Building Bridges to Improve Co-production in Trials and Its Reporting | *A Mixed Methods Research Analysis*

Amy Price

Thesis submitted for the degree of

Doctor of Philosophy in Evidence-Based Health Care

Kellogg College, Department of Continuing Education

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Supervisors

Professor Mike Clarke, and Professor Su May Liew

Thesis Advisors

Jeremy Howick PhD and Sara Schroter PhD

Abstract

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Background

Participatory trials conducted over the internet are growing in scope with minimal guidance for Patient and Public Involvement (PPI). Replication and the use of trial findings in decision-making may depend on the methods used to conduct and report these trials.

Aim

To assess which research methods might be adapted to improve the conduct and degree of patient and public co-production within trials and in the work leading up to them.

Methods

A mixed-methods participatory action approach was used which included a blend of different studies, as noted under Findings.

Findings

Overall, I have shown why and how research teams struggle with building protocols for online trials and the design, conduct, and reporting of public involvement in trials generally and specifically in online trials. They express conflict about where and how to report PPI succinctly without interfering with reporting and research discussion. For instance, my systematic overview provides background from existing research on PPI in clinical trials' design generally and my thematic analysis of social media comments about clinical trials found PPI increases the quantity and quality of patient relevant priorities and outcomes, enrolment, funding, design, implementation and dissemination and yet roles and research boundaries were not clearly understood. An assessment of reporting quality and the methods used for self-recruited online trials of self-management health interventions, which I augmented with a survey of authors of online trials reporting quality found methods were poorly reported and seldom replicable. While a series of analyses on the use of public involvement statements in The BMJ, and surveys on supplementary materials, data sharing and dissemination found that simply requiring reporting of these areas increased quantity and then quality. Finally, an online Delphi identified consensus about what to include in the protocol for a participatory online trial.

Conclusions

This thesis demonstrates co-production with the public across multiple research designs with minimal funding is possible and improves research. Guidance for protocols and reporting methods in participatory online trials was identified as beneficial by stakeholders. The post-thesis development of a multi-use online trials participatory protocol template, online training and the research reporting guideline is underwritten by Stanford University.

Personal Statement

Background

I sustained traumatic brain injury (diffuse axonal injury) as well as other trauma, internal injuries and broken bones. I rehabilitated the associated learning disabilities sufficiently to apply to earn my doctorate at Oxford in EBHC.

The disabilities were severe enough that both sides of the four-year multi-national lawsuit agreed I would require lifelong institutional care. My intellectual capacity changed from the highest recorded in 10 years in BC (a province of Canada) to the bottom 2% recorded for my age group in the USA. I used the money to go to school because when you are learning disabled no one will fund you and for once in my life I invested in me.

I found rehabilitation programs which I completed online with the guidance of a treating neuropsychologist who recorded objective evidence of improvement.

When I showed another neuropsychologist whose program I used, the early brain scans, he cried. The lesions were recorded on an .02 tesla shopping mall MRI. As can be imagined when repeated on a 3 Tesla by an MRI expert, the results were much more dramatic. At this point I want to than Dr Dave Stevens my TBI mentor who encouraged me to farther.

I was instrumental in changing the law in Canada for those who have sustained brain injury. This came about as my neuropsychologist gave me the homework assignment of writing a letter to make a difference. The letter first went to the minister of Banking and Finance who asked if he could forward it to the Prime Minister. This set the wheels of change in motion. Even a brain damaged person with a clear argument can change policy.

I am immensely grateful to The Open University who accepted me and provided disability assistance when I was too damaged to go to classes. I did not want to be limited by only “the patient experience” It is the evidence, the science and the ability to appraise the literature that made the way for rehabilitation and recovery. That is why I applied to The Evidence Based Health Care Programme at the University of Oxford. The DPhil experience has shaped my life and has forever changed my perceptions.

The Message

When you choose to reframe your destiny, your tools can come at unlikely times and through unusual sources. The future of the seed is within itself and your future is waiting on the inside of you. Go and meet it. When adverse circumstances surround you like quicksand it is more important to learn to float to the top where there is a solution than to sink and struggle with a blaming mentality.

The way to reclaim yourself is by giving the present your full attention. Your diligence now will prepare the future. You will mess up; forgive yourself and try again. Life is like an ocean, there is always another wave, wait for the next one and use past experience to improve your learning curve. Kindness and laughter are yours to enjoy. Follow your dream and back yourself. In the end who you are matters more than what you do.

Acknowledgements

I want to first acknowledge my husband Dr DJ Price who encouraged me to continue through thick, thin and personal tragedy. Our daughter Kathleen who told me the difference between those who got a doctorate at Oxford and those who didn't was that the ones who succeeded started by writing an application. Our son, Ryan and his children, David and Jacob, who fed me and watered me so I could write up.

Professor Rakesh Biswas, who introduced me to writing journal articles and the experience of working with his medical students from Asia. Professor Andrew Miles who offered guidance, expertise and waived publishing access fees that allowed me to publish . Jo Kirkpatrick, my friend who painstakingly corrected all my references before I could do them because of partial blindsight and provided friendship and help through all the publications.

The BMJ helped to shape me through the leadership of Dr Tessa Richards, who brought me on board as a research fellow and who along with Dr Sara Schroter and Dr Rosamund Snow paved the way for me to join The BMJ as an editor. Dr Richards has quietly and persistently championed patient partnership and dignity around the world. Special thanks to Professor Elizabeth Loder and The BMJ research team who taught me by example how to write to get published and how to hold group meetings online.

Multiple thanks to Dr Brian Alper, the founder of Dynamed Plus, Professor Glyn Elwyn, Dr Zbys Fedorowicz and Dr Esther van Zuuren who worked with me on methods, the skills of coding as a medical analyst, shared decision making and who freely provided methods advice with accuracy and kindness.

It is my greatest honor to work with Professor Larry Chu and to learn together as his co-production partner and with the Stanford Medicine X family as a senior research advisor. I will forever remember his kindness, support, wonderful ideas, mentoring skills and gentle leadership.

Thank you, again Jazmin Geer, Lenny Vasanthan, Julie Sprakel, Michael Mittelman and Dr Loai Albarqouni my wonderful research partners who helped to make this research a reality.

Statement of Contributions

This doctoral thesis is independent and original work of which I, Amy Price am the sole author. Academic supervisors Professor Mike Clarke, Professor Su May Liew and retired supervisor Professor Amanda Burls as well as thesis supervisor Dr Sara Schroter (senior researcher at The BMJ) contributed supportive guidance on the overall research strategy, protocol, analyses, publication and presentation of results. Professor Clarke joined the supervisory team later and his wisdom guided me towards a successful Transfer of Status and he was steadfastly present and constant for every meeting. Dr Jeremy Howick my college supervisor was a friend and mentor who stuck with me through the failures, he offered strategies and resources as he encouraged me to continue The director of EBHC, Professor Carl Heneghan was insightful and prophetic in his guidance, which I followed implicitly. Dr Adrian Stokes provided just in time encouragement and helped me through the administrative maze.

CUREC guided the research concerning ethics as I used a variety of research methods and had to write pro-formas. The Health Experience Group (Oxford) and Professor Louise Locock provided consultation with structure and methods for Chapter 3. Amanda Burls, who has retired, contributed significantly to the early part of the Thesis and several of the associated publications. Nia Roberts, Information Specialist, University of Oxford, Bodleian Library assisted in developing the search strategy for the systematic overviews in Chapter Two and in Chapter Six. Dr. Anne Brice built the ORCHID database with the help of Professor Amanda Burls and Amy Price and this was used in Chapter Four. Dr Brice updated the database for the thesis and for publication.

The doctoral thesis was about building bridges to improve co-production in trials and its reporting and to do this I coproduced and collaborated with multiple contributors who are named in the contributor section for each chapter. The thesis was self-funded. I could not have done this work without the help of volunteers who were patients, medical and other students plus patient advocates and all those who wished to be are named at relevant points in thesis. We painstakingly learned together and I will be forever grateful for their patience, kindness, encouragement and diligence.

Table of Contents

Building Bridges to Improve Co-production in Trials and Its Reporting | *A Mixed Methods Research Analysis* **1**

Abstract 2

Personal Statement 3

Background 3

Acknowledgements 4

Statement of Contributions 5

Table of Contents 6

Chapter One | Thesis Introduction **11**

Background 11

Rationale for PPI and Co-Production in Online Trials 15

References 25

Chapter Two **28**

Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews **28**

Abstract 28

Introduction 29

Methods 31

Results 37

Strengths of Public Involvement 46

Weaknesses of Public Involvement 48

Opportunities for Public Involvement 50

Threats to public involvement 50

Discussion 51

Conclusions 56

Declarations 58

References 59

Chapter Three | Mind the Gap in Clinical Trials: A Participatory Action Analysis with Citizen Collaborators **65**

Abstract 65

Introduction 67

Methods 67

Results 69

Discussion 76

Conclusions 79

References 81
Chapter Four 84
SMOOTH: Self-Management Open Online Trials in Health | An Analysis of Existing Online Trials 84
Abstract 84
Background 86
Methods 88
Results 95
Discussion 104
Future Directions and Conclusions 108
Methods and Public Involvement Survey of Corresponding Authors of Existing Online Trials 113
Abstract 113
Introduction 114
Methods 115
Results 119
Discussion 127
Conclusions 130
References 132
Chapter Five | Reporting and Publishing Gaps, Growth, and Methods in Patient and Public Involvement 139
Introduction 139
Section One | Frequency of reporting on patient involvement in research studies in two BMJ Journals 141
Section 2 | The Self-Reported Needs of Patient and Public Reviewers at The BMJ 148
Section 3 | The Role of Supplementary Material in Journal Articles: Surveys of Authors, Reviewers, and Readers 155
Section 4 | How Frequently are Research Trial Results Disseminated to Participants and in What Format? A Survey of Trialists 160
Section Series Conclusion 166
References 169
Chapter Six | Informed Consent in Randomized Controlled Trials: An Overview of Systematic Reviews 171
Abstract 171
Introduction 172
Methods 175
Results 179
Discussion 198
Conclusions 200

References 202
Chapter Seven | Protocol Lab for Online Trials Delphi (PLOT-D) 205
Abstract 205
Introduction 206
Methods 210
Results 222
Discussion 239
References 243
Chapter Eight | Thesis Conclusion 245
References 251
Word Counts by Chapter 252
Appendices Table 253
Registration and protocol 258
Supplementary data 258
Chapter 7 PLOT-D Appendices 263
PLOT-D Round 1 Background Discussion 263

Table of Figures

Figure 1 Taking Steps to Introduce Co-production to the Research Process 18
Figure 2 ORCHID cumulative growth of randomised controlled trial reports by year 1989-2014 [42] 21
Figure 3 Conditions studied in online trials with 5> trials in the ORCHID database through 2014 22
Figure 4 PRISMA Flow Diagram 37
Figure 5 Quality Appraisal 41
Figure 6 Patient and Public Involvement Methods Reported 43
Figure 7 Ways review authors implemented PPI 44
Figure 8 Outline of the SWOT with the themes used for analysis 46
Figure 9 SWOT Framework and Perspective* 70
Figure 10 PRISMA Flow diagram 95
Figure 11 Intervention types 99
Figure 12 Interventional and general outcome types 99
Figure 13 Figure 13 Risk of Bias across trials 103
Figure 14Methods by which patient research volunteers were recruited 121
Figure 15 The ways researchers chose to communicate with PPI volunteers 123
Figure 16 Results on queries for where additional reporting guidance would be helpful 125
Figure 17 Will Stahl-Timmins, Guidance for BMJ Patient and Public Reviewers | The BMJ 150
Figure 18 Views by group on the value of PPI relevant supplemental materials Open-Ended Survey Comments 158

Figure 19: Diagram for Informed Consent Overview PRISMA 180
Figure 20 Included reviews and their reporting completeness 185
Figure 21: Participant feedback methods 187
Figure 22: SWOT Framework 188
Figure 23: Coding themes for informed consent 189
Figure 24Delphi research review 207
Figure-25 Online Delphi process outline 214
Figure 26 Delphi Countries Collage 223
Figure 27 Flow chart used for Delphi research reporting 224
Figure 28 Example of graphs shown to participants in the integrative group 225
Figure 29 Example of graphs shown to participants in the consecutive group 226
Figure 30 Example of graphs shown to participants in the role specific groups (example only, numbers vary by group size) 226
Figure 31 Overall consensus by category 238
Figure 32 PPI from practice to policy change 245
Figure 33 NIHR: moving towards co-production 246

