#) number is the mandatory reference number allocated by the European Medicines Agency (EMA) for CTIMPs authorised after 1 May 2004.
- The [International Standard Randomised Controlled Trial Number \(ISRCTN\)](#) is a simple numeric system for the identification of clinical trials worldwide. The ISRCTN Register accepts the registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in a human population. This includes both observational and interventional studies, including retrospective.
- Clinical research may be registered at [ClinicalTrials.gov](#)
- The [Research Registry](#), (not a Primary Registry in the WHO Registry Network) accepts observational, interventional studies, systematic review and meta-analyses, including retrospective.

# APPENDIX VIII

## Terms of reference

### HRA Research Transparency Forum

#### Background

The Health Research Authority (HRA) is tasked to promote research transparency as a statutory function under clauses in the Care Act. To do this effectively it will need to shape this UK wide and work with others to implement shared solutions. Until now the HRA engagement has been through consultation, including stakeholder workshops. This has been formalised through the establishment of an HRA research transparency forum.

The same model was adopted in 2012 in the establishment of the Collaboration and Development Forum, previously named Collaboration and Development Steering Group, to support and steer key elements of HRA and members' business that contribute to the delivery on defined projects and work streams to streamline and improve the research journey in the NHS.

#### Terms of reference

A HRA Research Transparency Forum to support the HRA in delivering its statutory duties to promote research transparency.

A forum established by the HRA with a remit to:

- Identify and advise the HRA on priorities for action
- Consider wider changes that the HRA needs to be aware of in considering solutions
- Agreeing common principles to underpin solutions
- Promulgating action to achieve these solutions within member organisations or activity area
- Monitoring implementation and improvement.

The Forum will:

- Advise the HRA on issues that which can possibly be addressed by HRA or Forum members and that may be considered within business planning of HRA or other Forum members to promote research transparency. This may include informing HRA and others' contributions to existing agendas
- Advise HRA and forum members on activities undertaken by members to achieve improvements to promote research transparency
- Discuss and agree key principles that would need wider adoption outside the HRA to enable the implementation of HRA driven solutions
- Endorse the principle of common formats and solutions for the HRA to implement
- Actively support and promote the work of the HRA in improving the environment for research in the UK

The Forum will meet quarterly, Chaired by the HRA Chief Executive.

The membership will be reviewed regularly. As of July 2016 membership includes;

ABPI  
AHPPI  
Alltrials  
BioMed Central  
BMA  
BMJ  
Cambridge Teaching Hospital  
Cancer UK  
CCRA  
Cochrane  
Devolved Administration representation  
EMIG  
EQUATOR  
ISRCTN  
MHRA  
Oxford University  
Research Registry  
UKRIO  
University College London  
Wellcome Trust  
Researchers  
REC Members

Secretariat – HRA

The HRA will not in any event record the meeting and any member of the group may only record the meeting with the explicit consent of all present and this must then be noted in the minutes.

# APPENDIX IX

**HEALTH RESEARCH AUTHORITY**  
**TRANSPARENCY FORUM – 21 July 2016**  
**Skipton House, London & by telecon**

Present (Inc by telecon)	Initials
Riaz Agha	RA
Ed Blandford	EB
Jennifer de Beyer	JB
Tim Clarke	TC
Cindy Coper	CC
Mark Edwards	Me
Alex Fowler	AF
Tim Hardman	TH
Simon Kolstoe	SK
Toby Lassersen	TL
Jayne Lawrence	JL
Elizabeth Lund	EL
Jennifer O'Callaghan	JO
Hannah Quigan	HQ
Daniel Sharahan	DS
Iveta Simera	IS
Jacintha Sivarajah	JS
Bill Davidson	BD
Jim Elliott	JE
Tom Smith (Chair)	TS
<b>Apologies</b>	
Janet Wisely	
Mike Hammond	
Kiron Koshy	
Sile Lane	
James Parry	
Joanne Slee	
Matt Sydes	
Marc Taylor	
Sue Dilks	
Helen Faure	
Trish Groves	
Carolyn Reed	
Carolyn Singh	
Tim Sprosen	
Hollie Chandler	
Ian Wilkinson	
Ulrike Lorch	
Jagjit Sidhu	