Tables

Table 1 Included reviews 39
Table 2 Getting started with PPI 54
Table 3 Working with Patient and Public Research Partners 55
Table 4 Trial report and country of origin 97
Table 5 CASP RCT Quality Appraisal 100
Table 6 Protocol and reporting suggestions 108
Table 7 History of corresponding authors work on trials 119
Table 8 Types of PPI used throughout a trial 122
Table 9 PPI activities and acknowledgment of PPI in writing up and dissemination plans 124
Table 10 PPI Declaration Classification for Quality 143
Table 11 PPI Contributions of Patient and Public involvement in manuscripts before and after introduction of mandatory PPI statement in BMJ and BMJ Open 143
Table 12 Appraisal of quality of BMJ Open PPI Declarations 145
Table 13 P&P Reviewer activity at the BMJ 2014-2018 151
Table 14 Comparison of Peer and P&P reviewers at The BMJ 151
Table 15 Patient and Public Reviewer Suggestions to The BMJ 153
Table 16 Author, Reviewer, and Reader Perspectives on the Value of Additional Tables of Data and Completed Checklists for Reporting Guidelines by Group [a] 158
Table 17 Dissemination Findings 162
Table 18: Public involvement in the dissemination of the research 163
Table 19 Table of Included Reviews 181
Table 20: Ethics compliance reporting in informed consent 186
Table 21: What consent aspects the reviews reported 187
Table 22 Delphi Questions 1-3 228
Table 23 Delphi questions 4-5 229
Table 24 Delphi Questions 6-8 230
Table 25 Delphi Questions 9-11 231
Table 26 Consensus for Delphi items 232

Table 27 Delphi similarities and disparities 234
Table 28 Consensus in groups but not main Delphi 235
Table 29 Stakeholder priorities 236
Table 30 Word count excluding bibliography, declarations, tables and figures 252
Table 31 Appendices Table and locations 253
Table 32Overview search terms for MedLine 256
Table 33 Excluded Studies PPI in design chapter 2 257
Table 34 Search terms for overview of informed consent 258
Table 35 Table of Excluded studies Over for informed consent 260
Table 36 Q17 265
Table 37 Q18 266
Table 38 Q19 266
Table 39 Q20 268
Table 40 Q21 269
Table 41 Q22 269
Table 42 Q23 270
Table 43 Q24 271
Table 44 Q25 271
Table 45 Q26 272
Table 46 Q 27 273

Chapter One | Thesis Introduction

Background

The research question began with a research problem and this was finding ways to co-produce better research methods with patients and members of the public over the internet. Societal involvement by citizens in their own health and health care is not only desirable in principle[1], but it can also lead to better health outcomes[2]. However, research shows that even patients who are active and involved in their own care and in research may need support to frame research questions effectively[3]. In addition, there are many barriers to patients taking control of their own health including the healthcare culture[4], patients' own attitudes and knowledge[5] and a relative deficit of research into questions about the effectiveness of self-management of health compared to pharmacological and physician-management focused research.

This thesis investigates how research methods, public involvement, and research reporting might influence the viability of online trials and participatory research design. The findings will inform the development of a participatory online trials protocol reporting guideline that will be co-produced by a team of research professionals, clinicians, and citizen collaborators.

Thesis Aim

To examine how online trials can be used as a medium for patient and public involvement in health research and to explore how public and patient involvement co-production and a standardized guideline for reporting might be used to build better protocols and so influence trial quality and participant understanding.

Objectives

1. To establish what is known about patient and public involvement in the design of clinical trials through an overview of systematic reviews (Chapter 2)
2. To engage with the perspective of participants in clinical trials through online sources using citizen volunteers as authors and research team collaborators to inform practical development about the values, preferences and priorities of trial participants (Chapter 3)
3. To establish what is known about best practice in conducting online trials through the systematic identification of existing self-recruited online randomized trials of self-management interventions, analysis of their methodological strengths and weaknesses, and review of how patients and members of the public were involved in the research process (Chapter 4)
4. To investigate how mandatory public involvement reporting, Patient and Public reviewers, the use of supplementary materials, and current dissemination practices impact the reporting and publishing of Patient and Public involvement (Chapter 5)
5. To identify uncertainties around informed consent and to systematically review the evidence on this to inform an online Delphi (Chapter 6)
6. To conduct an online Delphi using a participatory action research approach to develop a post thesis research reporting guideline and a multi-use protocol template to use in writing protocols for participatory self-recruited online trials (Chapter 7)
7. To include public and patient involvement with some degree of co-production for each objective within the limitations of unfunded research, a variety of research designs, and as a new researcher. (All chapters)

Research design

The participatory research design was chosen to meet the research objectives by facilitating the understanding of cultural influences and human values while integrating multiple research methods. This thesis uses a mixed-methods design that is first sequential by study and then is concurrent within the studies. It adopts a participatory action research framework with citizen inclusion as research collaborators.

Thesis Methods Overview

This research uses a mixed-methods participatory action research (PAR) approach where the objectives involve community participation and action. PAR seeks to understand the world by working collaboratively to change it following reflection[7]. PAR emphasizes collective inquiry and experimentation grounded in experience and social history. Throughout each segment in the program of research presented in this thesis, opportunities were available for citizens to engage with the research and add to the body of knowledge through co-production and research collaboration[8]. For the purpose of this research, the size of the citizen participation groups was limited in order to manage administrative, personnel and resource costs.

The thesis contains embedded research within the chapters in the form of a "*Study within a Trial*" (SWAT) or a *"Study within a Review"* (SWAR). These embedded studies are efficient and timesaving as they can make full use of ongoing research by embedding the testing of practical concepts to produce better evidence to manage and problem solve uncertainties faced in future studies. The results can be reported within the report of the host study, separately in the literature and in the repository, where the registered methods are free for anyone to use or adapt. SWATs can increase awareness and interest in methods research, while the SWAT repository provides a location to store, disseminate

and modify the methods. I found the submission templates useful for structuring and mapping my research methods and to refine my aims into a realistic focus according to what the methods could be expected to produce. The SWAT and SWAR initiatives were established by the Northern Ireland Methodology Hub and the development of the repositories was supported by the Medical Research Council Network of Hubs for Trials Methodology Research (MR/L004933/1-R50).

Thesis Structure

The presentation of each research study begins with an abstract and concludes with contributory statements and research declarations, along with a lead in to the subsequent study by objective. The appendices are in a table of the chapters on page 243 with links or page numbers to where materials are stored and this is followed by the word count table. Data extraction and qualitative coding can be made available by Amy Price on reasonable request dr.amyprice@gmail.com

Citizen Collaboration | PPI Co-Production

Each study for objectives 1-6 included citizen participation and feedback and in many cases the research was co-produced by Patient and Public involvement research partners as stated in objective 7. Information gathered from and with the citizens was used as a learning mechanism for future protocol guideline development.

Rationale for PPI and Co-Production in Online Trials

"Co-creation and community nurture engagement to invite the public inside, so that they can influence and co-create healthcare, research and community. The public is the sensor that powers influence. They build evidence into practice" (Amy Price 2013*)*[12].

The growing public thirst for knowledge about research and health interventions can be used to benefit public health. The transition to the public doing research for themselves seems inevitable. It is already happening, individuals who thought about how to meet a need have partnered with researchers to deliver 3D limbs, pancreatic cancer tests, inexpensive microscopes made of paper and brain valves to relieve cranial pressure[13].

"*The patient is not an entity, but a person and that person can be a medical problem solver (Amy Price, 2014)*[13] *".*

However, the existing literature for involving the public in research and for participatory online trials is limited in approach[14] as it tends to focus on patient values and experience[15] rather than active adoption, implementation, and application of public involvement in research.

Elinor Ostrom and Oliver Williamson are Nobel laureates whose research demonstrated that ordinary citizens are capable of managing and sustaining resources without outside control. They assert co-production occurs by combining professional expertise with the energy expenditure, wisdom, experience, and skills of end users[16] nurtured through the core standards of love, empathy, watchfulness, care, reciprocity and willing instruction[17]. This does not imply equality in skills or ownership but equal respect, voice, and access to shared resources. In health research, as in life, partnerships are seldom equal, likewise with the distribution of skills. Shared access to skills and knowledge in healthcare can

multiply influence and scaffold community members to enrich resources that are held common.

"*A resource arrangement that works in practice can work in theory*". (Ostrom's Law) [18]

Online self-recruited clinical trials may provide an opportunity for technical scaffolding by deploying computers as expert learning reservoirs that learners can use to scaffold each other[19,20]. The concept of technical scaffolding was operationalized in the Hole-in-the-wall Education Limited (HiWEL) project, where computers were placed inside selected village walls in rural India and curious but previously illiterate children taught themselves and each other to read, and acquire math and science skills while exploring together through computers[21].

Another online community scaffolding example is the citizen science Zooniverse Galaxy Zoo project[22]. In this project, the researchers knew that humans were superior to machines for classifying information but did not have enough staff for making simple classifications, so they turned to the public for help. The citizen volunteers were provided with tools and minimal instruction as they worked alongside researchers to analyze images from NASA's Hubble telescope and classify them, thereby assisting scientists in understanding the origin of galaxies. All that was expected from the citizens was that they assist with the classification tasks but, even without formal training, they accomplished much more.

The citizen scientists were able to progress knowledge of the physical universe, improve automated data analysis and contribute to machine learning through engaging in simple classification tasks[23]. As contributors, volunteers noticed things they could not explain and set out to develop their own hypothesis. The citizens communicated, banded together and discovered a new galaxy[24]. They honed their skills interdependently, not by being spoon

fed plain language astronomy but instead by searching the internet, combing social media sites and gleaning information from professional astronomers who were willing to help with definitions and theory while showing them by example how to critically appraise the information they observed[23,25].

Although PPI and co-production in online research in research is an emergent practice, in medicine more generally, self–management and self-care initiatives in healthcare have reduced costs and increased quality of life. For example, patients remotely manage complex conditions like diabetes[26], anti-coagulation therapies[27] home kidney dialysis, tube feeding, pain pumps, thyroid care and asthma. These interventions are potentially lethal when used incorrectly and yet results show patients and the public are competent partners with clinicians in their own health care[28].

There are differences between PPI which is doing research with patients as partners and qualitative research where researchers learn through patient experience and then represent or define the patient "voice". As noted by Liabo et al, "*Providers of data and active partners are both crucial to health research, and conflating the two is counterproductive to ethical, valid, and patient focused research*".[29] Serving as a research participant or interviewee is not co-production[1].

In PPI, research is conducted 'with' or 'by' members of the public and patients rather than 'on,' 'to,' 'about' or 'for' them[30.] Co-production in healthcare research is the activation of Patient and Public involvement in which patients and members of the public work with clinicians and researchers to create, redesign and build medical research. Involvement and co-production can also be initiated by the public when they seek researchers and clinicians to partner with in research. PPI and co-production are not competing approaches but rather

they can be conceptualized as a continuum where the amount of involvement and/or co-production is decided by the research question, available skills of academic and lay researchers plus the availability and suitability of resources and research. For example, in a meta-analysis, statistics may be too complex for PPI partners to co-produce, however they might co-produce the research question or be involved in commenting on the manuscript. Researchers can bring methodological expertise in design, experience with trials and technical skills to the table, while clinicians have relevant treatment perspectives to reconstruct how medicine is practised in the face of co-morbidities along with the behaviour and patterns this might elicit. Patients can bring experiential knowledge about living with the condition of interest, while the public as partners can share insights from a social perspective. In contrast with traditional Patient and Public engagement, citizens are not only consulted, but they are part of the conception, design, steering, implementation, and management of the research. Figure 1 illustrates how PPI can work in co-production.

Taking Steps to Introduce Co-production to the Research Process



Figure 1 Taking Steps to Introduce Co-production to the Research Process

There are practical and pragmatic reasons why we need co-production in research in general and research conducted online in particular. Co-production can provide perspective and experience from living with a condition, or intervention, on how to improve the design, analysis and implementation of research as well as to advocate for the change and reforms that matter to end-users. Co-production can influence populations and cultures where researchers have limited access and are considered "outsiders". Co-production can improve policy by increasing the delivery of health research that is immediately usable for clinical practice and can increase participant recruitment rates because when study design is co-created with end-users it may be more palatable to participants[31]. Testing and equipment costs can be reduced because the testing is validated by end-users rather than laboratory models, thus making it one step closer to seamless implementation as shown by Levitan and colleagues[32]. Co-design and co-development can enhance communication between science, medicine and the public while increasing healthcare literacy.

Since the 1990s, and prior to the rise of social media and PPI in government policy, organisations such as the patient community *"Association of Cancer Online Resources"* (ACOR) have adopted PPI and hosted online communities to connect patients, clinicians, researchers and policy makers in order to share research, increase health literacy, and to provide peer to peer support[33]. By 2011, there were some examples of PPI in clinical trials including the "*Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2*" (I-SPY 2) trial. This was where the work of PPI was championed by 25 advocates with breast cancer[34] who were responsible for improving participant consent forms, protocol optimisation, and increasing recruitment.

In the "*CATheter infections in Children"* (CATCH) trial, parents, clinicians and researchers co-developed surveys and focus groups for deferred consent for emergency research involving children with life threatening conditions and by working together, they found practical and compassionate solutions[35]. Co-production was pivotal in defining and co-authoring core outcome sets and scales for rheumatology research through the "*Outcome Measure in Rheumatology*" (OMERACT) conferences[36] and "*Patient Involvement in Outcome Measures for Psoriatic Arthritis"* (PIOMPSA) meetings; [37] with patients suggesting reducing exhaustion as a relevant patient important outcome measure, which researchers had not previously considered.

Several studies have reported a "return on engagement" for co-production activities, such as the "*Prostate testing for cancer treatment trial"* (ProtecT) where after rebuilding consent forms with patients, recruitment improved by 40-70% with significant gains in participant satisfaction and retention[31]. The "*Improving dentures for patient benefit*" (IMPROVDENT) trial worked with patients and members of the public to make the intervention "user friendly" and this resulted in fewer appointment cancellations and timely recruitment[38]. The "*Stroke with Transfusions Changing to Hydroxyurea*" SWITCH trial investigators reported that PPI improved trial conditions by eliminating unneeded procedures, forms and appointments and by ensuring that the burden of participation was similar for intervention and control groups. These actions increased participant retention, and reduced trial costs by £2.5 million[31].

A quadriplegic ventilator-dependent psychologist living with amyotrophic lateral sclerosis (ALS) led the project that developed the ALSFRS-EX extension to the ALS functional

rating scale[39]. The scale has been translated into multiple languages for use in the US Department of Veterans Affairs Repository Brain Bank and much of this work was completed online[40]. Recently, the pharmaceutical industry noted the monetary value of PPI co-production for increasing clinical trials efficiency, suggesting a 500-fold return on investment through the avoidance of under-recruitment and protocol amendments[31].

"Orphan interventions" like fluid therapy or ice caps or 'home remedies' are of little profit to drug or device companies and the evidence base for such interventions in most cases is limited, but benefits amongst patients and clinicians are widely reported[41]. These interventions might be co-produced with patients and members of the public and then tested with an online platform. The Online Randomized Controlled Trials of Health Interventions Database (ORCHID) is used to show the cumulative growth online trial reports by 1989 -2014 by Brice, Price and Burls[42,43] (Figure 2)

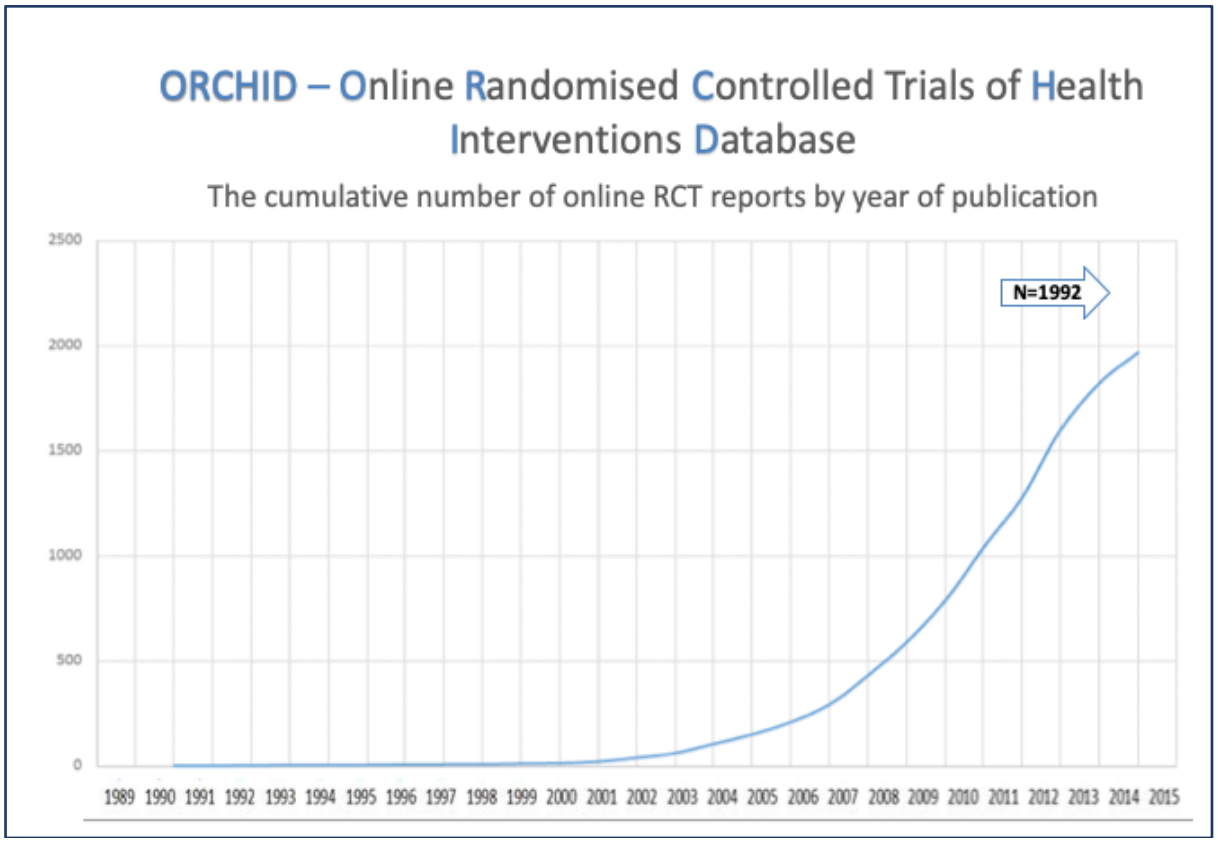


Figure 2 ORCHID cumulative growth of randomised controlled trial reports by year 1989-2014 [42]

There is interest on the influence of diet, sleeping habits, behavioral change, and exercise but the costs and resources and validated methods needed to produce reliable evidence mean that the current system of research generation provides insufficient motivation for research on topics such as these, despite their importance to the public[44]. Figure 3 reports the number of online trial conditions containing 5 or more trial reports contained in ORCHID up to the end of 2014.

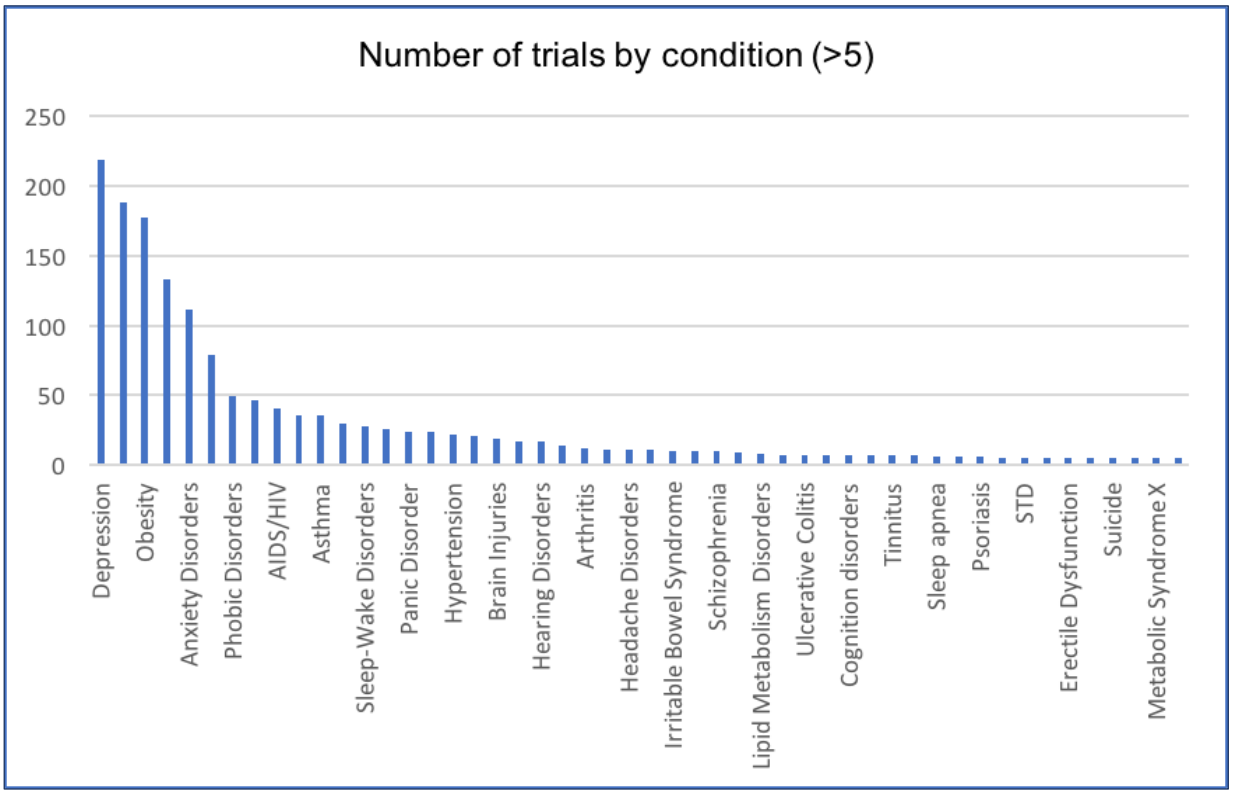


Figure 3 Conditions studied in online trials with 5> trials in the ORCHID database through 2014

The formation of online participatory clinical trials could serve as a catalyst for change in wellness and prevention health care and contribute to effective low-cost problem solving in health research[45].

Online trials face similar challenges to traditional trials to determine validity, data security, methodology, meeting the needs of multiple demographic communities and

provision of clear outcomes, and avoidance of inaccurate media reporting[46] This means end-user accessibility needs must be matched with ethical and methodological rigor. There are concerns about how liability in national and international settings will be managed, including how quickly a participant would have access to adequate compensation and care if an adverse event took place[47].

Recruiters worry that participants may double dip or dual enrol by assuming multiple identities in order to maximize their chances of finding an effective intervention or to take advantage of incentives and that this would reduce or negate the trial's validity.[48,49,50] Selecting a suitable incentive is also difficult. What would be regarded as a small incentive in one country may be equivalent to a salary in another, thus bringing about an ethical quandary[51]. Data security, ethical standards and safe harbour legislation also varies from country to country and is without an agreed international standard[52]. Additionally, participants may self-select outcomes based on their individual preference. Participants may understand ethical concepts differently, which can influence how consent is understood and the perception of what is required[53]. The opportunity for these elements to introduce bias or data corruption into the trial's estimate of the effect of an intervention are a concern, and are not to be ignored when considering the overall validity of participatory online trials. This makes it especially important to understand how PPI and co-production have been implemented and evaluated in the past and several systematic reviews have been conducted to investigate this. Therefore, to establish what is already known about the state of PPI in clinical trials, we conducted the study presented in the next chapter on "*Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews"*.

In addition, as this thesis was unfunded, I had to be creative in finding and training research partners. I had to train myself and then train others, including those without research experience to use research methods and software tools . As I did so, patterns of what might work emerged and I developed methods to test them which were embedded within the studies, so that others might learn with me or after me and so I could remember and apply what worked in other studies.

Acknowledgements

Figure 1 was co-created with Professor Larry Chu, Stanford Medicine X

Versions of Figures 2 and 3 were first presented at Medicine 2.0 then published in Digital health and finally published in the Anne Brice DPhil Dissertation

Brice A, Price A, Burls A. Creating a Database of Internet-Based Clinical Trials to Support a Public-Led Research Programme. Medicine 2.0 Conference 2014.

Brice A, Price A, Burls A. Creating a database of internet-based clinical trials to support a public-led research programme: A descriptive analysis. Digital Health. 2015;1(0):1-1

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Chapter Two

Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews

Abstract

Background

Funders encourage lay-volunteer inclusion in research, but this is not without controversy or resistance, given concerns of role confusion, exploratory methods and limited evidence about what value this brings to research. This overview explores these elements.

Methods

Eleven databases and gray literature were searched without date or language restrictions for systematic reviews of public involvement in clinical trials design. This systematic overview of patient and public involvement (PPI) included 27 reviews from which areas of good and bad practice were identified. PPI strengths, weaknesses, opportunities and threats were explored through use of meta-narrative analysis.