Item	Item details	Action / Outcomes
1	<p><b>Welcome and Introductions</b></p> <p>TS welcomed all to the meeting, introductions were made and apologies noted (as above). It is envisaged that telecon facilities will continue to be available for future meetings, as today, which it is hoped will assist with diary availability.</p>	
2	<p><b>Terms of Reference</b></p> <p>The ToR were reviewed and noting the previously held discussion on membership, suggestions for consideration to invite included; AMRC, BioIndustry Association, UUK and the Royal Colleges.</p>	TS to action invites
3	<p><b>Notes of the previous meeting</b></p> <p>The notes of the previous meeting were noted as accurate. The actions from the last meeting, appreciating the time interval, were all closed with the exception of the item; Specific issues relating to registration of epidemiology studies. A meeting is planned with HRA, ISRCTN &amp; the <b>Research Registry</b> to look at the issue.</p>	c/f HRA, ISRCTN, Research Registry
4	<p><b>Update from Partners</b></p> <p><b>Discussion held on updates from Partners, substantively around presentations from ISRCTN and the Research Registry.</b></p> <p>ISRCTN DS updated the meeting, c15k records on registry, 30%+ with plain English summaries, c6% observational studies. ISRCTN working with others in terms of developing guidelines for observational studies. Pilot will uploading basic results from research as an additional file / link to where results stored to start in August. Peer reviewed publication is distinct from this results pilot. Email prompts will be sent to researchers at the end of the trial and again after the date of intended publication.</p> <p>Meeting noted this developed with interest and asked, if appropriate, at a future juncture if an update could be shared with the meeting group.</p> <p><b>Research Registry</b> <b>Note registry is not WHO accredited although fields are similar to that of other registries, is without fee to researchers. Established Feb'15 and c1,200 records from 70+ countries.</b></p> <p>The meeting had a discussion following both presentations, the opportunities for researchers to register studies, data sharing as opposed to publication of results and the availability of registries for retrospective registrations and registrations of observational studies.</p>	
5	<p><b>HRA update- 2016 Business plan</b></p> <p>Business plan available on the HRA website, in line with previous undertakings. Specific updates on EQUATOR workstreams, HRA Approval &amp; PPI Involvement on</p>	

	<p>agenda.</p> <p><b>Discussion scheduled with ISRCTN and the Research Registry in terms of guidance for observational study registration.</b></p> <p>The meeting noted that in relation to the HRA website that last year there were 47 requests for deferrals of research summaries all of which were agreed.</p> <p>In terms of requests for a deferral of the requirement to register clinical trials, there were 44 last year and 9 within the first quarter of the current year.</p>	
6	<p><b>Update on clinical trial registrations</b></p> <p>Meeting noted that following the previous monitoring of clinical trials in August 2015, a follow-up process had been undertaken in January 2016, as previously outlined to the Forum. The outcomes will be publically available in due course.</p> <p>In summary;</p> <p>For the 325 Phase 1 clinical trials during the monitoring period securing a favourable opinion, in January '16 77% were accessible on a P1 trial registry (from 64% in Aug '15), 15% had sought and still had a deferral in place with only 8% (prev 23%) being not found on a registry and no deferral in place. Correspondence to this final category of research had been made and response gained from all but 10 (3%).</p> <p>For the 169 Medical Device clinical trials monitored, 85% were accessible on a publically accessible registry (from 48% previously), with 15% not accessible and correspondence to this category of research had been made and response gained from all but 19 (11%).</p> <p>For the 300 Clinical Trials, other than CTIMPs or Medical Devices monitored 80% were accessible on a publically accessible registry (from 48% previously), with 20% not accessible and correspondence to this category of research had been made and response gained from all but 27 (9%).</p> <p>Noting the reasons offered for non-registration, Further monitoring in relation to this condition in relation to favourable ethical approval will be undertaken.</p>	
7	<p><b>EQUATOR workstream developments</b></p> <p>EQUATOR is undertaking two projects for the HRA in relation to Transparency:</p> <p>First on question A51 of IRAS ethics application – ‘How do you intend to reports and disseminate the results of the study?’ to ensure that research understand the full extent of their commitment to responsibly share their research findings</p> <p>Second on how HRA may facilitate access to study document collected to support future reach and increase transparency and research efficiency.</p> <p>Presentation made to meeting and discussion gave rise to points of refinement for survey. Points raised included, that work would be building upon previously stated principled of transparency, offers to speak with IS directly outside of the meeting, commercial aspects of research, should reporting also extend to primary and</p>	