Results

Inclusion criteria were met by 27 reviews. Confidence in the findings was assessed using CerQual, Nice-H, CASP for qualitative research and CASP systematic reviews. Review quality ranged from high (n=7), medium (n=14) to low (n=6). Four reviews report the risk of bias. Public involvement roles were primarily in agenda setting, steering committees, ethical review, protocol development, and piloting. Research summaries, follow-up, and dissemination contained PPI, with lesser involvement in data collection, analysis, or manuscript authoring. Trialists report difficulty in finding, retaining, and reimbursing volunteers. Respectful inclusion, role recognition, mutual flexibility, advance planning and sound methods were reported as facilitating public involvement in research. Public involvement was reported to have increased the quantity and quality of patient relevant priorities and outcomes, enrollment, funding, design, implementation and dissemination. Challenges identified include lack of clarity within common language, roles and research boundaries; while logistical needs include extra time, training and funding, Researchers report struggling to report involvement and avoid tokenism.

Conclusions

Involving patients and the public in clinical trials design, can be beneficial but requires resources, preparation, training, flexibility and time. Issues to address include reporting deficits in the areas of risk of bias, study quality and conflicts of interests. There is a need for improved dissemination strategies to increase public involvement and health literacy. Improvements in funding, training, and reporting of PPI are needed to facilitate meaningful and effective PPI.

PROSPERO registration: CRD42016032288

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016032288

Chapter Two Highlights

Meets Objective 1: To find what was known about patient and public involvement (PPI) in the design of clinical trials through an overview of systematic reviews.

We found PPI brought improvements in:

- quantity and quality of patient relevant priorities and outcomes
- enrolment, funding, design implementation and dissemination.

Further advances could be made by:

- Improving language clarity
- Defining roles and research boundaries
- Provision for PPI time, training, and funding.

Take home points: Researchers struggle with the how, why and where of reporting PP1 and wanted to avoid tokenism.

Introduction

The requirements for the planning of Patient (or Personal) and Public Involvement (PPI) in research has increased to encourage research that is 'with' or 'by' members of the public and patients rather than 'on,' 'to', 'about' or 'for' them (definition is from INVOLVE as cited in Crocker and colleagues. [1] However, the lack of standardized reporting for PPI makes it difficult to identify in reports of research. Consistent reporting of the design, conduct, analysis, and interpretation of the PPI in clinical trials could facilitate reproducibility and reduce correctable error[2,3]. Researchers report they lack PPI training and experience[4]. In addition, impaired communications between patients, clinicians and researchers are well documented and may obstruct meaningful involvement[5,6].

This systematic overview of systematic reviews was undertaken to gather research into a single document to identify available evidence and best practice for PPI in the design of clinical trials[7]. It summarizes what has been found and reported about PPI in clinical trials;

identifies the context, methods or processes that facilitate PPI[8]; collates the perceptions of the influence of PPI on the research process, outcomes. and dissemination of results; and promotes the uptake of effective strategies to improve PPI in research and reduce resource costs and that might result from ineffectual PPI.

Why it is important to do this overview

Research in this field varies in quality, scope, size, and focus, making a systematic overview a practical option[8,9]. This enables comparison and critical appraisal of choices made in review selection and can collate, analyse and interpret study results across the separate reviews.

Research Question

What can we learn from existing systematic reviews about involving the public and patients in the design of clinical trials in terms of:

1. How patients and the public are involved in the design of clinical trials
2. What is known about good and bad practice for PPI in the design of clinical trials
3. How the value of PPI is perceived
4. How PPI is reported

Aim

To undertake a systematic overview of systematic reviews of the reporting of PPI in the design of clinical trials.

Objectives

1. Identify existing systematic reviews that examine PPI in trials.
2. Critically appraise these reviews to assess their methodological quality.

3. Extract data from these reviews and use these data to describe how, and to what extent, the public and patients have been involved in trials (other than as participants).
4. Seek examples of what worked and what did not to identify good practice.
5. Identify methods and areas of involvement with positive or negative effects on trial design
6. Identify research gaps in PPI in trials design.
7. Identify good practice in the reporting of PPI.

Methods

Research for consideration

Systematic reviews and overviews published in any language that reviewed existing public or patient involvement in clinical trials (other than as participants) were eligible. The involvement could include but was not limited to, prioritization of the research question, involvement in the design or conduct of the trial, analysis, presentation of results, or plans for the dissemination of findings. A review could include quantitative or qualitative or mixed methods studies. Reviews of PPI in clinical trials were eligible if they searched a minimum two databases, appraised the included studies, provided summary findings and included a synthesis of the data and the information retrieved[10].

Outcome measures

The outcomes of interest were PPI employed in clinical trials design, the impact of PPI on research design and the tensions, barriers, recommendations, and strategies relating to PPI as reported in the studies included in the reviews.

Data Sources and Search Strategy

The following databases were searched from 1995 until December 2015: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Embase, CINAHL, PsycINFO, Science Citation Index, Cochrane Library , Database of Abstracts of Reviews of Effects, PROSPERO, Global Health Library, Health Technology Assessment, The Joanna Briggs Institute EBP Database, McMaster Knowledge Translation and WHOLIS. There were no restrictions on language or publication status. The general search terms for MEDLINE were reviewed by the authors and a medical librarian and adapted for each database.

The PRESS checklist[11] was used to ensure inclusion of essential elements in the search strategy. Reference lists and search terms of reviews captured by the initial searches were searched for additional reviews and topic experts were contacted. We searched PROSPERO for protocols and followed up conference abstracts identified through the database search that met inclusion criteria to see if they had been published in full (see Appendix 2:1)

Public Involvement

Volunteers from the Cochrane Task Exchange and Empower-2-Go assisted with screening, data extraction, analysis, prioritizing what to report and editing. The dissemination plan for the overview included promotion via social media, presentation at conferences, and dissemination to patient advocacy groups. Volunteers were invited to review the paper for readability and work collaboratively to build presentations to represent the overview.

Embedded research | Study within a Review (SWAR)

We conducted our embedded study within a review (SWAR) [92] to learn how to train people better. A variety of software tools are now available to help with the systematic review process but a sizable investment can be required for training and support in their use. Furthermore, if users feel uncomfortable or frustrated with the software, they might lag in the task they were working on or abandon the software and complete the task in another way.

I used an observational comparative study design to assess the effects of four learning support interventions for systematic reviewer software using:

1. Written instructions including frequently asked questions (FAQs) only without trainer interaction
2. Oral instructions with immediate feedback and screen share
3. Screenshot video with choice of feedback time and method (e.g. auditory, written or screen share)
4. Written instructions alone (comparator)

The primary outcomes were task completion and number of support interactions and the secondary outcome was learner rated self-confidence.

Screening and Selection of Reviews

All citations were screened in RAYYAN[12], a free online tool that allows the use of unlimited volunteers, tracking and blind review. To improve screening accuracy, retrieved citations were screened by me (AP) and then rescreened by me 4 weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[13]. A random sample of 6% of titles and abstracts were double screened by co-authors, LA and JK. Full papers were retrieved for articles that appeared eligible or

potentially eligible on the basis of their title and abstract, and for a 1% random sample of those judged to be ineligible to check for correct exclusion[13]. Reviewers were not blinded to author, institution, or journal.

Full Paper Retrieval

Full papers were downloaded to a shared folder and de-duplicated in Mendeley[14], where overview authors could write and share notes, add questions and additional data. Two authors (AP,LA) screened the retrieved full papers independently to match them against our eligibility criteria. Papers were categorized as include, exclude or unsure. Papers classified as unsure were discussed and agreement at all stages was reached by consensus of three authors.

Data extracted from included reviews

Two review authors (AP and LA) independently extracted key data for included reviews, using a specially prepared data extraction form in EPPI reviewer[15] which I piloted on a small sample of reviews and reviewed with my supervisors. Data on public involvement in clinical trials design and preparation was extracted, covering exploration of roles, policy, impact, reporting, interventions, and theoretical frameworks. Relevant data about PPI was included even when the primary focus of the review was not PPI. Table-1 reports the type of review used for the research question as this influences the way the data were collected and how reviews might score in reporting quality checklists. All findings were reviewed and discussed by three authors (AP, LA and JK) until consensus was reached.

Quality Assessment

The CASP[16] checklists for systematic reviews[17] were used as a preliminary screening tool when assessing systematic reviews for eligibility. The first three questions are general and

can be used to include or exclude the review. The NICE Quality Appraisal Guidelines for Qualitative Studies Appendix-H form[18] was used to determine whether the research questions and theory underpinning reviews were appropriate for the outcomes sought. The following domains were included when assessing quality: aims, methodology, search quality, recruitment, data collection, data analysis, reflexivity, ethical considerations, findings, and research contributions.

Risk of Bias

Confidence in the Evidence from Reviews of Qualitative Research (CERQual)[19,20] was used to summarize confidence in the findings of the reviews of qualitative research. This is based on four components: limitations of methodology, relevance to the research question, coherence and the adequacy of the data presented. CerQual enables ratings of "high", "medium", "low" and "very low" (although this final rating was not needed because such reviews were not eligible). The starting point of 'high confidence' reflects that each review finding is a reasonable representation of the question of interest and is downgraded if there are factors that would weaken this assumption[19]. After assessing all four components, authors agreed on overall confidence in each review finding and the relevance to our research. NICE, CASP, risk of bias, conflict of interest and CerQual (CQ) ratings were aggregated and reviews were categorized as Low <10.5 Medium>15 High >21 confidence. All measures were pre-specified prior to analysis. The assessment of each review is shown in figure 3.

Thematic Analysis

I prepared a strength, weakness, opportunity, and threat (SWOT) framework and discussed this with my supervisors and volunteers. EPPI reviewer, Excel and NVIVO were used by three authors (AP, LA and JK) to organize the data into themes and code it for analysis.

This made it possible to identify and agree on methods and areas of involvement with positive or negative effect on trial design and to identify research gaps. The SWOT approach is used in healthcare research[21,22] to help teams to analyse data individually and then reach consensus on how to present their findings.

Descriptions of Information Presentation Forms

A summary is presented for each included review in Table 1. The excluded reviews summary contains citations and reason for exclusion and is located in the results section below under the heading full-text screening.

Results

Search Report

Figure-4 uses a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to outline the process of study selection [23].

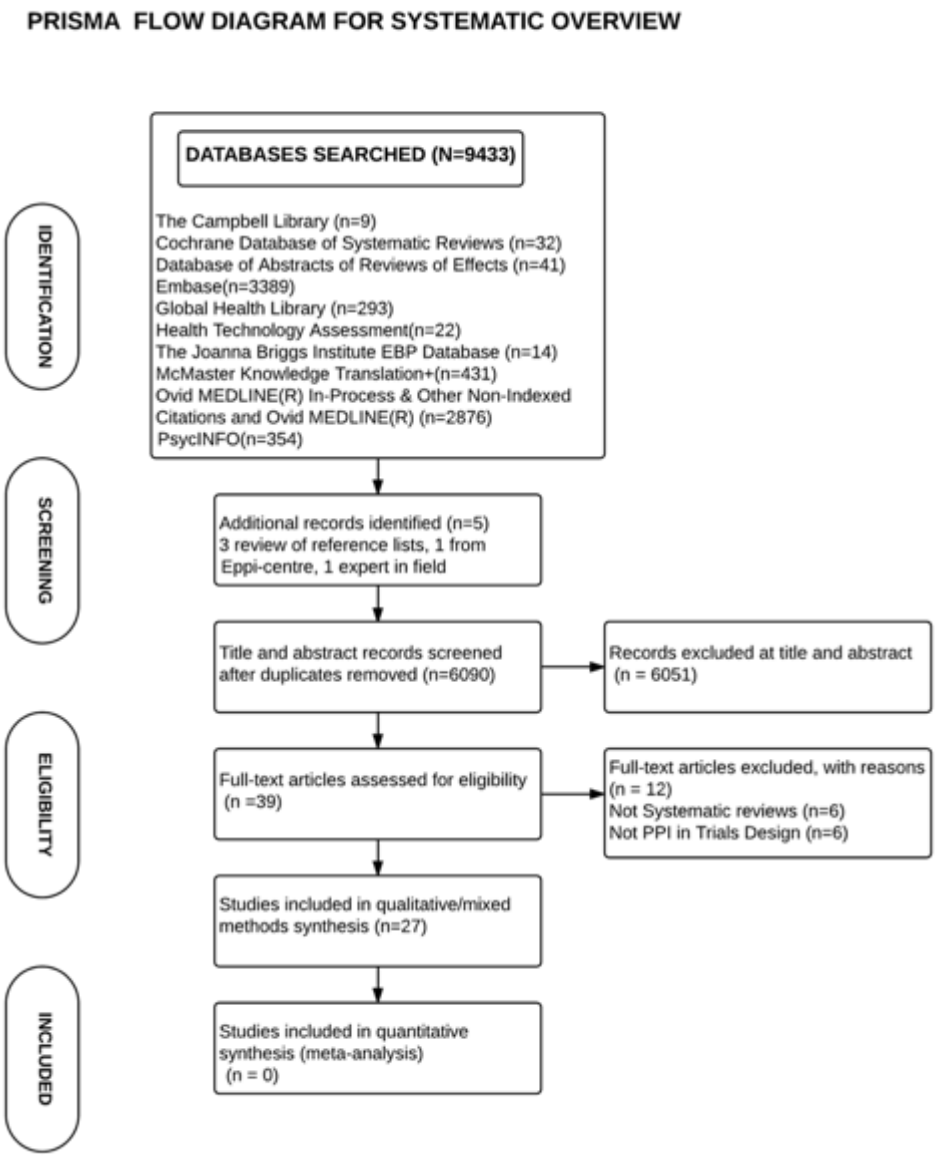


Figure 4 PRISMA Flow Diagram

Our search of 11 databases yielded a total of 9433 records. Three additional records were found by searching the reference lists of included reviews, one more was included from the EPPI Reviewer database and one review was identified by an expert in the field.

Title and Abstract Screening

After de-duplication, 6090 records remained. To improve screening accuracy, I screened retrieved citations and rescreened them 4 weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[13]. A random sample of 6% of titles and abstracts were double screened (by JK and LA) and for a 1% random sample of those judged to be ineligible to check for correct exclusion. Full papers were retrieved for articles that appeared eligible or potentially eligible on the basis of their title and abstract. The agreement was 100% before discussion and 6051 records were excluded leaving 39 potentially eligible articles[24–62] for full-text screening.

Full-Text Screening

Two authors, (AP and LA) independently checked the full text of 39 articles[24–43,47,57–62 44–46,48–50 51–56] for eligibility. Twelve[44–46,48–50 51–56] of these were excluded. Reasons for exclusion were; no public involvement in trials design [44–46,48–50] (n=6) and not a systematic review[51–56] (n=6). Twenty-seven reviews [24–43,47,57–62] met inclusion criteria for data extraction and analysis (Appendix-2, Table-5 Excluded Studies). Interrater agreement prior to discussion was Kappa= 0.862 (SE = 0.067, 95% CI= 0.732 - 0.992) and consensus was reached by discussion.

Included Reviews

Table 1 shows the citation number, first author, year of publication, type of review method, research question focus, number of included studies and funding support type for each included review.

Table 1 Included reviews

Citation	Author reported review design	PPI Review Question Focus	Studies	Funding*
Bailey 2015[24]	Mixed Methods	Disabled children	22	Gov, Priv, Acad
Boote 2010[25]	Narrative & Case Examples	Primary health research design	7	NR
Boote2012[36]	Narrative & Case examples	Organizational approaches to reviews	17	Res
Boote 2015[47]	Bibliometric	Review of PPI literature	683	NR
Brett 2010[57]	Narrative	PPI concepts, measures, outcomes, impact	98	Acad, Priv, Gov
Brett 2014[58]	Mixed Methods	Impact service users, researchers, communities	Not stated	Gov
Brett2014[59]	Mixed Methods	Impact health, social care	66	NR
Concannon 2013[43]	Mixed Methods	Stakeholder involvement in Comparative effectiveness research and PROMs	70	Gov
Degeling 2015[60]	Scoping	Public deliberation health, policy research	78	Gov, Priv
Domecq 2014[61]	Narrative	Patient engagement	7	Gov
Forsythe 2014[62]	Narrative	Rare diseases	35	Gov
Fudge 2007[26]	Qualitative	Older people in health research	35	Priv, Gov
Gysels 2012[27]	Narrative	End of life research participation	20	Gov
Hanney 2013[28]	Mixed Methods	Benefits for healthcare performance	33	Gov
Hubbard 2008[29]	Narrative	Affected by cancer	52	Gov
Jones 2015[30]	Qualitative	Reporting in surgical research	8	Res
Lander 2014[31]	Qualitative	Biomedical research and innovation	46	Acad, Gov
Mockford 2012[32]	Mixed Methods	Impact UK National Health Service (NHS)	28	Gov

Nilsen 2013[33]	Mixed Methods	Development in research healthcare policy, practice guidelines	6	Priv
Oliver 2004[34]	Qualitative	Agenda setting NHS used evidence-based approach	286	Gov
Salvi 2005[42]	Mixed Methods	PPI mental health service users	35	NR
Shippee 2015[35]	Scoping	Research framework for engagement of service user, patient	202	Gov
Smith 2008[37]	Mixed Methods	Nursing, midwifery, health visitor research evidence and practice	416	Gov
Stewart 2011[38]	Qualitative	Effect of patient feedback on clinician research priorities	258	Priv
Stokes 2015[39]	Mixed Methods	Collaboration, coalitions, and partnerships through social media	11	Priv
Tillett 2014[40]	Mixed Methods	Outcome measures psoriatic arthritis	63	Ind
Tong 2015[41]	Qualitative	Research priority setting, kidney disease	16	Gov

* *Type of funding is classified as industry (Ind), private foundation/organizations (Priv), governmental (Gov), academic (Acad), researcher (Res) or not reported (NR).*

The total number of participants in the studies included in each review was not consistently reported across the reviews. The total number of studies for the 26 reviews was 2493 (range: 6-683; mean: 104; median: 35). The number of participants per study and their PPI roles were not consistently described. The use and definition of gray literature was variable.

Twelve included reviews reported government funding [27–29,32,34,35,37,41,43,58,61,62], five had mixed funding [24,26,31,57,60], three had private funding [33,38,39], two were explicitly funded by the researcher [30,36] and one was funded by industry [40]. Four reviews did not report funding sources [25,42,47,59]. All academic funding reported was combined with other funding. Any impact or influence of direct or indirect industry funding was not reported. For example, it was unclear if academic, private/public foundations, government departments or researchers were indirectly funded, employed or working on behalf of industry partners

(Table 1). Tarpey and Bite (2012) report 75% of industry had no plans for public involvement in research[63] and yet the work of Ehrhardt et al[64] report industry funding was six times more prevalent than other forms of funding for clinical trials.

Quality Appraisal and Methodological Assessment of Included Reviews

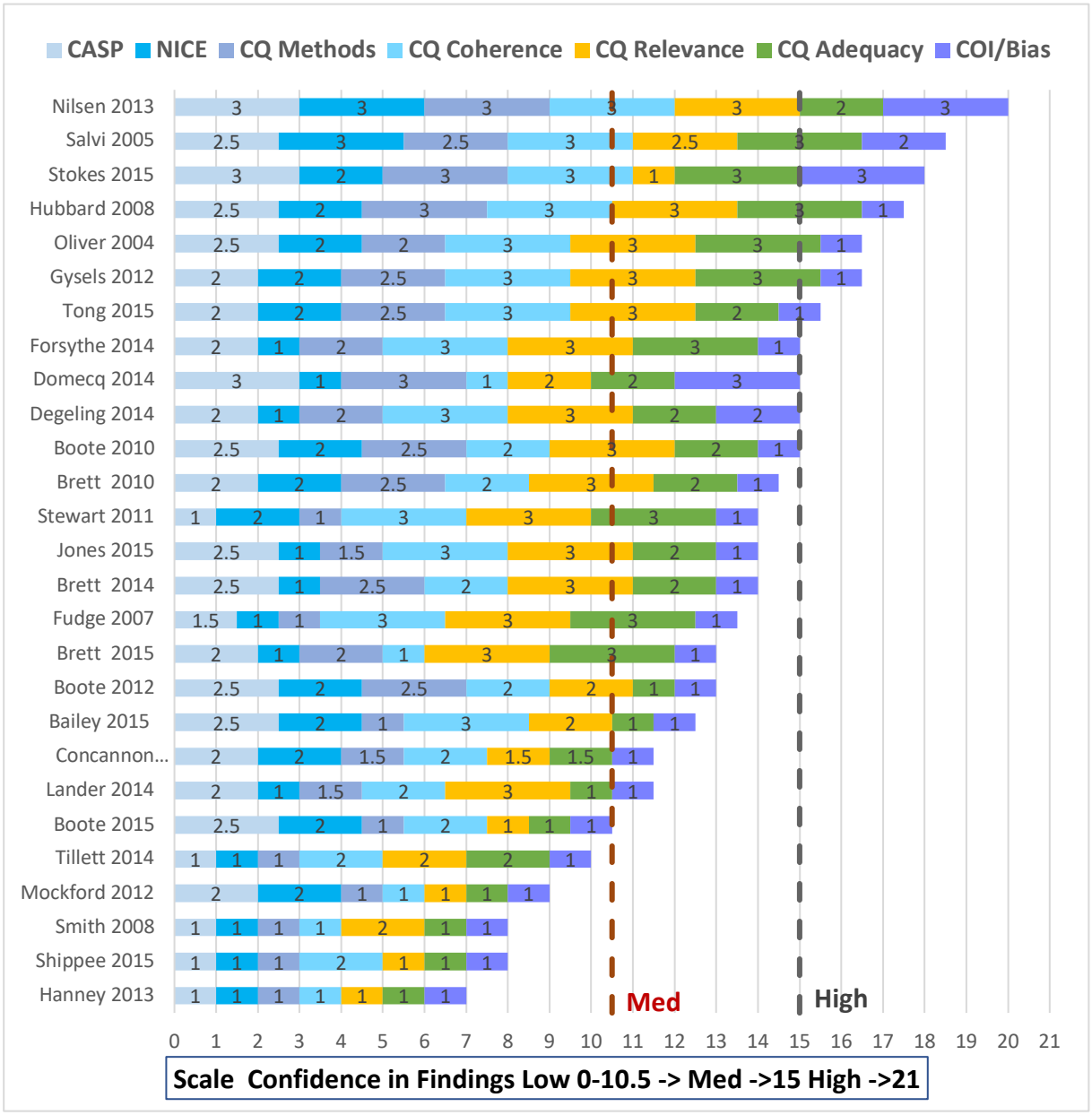


Figure 5 Quality Appraisal

Quality Appraisal using CASP, NICE, Risk of bias (ROB)/conflict of interest (COI) and Critical appraisal by CerQual (CQ) appraising four sectors; quality of methodology, coherence, relevance and adequacy and reporting of bias or conflict of interest with scores each ranging from 1-3, low-high for a composite score of 21.

The assessment of confidence in the findings for our review question (Figure-5) was completed by myself (AP) and two authors (LA and JK). The included reviews were categorized as low [28,32,35,37,40,47] (n=6), medium[24–26,30,31,36,38,43,57–62] (n=14) high[27,29,33,34,39,41,42] (n=7). Conflicts of interest and risk of bias were reported for their included studies[33,39,42,61] in four of the included reviews. In two reviews, this was referred to but not reported by individual study[42,60]. As expected, although some reviews might have been good enough to answer their research question, they were a substandard source of evidence for our research question. For example, three scoping reviews [35,47,60] scored low on quality because they looked only at abstracts and case studies, but they still contained useful information for our research questions. Likewise, studies measuring frameworks or seeking impact across research fields[57] contained valuable background information, but this was peripheral to the overview aim. The quantitative data reported was descriptive, heterogeneous and scattered across reviews making it a poor fit for meta-analysis and of relatively little relevance to our overview.

Extent of PPI involvement

PPI was more frequent in the form of researchers asking members of the public and patients for feedback on the trial design or citizen to citizen interaction such as moderating forums and recruiting participants, rather than in active participation for hands-on research tasks such as study design, ethical review, policy, recruiting, analysis and dissemination. PPI impact was reported in 14 reviews using many formats. Four reviews[32,57–59] written by authors working together on the question of impact investigated the reporting of impact and have proposed reporting guidelines[55], however, these reviews were hampered by inconsistent reporting within individual studies. Figure-6 shows how PPI was reported across the reviews and the methods of public involvement for various tasks. It shows

surveys and focus groups were dominant methods of involvement, yet all 27 included reviews reported the use of multiple tasks and methods.