	<p>secondary indicators, should have record that benefits research community and notes the outcomes against the effort and resources required.</p> <p>Feedback from meeting to be incorporated into survey before launched  Link once survey live to be highlighted to meeting group  Members asked to communicate this link to stakeholders and partners  Update to be brought to the next meeting</p>	<p>IS  TS  ALL  IS</p>
8	<p><b>Public involvement in ethical review</b></p> <p>BD noted that with HRA Approval there is the separate assessment with roll-out now is the assessment of legal and governance compliance that was previously duplicated across the NHS. In addition to streamlining HRA Approval also gives a broader opportunity once the programme is in 'steady state'. Centralising amendments has identified need for a new approach.</p> <p>Assessment could also inform the REC opinion, within current remit to address inconsistencies and aim to reduce provisional opinion rates. Assessors would be able to apply standards where a judgment is required so that standards can be raised without introducing a burden on the REC process.</p> <p>Public involvement is one area that in due course we may support the work being implemented not just by new question in IRAS but also some assessment against standards by staff assessors so the REC can consider both.</p> <p>Currently timescales on HRA Approval are good, there issues around Amendments have been noted. There are plans being developed to address Amendments backlog.</p> <p>JE updated on the joint work with INVOLVE on the Impact of public involvement on the ethical aspects of research and public involvement in research and research ethics committee review (link to papers <a href="http://www.hra.nhs.uk/resources/public-involvement-research/">http://www.hra.nhs.uk/resources/public-involvement-research/</a> ) seeking that partners assist in disseminating of documents (including to Sponsors) , driving improvement in making studies more relevant, increasing participation rates and the value of results.</p> <p>If the questions on IRAS relating to involvement were enhanced, it may assist RECs to encourage greater levels of involvement and challenge where omission.</p>	
9	<p><b>AOB</b></p> <p>Referendum impact /EU Clinical Trial Regulation</p> <p>Meeting noted that leaving the EU may be an opportunity for increased levels of research activity within the UK and noted the HRA's statement that will continue to work to ensure UK is a great place to undertake research and public confidence in research continues to develop.</p> <p>EU Consultation on 'Summary of Clinical Trial Results for Laypersons'  Consultation highlighted.</p>	
10	<p><b>Next meeting</b></p> <p>Thursday 08 December 2016, 1.30 – 4pm Skipton House/ telecon</p>	

# APPENDIX X



# Clinical Trial Registration update

Transparency Forum Meeting  
21 July 2016

## Medical Device Clinical Trials (monitoring period 1 January 2015 to 30 June 2015)

	August 2015		January 2016	
Total number of medical device trials with a FO during the reporting period	169		169	
Total number of medical device trials identified on a publicly accessible database at the end of the monitoring period	82	48%	144	85%
Of the total number registered, those found on ISRCTN	14	(8%)	20	(12%)
Of the total number registered, those found on clinicaltrials.gov	68	(40%)	88	(52%)
Total number of medical device trials not registered but details of the trial could be found on the UKCRN site	19	11%	27	(16%)
Of the total number registered, those found on researchregistry.com*			9	(5%)
The number of medical device trials that could not be found or not know to have registered; (breakdown of response to these below)	68	40%	25	15%
Of the medical device trials not found or not known to have registered: Reply received			6	(24%)
Of the replies received, those which stated that registration not yet required (e.g trial not yet recruited / trial not yet started / trial terminated before recruitment commenced)			5	(83%) Of those where reply received
Of the medical device trials not found or not known to have registered: No reply received			19	(76%)



For Transparency Forum Meeting discussion

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## Clinical Trials other than CTIMPs or Medical

	August 2015		January 2016	
Total number of other trials with a FO during the reporting period	300		300	
Total number of other trials found on a publicly accessible database	144	48%	240	80%
Of the total number registered, those found on ISRCTN	75	(25%)	86	(36%)
Of the total number registered, those found on clinicaltrials.gov	69	(23%)	94	(39%)
Total number of other trials not registered but details of the trial could be found on the UKCRN site	36	12%	48	(20%)
Of the total number registered, those found on researchregistry.com*			11	(5%)
German clinical trials database			1	(0.5%)
The number of other trials that could not be found or not known to have registered	120	40%	60	20%
Of the other clinical trials not found or not known to have registered: Reply received			33	(55%)
Of the replies received, those which stated that registration not yet required (e.g trial not yet recruited / trial not yet started / trial terminated before recruitment commenced)			9	(27%) Of those where reply received
Of the other clinical trials not found or not known to have registered: Reply not received			27	(45%)



For Transparency Forum Meeting discussion

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