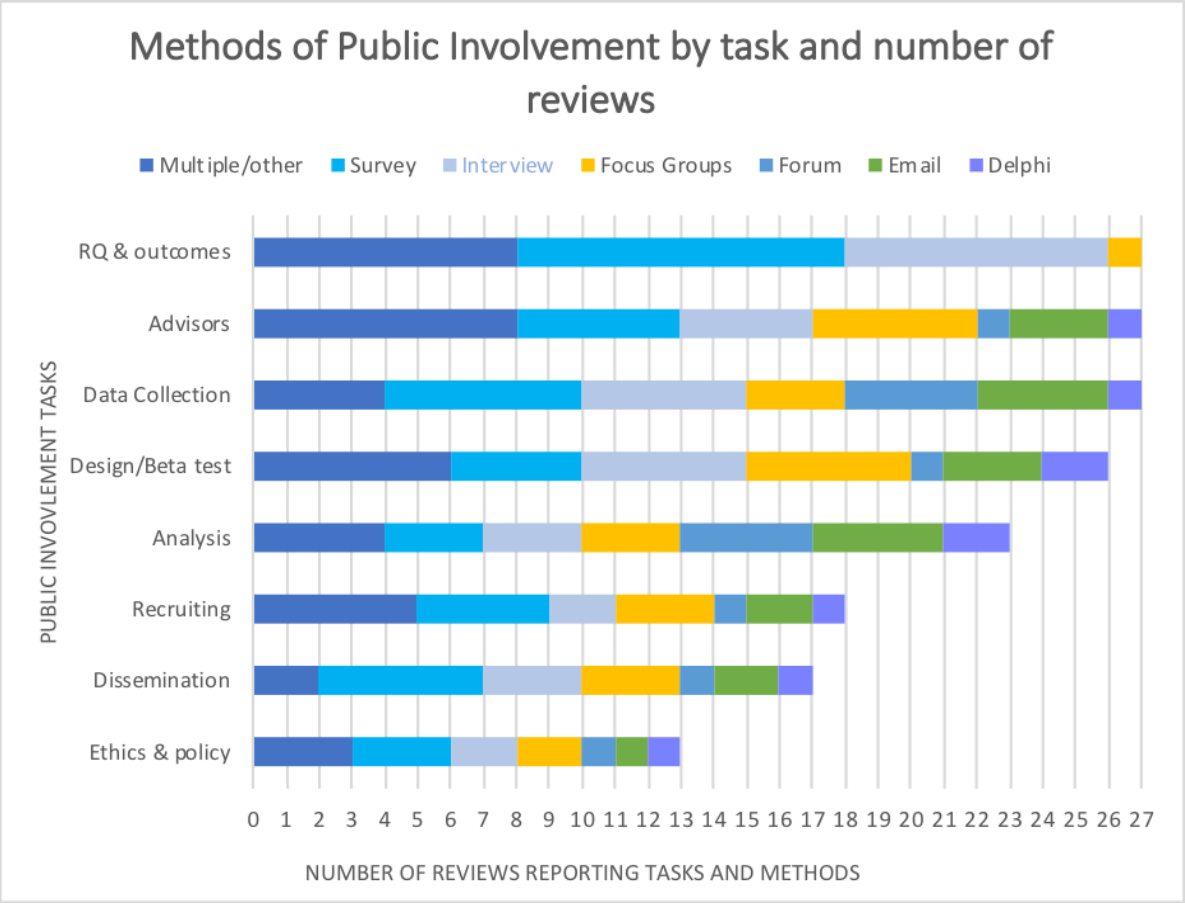


Figure 6 Patient and Public Involvement Methods Reported

PPI reported in primary research within the reviews (n=27) grouped by task and method, RQ (research question), combination (multiple PPI tasks and methods reported), Multiple/other refers to multiple tasks and other methods such as peer to peer interviewing/support, administering interventions.

Reviewers' use of PPI in their review

We recorded how review authors reported public involvement in their own reviews to supplement the inconsistent reporting of the numbers of studies or participants involved in tasks. Fourteen reviews did not report any PPI in the review and activities were frequently passive. For example, the public was updated by review authors and then were invited to advise or comment on the review, rather than engaging the public directly with the data. This is shown in Figure 7, where 11 reviews report the use of an advisory board. PPI

extended to collaborative screening of the literature in three reviews, and analysis and study design roles were largely advisory as recorded in the multiple/other category with seven reviews. The reviews report lack of funding as a barrier to PPI in the conduct of their review, and two reviews reported offering compensation for PPI.

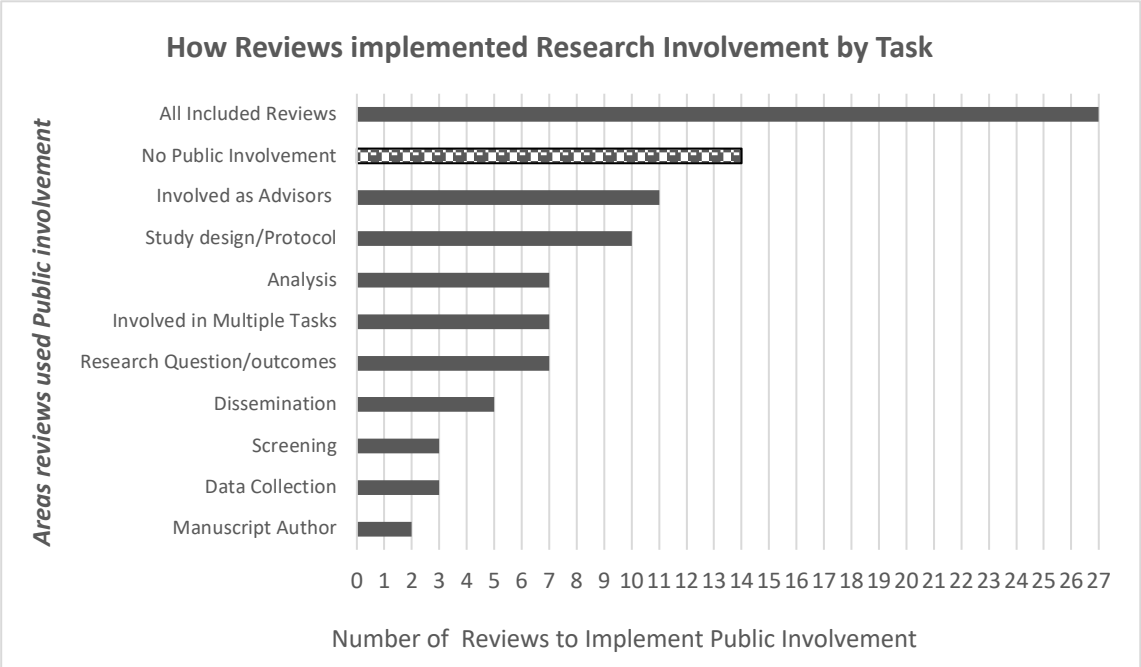


Figure 7 Ways review authors implemented PPI

Our PPI for this Systematic Overview

One volunteer from the Cochrane Task Exchange and three volunteers from Empower-2-Go assisted with screening, data extraction, analysis, synthesis, prioritizing what to report, and editing of this systematic overview. One lay volunteer and co-author fell ill and other volunteers completed her tasks. Volunteers helped with dissemination planning, presentation of the overview and continue to work with me to prepare teaching materials for Stanford free online courses, three university summer schools and conferences. The volunteers suggested improvements for the tables and figures, and reviewed the manuscript prepared for journal publication for readability.

Results for the Study Within a Review (SWAR)[92]

The most successful and preferred mode of instruction for trainer and trainees was Intervention 3: Screenshot video with choice of feedback time and method (e.g. auditory, written or screen share). Learners report this method offered them autonomy to learn on their own but with availability for immediate phone or video conference support as needed. The written instruction arms, interventions 1 and 4 resulted in people signing on but not finishing tasks. Those assigned to intervention 2 reported that they lacked confidence and this was reflected in doubling the need for instructor contact required in intervention 3. The unexpected bonus of intervention 3 was that the possible problem of difficult or non-responsive software was resolved quickly as both learner and trainer were using the software together and learners were more likely to correctly identify problems as technical issues rather than blame the problem on their personal lack of skill.[92]

Thematic Analysis of Public Involvement

In this section, as shown by Figure 8 we report what was learned from existing systematic reviews of primary research for involving the public and patients in the design of clinical trials through a SWOT analysis. This allowed coding of the narratives to answer the overview objectives.

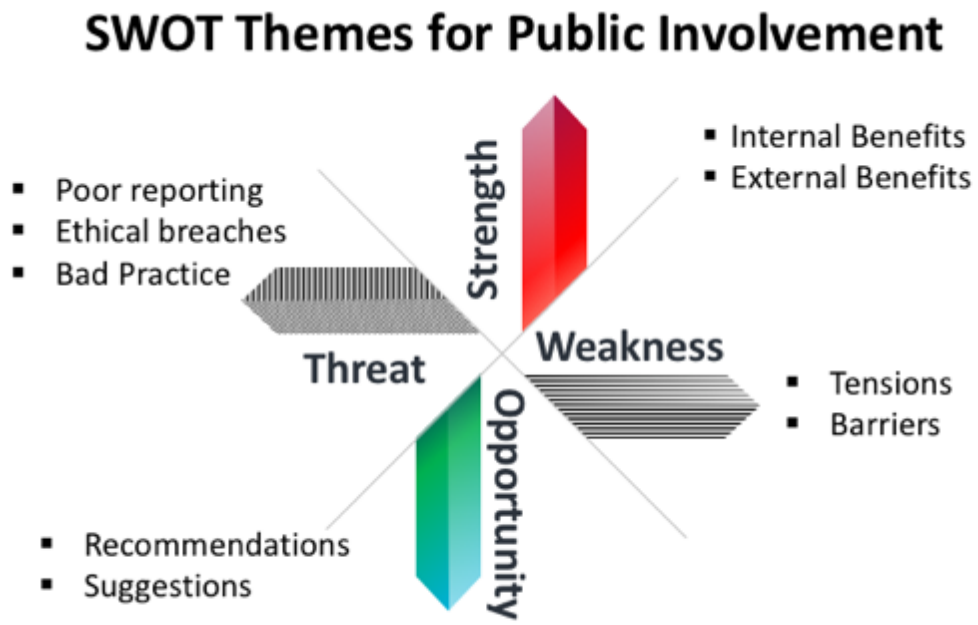


Figure 8 Outline of the SWOT with the themes used for analysis

Strengths of Public Involvement

Strengths were coded using themes of internal and external benefits. Twenty reviews contributed to these themes [24–26,29–34,36,39–42,51,57–62] . Some reviews did not report strengths because they were scoping reviews and that was not their focus or they discussed only frameworks for design without specific mention of benefits.

Internal Benefits

Shared internal benefits of PPI include knowledge of conditions, interventions and expanding of perspectives [28,59]. Negative stereotypes and power imbalances were lessened through working together and were replaced by mutual respect. Researchers were encouraged by volunteers' resiliency, innovation and tenacity and report newly acquired motivation and inspiration to work towards solutions[30,33]. Patients cite greater confidence,

research literacy, hope, trust and a sense of community. They felt participating gave their lives purpose, meaning, and identity[24,58]. Patients also report learning more about their condition during trials, helping them to feel valued, empowered and validated. [24,28,58,59]

External Benefits

Consultation with volunteers contributed to salient, pragmatic study designs and raised issues that researchers would not otherwise have anticipated .[25, 26,29, 57-59,61,62] Volunteers improved recruiting, interviews, influenced policy setting, and accessed funding for research[57-59,61,62]. In addition, there was community influence where PPI was considered a factor in de-stigmatizing mental health, age issues, disease stereotypes, and cultural challenges.[24,42,41,43]

The external benefits of PPI were reported from early stages in the design of a clinical trial, including in protocol consultation, setting user-focused research objectives and finalizing research questions; developing questionnaires, interview schedules, and consent processes; planning data analysis, user testing, and implementation and dissemination[25, 26,29, 57-59,61,62]. Volunteers were also reported as helping with practical problem-solving skills, depth, and perspective [26,29.53]. PPI contributions to recruitment and follow-up timing, strategy, lay materials and protocols, funding applications, and research manuscripts were reported to increase relevance and add research value[25, 26,29, 57-59,61,62]. Progress was noted for research awareness, literacy, transparency, and training materials. This resulted in increased recruitment, retention, favorable policy integration and community trust[41,43]. These benefits were more frequent when there was bidirectional communication, collective decision-making, and research intervention delivery training available to support the volunteers. [34,43,62,63] .

Weaknesses of Public Involvement

Weaknesses were coded by tensions and barriers. Shared tensions and barriers were followed by those specific to volunteers, researchers, and organizations. Twenty-four reviews contributed to these themes[3,5–26].

Tensions in Public Involvement

Shared tensions revolved around unclear roles[5,6,8,16,17] absent or ill-fitting reporting guidelines[8,18], tokenism[6,8], exclusion[3,7,8,12] framework limitations[3,5,11,12,19,20], resource allocation[5,8,18,21] and administrative boundaries[18,19]. Research questions posed by patients were not articulated in ways they could be applied[5,11,12,16,19,21–23]. Jargon was blamed for exclusion and confusion[5,12,13], Tensions were balanced by an overarching desire to carve out a mutually agreed path[3,6,8,11,12,18,22].

Volunteers reported needing early involvement to propose constructive changes[3,6,8,12,18] They welcomed frequent updates and specific feedback with opportunities for reflection and shared decision making about the fate of the research[3,8,11,24]. Volunteers indicated that provision for their physical limitations was suboptimal[12,25]. They worried about inappropriate conclusions from composite outcomes but lacked opportunity to share these concerns and noted they would benefit from research methods training[3,12,22].

Researchers worried about maintaining methodological rigor and focus while adapting research design for patients[8,12,19] and report personal lobbying by volunteers for pet causes[19,24] Instances were reported where group dynamics changed and overly aggressive patients and those without respect for rules of confidentiality or data protection harmed the

research[19]. Researchers hesitated to involve people who were ill, who might slow the research pace and compromise deadlines that might be related to funding[7,11,12,19,25].

Organizations reacted to potential "scope creep" where research-irrelevant community concerns increase costs, time and threatened feasibility[8,12,13,19,20,24].

Barriers to Public Involvement

Shared barriers included those imposed by cultures[11,12,17,25,26]values[11,12,25] and power hierarchies[6–8,12,13,18,19,21,26].There was limited co-creation of knowledge or community engagement for health via coalitions, collaborations, and partnerships[3,5,8,12,13,16–18,26,27]. Some trialists took positions that PPI was a specialist area and not scalable across research disciplines[26]. Patients reported that involving them too late in a trial meant that the design was already funded and fixed and that the priorities and outcomes were not reversible, leaving them with only user experience to contribute[3,19,21,26]. They were vulnerable to negative attitudes or dismissive behaviour and felt overloaded when drawn into internal strife[6,8,12,19].

Researchers struggled to identify a lead for public involvement, a lack of relevant recruiting networks, difficulties with information about structured, practical methods of involvement, and insufficient time to plan for PPI[5,8,10,12,13,19,26].

Organizational or gatekeeper barriers ranged from concerns about data being hijacked by opinion rather being centered by evidence[6,8,12,17,19,26]. Organizations struggled between tensions of protecting vulnerable patients and appearing paternalistic due to legal and ethical constraints[7,12,19,25].

Opportunities for Public Involvement

Opportunities were represented by themes of recommendations and strategies. Nineteen reviews contributed to these themes [4,6–13,15,17–19,21–24,28,29].

Recommendations

A focus on triangulation of teams and clear direction by senior research team members can reduce assumptions. Transparency with time for questions led to better outcomes and good research practice. Research methods and PPI training increased parity between researchers and volunteers. Participatory designs enabled inclusion of participants and cultures across research designs. Using flexible responsive approaches to tasks increased the efficiency and quality of involvement. Researchers suggested combining interviews and focus groups to reduce scheduling conflicts and manage costs. Reviews suggest engaging volunteers in post-study reflection.

Threats to public involvement

Themes identified as threats are poor reporting, data contamination, ethical breaches, and bad practice. All included reviews contributed to this theme.

Poor Reporting

Threats centered around poor reporting and inadequate quality appraisal of studies and the absence of pre-study published protocols[5,8,10,13,18,19].Conflicts of interest revolved around patient-provider relationships, industry and undue influence of advocacy organizations.

Ethical Breaches

Volunteers reported fear to speak out due to threats of blacklisting or exclusion. Patients without training in ethics or research methods report feeling ill prepared to sit on ethics

boards, decide policy or provide good quality PPI[8,19] because they may inadvertently breach confidentiality or patient safety. Cases of premature exposure of data on social media or prepublication leaks by volunteers were reported[19].

Poor Practice

Planning, training, and information deficits hindered volunteers' ability to contribute[3,5,8,11,13,18–20,25,27]. Unpublished methods were lost opportunities for learning. Potential harms of PPI need to be balanced against potential benefits with the caveat that patients and carers might be vulnerable populations[8,11,19,25]. Mixed methods studies without registered protocols could be used to pander influence or exalt experience above evidence. PPI reporting relegated only to supplementary files and not reported or linked in the research made methods difficult to replicate[20]. Supplemental files are valuable for reviewing and learning from the research as they can contain a level of detail that may not be available in the main paper however if they are inaccessible or not linked to the paper their use is limited at best[30].

Discussion

Public involvement was reported as beneficial for volunteers, researchers, and systems in a variety of settings, including different stages of trial design, cultures and disease states. Better results were obtained where resources, preparation, training, flexibility and time were designated for PPI and where communication channels were transparent. The identified tensions and challenges are not uncommon in emergent research fields and may be mitigated by testing and modification of current methods and improved research reporting. Common language and research reporting needs could be agreed by use of a Delphi process where the stakeholders including patients and members of the public come to consensus on a common set of reporting priorities[73]. This could be piloted by testing a

multi-use protocol with built-in reporting mechanisms for PPI. Methods could be tested by using a study within a trial (SWAT)[74] and reported for others to replicate, improve, and validate. For example, in this overview a study within a review (SWAR)[92] found that a screenshot video with choice of feedback time and method (e.g. auditory, written or screen share) worked best to train research partners in systematic review software. Learners reported this method offered them autonomy to learn on their own but offered the availability of immediate phone or video conference support as needed.

As patients become research collaborators, provide recruiting testimonials, conduct interviews with participants and exert cultural change through social media declaring all conflicts of interest would be best practice[75]. However, standard competing interest declarations are insufficient to address relationships leading to unintentional bias or deliberate manipulation, as noted in an analysis of power relations and society/individual agency during research triangulation[76]. Disclosing prior roles between patients, researchers and referring clinicians can reduce the risk of bias[43] and identify indirect financial benefits in the form of industry influence[77] including medical device or intervention choices[78]. Agreed standardized declarations, started from protocol stages, introduced in reporting guidelines, and adopted by journal publishers may reduce the impact of conflicts of interest and bias, and increase reporting quality.

The overlap across the reviews included in this systematic overview in impact appraisal, research prioritization and choice of outcomes may contribute to an overstatement of equality between researchers and citizens. At present, well-meaning efforts including reporting of the impact of PPI in reports of trial could introduce selection bias and increase imbalances of power. Researchers are not evaluated as performance partners within

research manuscripts, but their research is evaluated after peer reviewed publication and impact is evaluated by external parties. DUETS UK[81] previously provided a platform where those navigating public preferences, priorities and research questions could find common ground,[82] but DUETS was subsumed by NICE and not maintained[83,84]. PCORI USA[65] and SPOR Canada[66] are investing in platforms to store priority setting results, core outcome sets and evaluation materials for PPI. These repositories may be preferable to stand alone research prioritization and core outcome sets[79] where journal paywalls, no immediate use case or user community, and the challenge of finding these scattered resources may hinder widespread usage[38,80]. In the interim, COMET[85] has produced a free to access online database of core outcome sets to promote their uptake. Kirkham and colleagues have defined a methodological approach for assessing the uptake of core outcome sets from findings of randomized controlled trials of rheumatoid arthritis listed on using ClinicalTrials.gov. This method may also prove useful for tracking the uptake of PPI and research prioritization[86].

Limitations of this research

The absence of dedicated funding for this systematic overview limited double screening to a sample of citations. Unspecified MESH terms at the time of the search may have compromised search sensitivity and specificity. Rogers et al have since independently conceptualized and validated the terms to prepare a MEDLINE search filter to identify PPI in health research[87]. The deficits in standardized language, research methods and reporting of PPI provided challenges for identifying search terms, assessing quality and risk of bias and this impacted our interpretation of data and scope of comparisons for the overview.

Differences between protocol and review

References in the protocol to quantitative methods, effect sizes, meta-analysis, GRADE[88], and AMSTAR[89] were not relevant to the final systematic overview because all included

reviews were reported qualitatively. We changed the emphasis to "value reported" rather than "impact reported" because the term impact was based on differing cultural assumptions across disciplines.

Suggestions

These suggestions were developed as a result of findings for good and bad practice in PPI and all the included reviews contributed to this theme. PCORI USA[65], SPOR Canada[66], INVOLVE UK[67] materials were reviewed for suggestions. Table 2-3 were developed with feedback from volunteers and review authors. The tables are used in informal researcher/volunteer training that I developed for The BMJ[68,69] and for Tabula Rasa an asynchronous online medical support learning network[70]. Tables 2-3 were adapted for use in an interactive workshop at The Cochrane Canada Symposium 2017[71] and as an element of the course structure at the FORCE11 Scholarly Communication Institute (FSCI) 2017[72]

Getting started with Patient and Public Involvement

Table 2 Getting started with PPI

From the Beginning
1. Involve members of the public at every decision-making level. 2. Introduce the patient caregiver and family perspective to each meeting. 3. Provide consistent oversight, task-specific feedback, and support.
Find and Cultivate
1. Identify partners through social media, advocacy groups, word-of-mouth, universities, within the community, schools, and forums. 2. Consider cultivating patient and advocacy groups to work with you. 3. Think about how you will fund the PPI and what the needs are, build this into your funding proposals. If you don't have money, consider what you can offer of value to volunteer research partners, be transparent and ask volunteer partners for ideas.
Setting the Scene
1. Use advance planning to build capacity and training, coordinate your resources and share your work plan and time structure with volunteers. 2. Develop a climate for open communication of Patient and Public experiences. 3. Change language from "patients are involved" to "patients are partners".
Getting ready for Public Involvement

1. Train everyone on the team who will work with volunteers. It builds community and transparency to train researchers and volunteers together or to train them separately and then bring them together to discuss the training. 2. Use interactive learning, problem-solving and keep it positive. 3. Training materials and ideas for involvement can be found at INVOLVE, PCORI, and SPOR or accessed through university research involvement teams 4. It is more about making the journey pleasant than doing everything right. Volunteers are mostly forgiving and flexible. 5. Bring in volunteers after you have planned for them so they can operate optimally and not be shaken by constant changes or disorganization.
Making PI Functional
1. Have lay volunteers choose their levels of involvement, be realistic and adapt expectations as they may be ill or have other jobs. For example, they might be fine for part of your research and then have a health crisis. 2. Honor your volunteers on the level to which they can commit and respect their time. 3. Keep tasks flexible, make time for training and questions. 4. Develop strategies for when volunteers are ill, have mental health, or cognitive challenges, need to be replaced or want to come back after recovery. 5. Consider involvement from the research, to dissemination, to implementation, to further development, or refining the intervention and for long-term follow-up 6. Integrate research volunteers into all research processes with a sensitivity to their ability and capacities, do not assume because they are members of the public that they are unable to contribute. 7. Use a Plan =>Build =>Test =>Reflect =>Refine approach and pilot everything with feedback.

Suggestions for Getting the Best from Public Involvement

Table 3 Working with Patient and Public Research Partners

Ongoing Support and Implementation
1. Develop your publication and implementation strategy early. Consider asking volunteers to help with plain language translation of your research findings and in the general knowledge translation of your work. 2. Volunteers with the necessary skills can build posters, infographics, presentations, peer-to-peer meetings, recruitment materials and can edit documents for clarity and ease of reading. 3. Volunteers can be trained to conduct interviews or focus groups with their peers. 4. Involve volunteers in both quantitative and qualitative research. This will help them to identify good research questions that are scientifically valid.
Training/Mentoring/Capacity Building
1. Provide training in research literacy and ethics, drawing on the many training programs that are available. 2. At every meeting have a jargon bin, when an unfamiliar term comes up, define it and use this to build glossaries. This will also make people aware of when they are speaking in jargon (even after they have understood the term). 3. Nurture a reciprocal learning relationship, letting volunteers know that you have made a long-term commitment to patient and public partnership in research.

4. Foster realistic expectations in volunteers and researchers and manage relationships with respect.

Inclusion Process
1. Involve volunteers at multiple levels. 2. Invest in building informed leadership and decision-making. Avoid silos. 3. Build together. 4. Use peer-to-peer mentoring and training. 5. Evaluate in an ongoing way. Is it working for everyone? What can we do better?

Building Trust and Community
1. Build community through shared understanding and cooperation. 2. Explore and take risks together. 3. Be transparent. Keep volunteers informed. 4. Support collaborative research from the top.

Reinforce Value and Validate
1. Give specific targeted, frequent feedback. A generic “thank you” is not as effective. 2. Let volunteers know how you are implementing their suggestions and why some suggestions will not work. Be transparent, respectful and kind. 3. Adopt “promise back” mechanisms.

Conclusions

PPI was wide-ranging and innovative in the included reviews. Public involvement in the decision-making process of designing trials was less common than consultation on what was already decided. PPI initiated at the protocol stage was identified with best practice as was resource acquisition for training, planning, and compensation. Involving lay volunteers for problem-solving provided insights, enhanced research design and served to identify weaknesses and barriers. Contingency plans were useful for adapting to disease progression and competing priorities. Short term tasks based on volunteer strengths, helped volunteers proceed with dignity and reduced guilt when task fulfilment was truncated by disability. Threats to research integrity might be averted through reporting personal conflicts of interest and appraisal of bias in mixed methods or non-quantitative research. The reporting of PPI in the methods section of clinical trial reports could aid replication and make methods available for others to adapt and refine. The use of PPI in dissemination planning, design, implementation, and distribution could increase public

involvement, contribute to health literacy and expand knowledge for patient values and preferences. The addition of patient reviewers by journals and the introduction of mandatory PPI declarations may contribute to health literacy and provide insights for future participatory research practice and these are areas we explore in later chapters.

Next Steps

Many of the findings in this study were echoed by our citizen researchers and by the data collected through social media mining in The Mind the Gap Research featured in the next chapter. Mind the Gap was the first research study undertaken for the thesis and provided an incentive to synthesize additional evidence and include other voices. Mind the Gap, and this overview, found that public involvement is more than managing research power structures and conventions. It became clear that when one voice is elevated this is at the cost of other voices. This is where the journey moves from simple public involvement or engagement in clinical trials into co-production and "everyone included" research.

Declarations

Contributions

I, Amy Price drafted and wrote the protocol, manuscript and completed the analysis for this systematic overview with feedback from supervisors, co-authors, and research volunteers. She is the guarantor for this research. The search terms were developed in collaboration with Nia Roberts. I sourced and trained volunteers, who with me jointly screened, data extracted and completed the analysis. All authors of the published journal article satisfy COPE recommendations for authorship, commented on the manuscript for that and approved its final version.

Acknowledgements

I commend the research volunteers who made this study possible. They contributed to refining the research question, prioritizing data, design, analysis, editing, designing and distributing dissemination materials and encouraging the team. They worked as uncompensated partners because the research did not have any dedicated funding. I am grateful for the innovation and support provided by Task Exchange[90], CerQual[19], and Eppi Reviewer[15]. I thank the developers of Rayyan[12] and Mendeley[14] who applied our feedback to design online applications for use in Patient and Public involvement. Lastly, I thank Dr. Sara Schroter (BMJ) for chart editing suggestions and help in improving the manuscript for journal publication and the consequential benefits for this chapter.

Chapter Two Outputs

Price A, Albarqouni L, Kirkpatrick J, et al. Patient and public involvement in the design of clinical trials: An overview of systematic reviews. *Journal of Evaluation in Clinical Practice* 2017;(July):1-14.

Price A. *Building Public Participation in Research,* 2017 Scholarly Communication Institute (FSCI) University of San Diego

Price A. SWAR 10 *Comparing training strategies for reviewers learning to use software tools for https://mistral-itn.eu/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWARStore/*

In addition, I was privileged to present the contents of this chapter through workshops in the UK, USA, Iran, and Canada.

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Chapter Three | Mind the Gap in Clinical Trials: A Participatory Action Analysis with Citizen Collaborators

Abstract

RESEARCH QUESTION
What are the strengths, gaps, expectations and barriers to research engagement in clinical trials as communicated through social media?

BACKGROUND
Clinical trials test treatments to provide reliable information on safety and effectiveness. Trials are building blocks where lessons from earlier research can be used to improve treatments, compare alternatives and improve quality of life. Participants enrol in trials to access the latest treatments, to help others and to advance science, but there are concerns. The priorities of those running the trials differ from those of participants and roles for public involvement in research lack clarity. In this chapter, I propose changes to bridge these gaps in the research culture through the use of Participatory Action Research (PAR) where stakeholders collaborate to improve research methodology, facilitate implementation and the practice of effective and safe treatments, galvanise citizen participation, multiply health knowledge, problem solve barriers to access and to explore the value of research volunteers as collaborators.

METHODS
PAR enabled inclusion of citizens as full collaborators in this piece of research. Social media data were gathered over 120 days until we reached saturation. De-identified data were organised into a SWOT framework and coded into themes for analysis. Following analysis, the authors prioritised potential solutions for improving research engagement.

RESULTS
The following were identified and categorised using the SWOT framework. Strengths included being informed and feeling supported, which remained constant through trial phases, disease burdens, and interventions. Threats included alienation, litigation, disparity and shaming. Poor management and barriers to inclusion were identified as weaknesses. Opportunities included improving resource management and information quality. Barriers were minimised when relationships between staff and participants were inclusive, respectful, tolerant and open to change.

Participants' communications ranged from fulfilment through trial involvement to disparities and rights violations. The use of the PAR approach provided a safe space without power imbalances where researchers and citizen worked as equals rather than as researcher and objects of research.

Ethics Registration in compliance with University of Oxford, CUREC # MSD IDREC-C1-2013-174
Protocol Registration: This study is registered with the Research Registry with the unique identification number, UIN: 670, Principal Investigator Amy Price, Title; Mind the Gap in Clinical Trials: A Participatory Action Analysis with Citizen Collaborators http://www.researchregistry.com

Chapter Three Highlights

Aligned with objective 2 To engage with the perspective of participants in clinical trials through online sources using citizen volunteers as authors and research team collaborators to inform practical development about the values, preferences and priorities of trial participants.

Strengths include:

- Being informed and supported
- Inclusive, respectful and tolerant relationships
- Two way understanding of limitations and constraints
- Flexibility

Challenges are:

- Barriers to inclusion
- Threats that include litigation, alienation, disparity or shaming
- Resource allocation and management

Take home points: Build reusable demographic trials data, manage risk and benefit sharing for awareness of adverse effects, employ pooled participant profit sharing, and construct well reported self-recruited online participatory clinical trials.

Introduction

Clinical Trials face unprecedented challenges even as the therapeutic potential for medicine and health science continues to increase. Sub-optimal research reporting[1] along with the use of surrogate, composite and subjective endpoints[2] combined with the failure to integrate patients' perspectives in trial design[3] can cause additional complications in other research and social care[4], shared decision making and guideline development[5] while failing to improve patient care in the real world.[2] Patients and members of the public may struggle with ways to frame their perspectives, so they are heard.[6]

This research explores the strengths, gaps, expectations and barriers to Patient and Public participation in clinical trials as communicated through social media. Increasingly, trials participants use social media to find trials and share their clinical trials experiences[13–15]; however, this is a little explored aspect of the patient voice.[16] Brice and colleagues (2015) noted in their descriptive analysis of online trials that current practice in research involvement offers limited methodological guidance to pave the way forward[17] and a 2019 Rand report shares similar findings.[18] This chapter presents the results of citizen volunteers and researcher professionals working together to analyse trial participant experiences and to propose viable solutions to bridge gaps in clinical trials research.

Methods

Research Question

What are the strengths, gaps, expectation and barriers to Patient and Public participation in clinical trials?

Research Design

This research adds to what is known by using a Participatory Action Research (PAR) approach to increase research knowledge for improving participation in clinical trials and by reporting on the value of research volunteers as collaborators.

Data Collection

We used Internet search engines from January 2015 to April of 2015 to search freely available content from blogs, LinkedIn, Twitter, Research Gate and via Symplur hashtags. Keywords used to locate data sources included; clinical trials, research participants, patient preference, shared decision making, Patient and Public involvement. The search netted 3196 comments and interviews. The data used for exploration and analysis also included summarised findings from the entire body of narrative interview studies on clinical trials by the Health Experiences Research Group at the University of Oxford, illustrated by video, audio and written extracts from the interviews, published on healthtalk.org.[19] Each Health Experience submission was counted as one interview. Snowball techniques such as asking social media users, patient groups and health technology professionals for additional leads to comments on clinical trials allowed us to expand the pool of relevant information until a saturation point was reached.[20]

The Research Team

The research team consisted of three graduate research authors and three volunteer citizen collaborators. Everyone contributed to the work using a PAR framework. The volunteer citizen collaborators were trained to code and to use NVIVO software in multiple three-hour sessions using pilot sample data.

The Coding Process

Following the data collection but before coding, all identifiers pertaining to organisations or individuals were removed by me. I supervised the coding process and was available to troubleshoot coding difficulties and serve as the deciding voice should coders fail to reach agreement. The data sources were randomised before the analysis to minimise bias and to divide comments equally amongst the coders. For example, if one commenter were to make 70 social media comments, these would be distributed evenly through the group. Interviews were counted as one comment for each interview. Data were organised according to Strengths, Weaknesses, Opportunities and Threats (SWOT), a framework that has been used in qualitative health research[21–24]. This framework helped coders to organise the data better and develop themes. NVIVO software was used to code the data with each entry independently coded by two researchers[25]. Discussion about coding, analysis and authoring took place via personal contact, SKYPE, email and telephone.

Results

Although we coded data written by trial participants, our data consisted of the comments; our research had no participants. To reduce confusion, we refer to the commenters and interviewees in the discussion as commenting trial participants or (CTPs). We coded 3196 comments; interviews were counted as one comment per person. The results for data coding and analysis were outlined using a SWOT framework[26] with the main categories as described under the headings of (SWOT) Strengths, Weaknesses, Opportunities and Threats (Figure-9). CUREC advised me that we were not required to seek consent for publicly available comments. In the interim between collecting and coding comments, the privacy terms for Twitter changed so after coding I re-identified the comments using

linguistic software and asked all Twitter poster's permission to use their de-identified comments before publishing them. This led to additional information coders agreed to use in the results and discussion. Our ethical agreement was that the CTP comments and interviews remain without hyperlinks or contain identities due to concerns that CTPs might face retaliation or a loss of privacy should their identities be relinked, dated, or disclosed.[27]

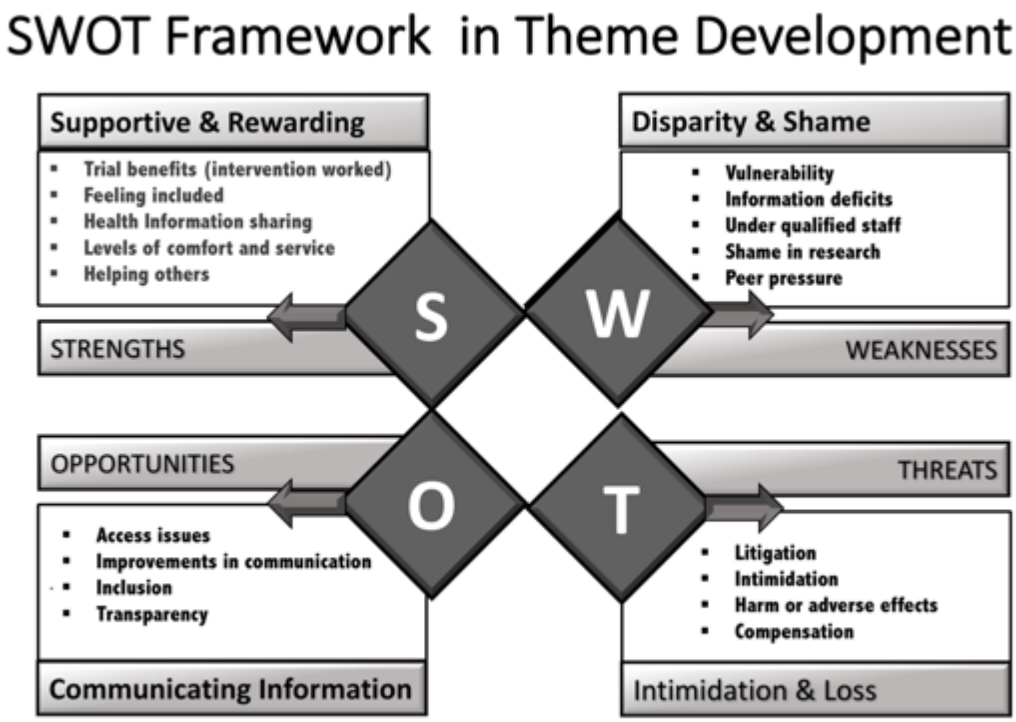


*Figure 9 SWOT Framework and Perspective**

**Strength perspectives were coded as themes of trial benefits, feeling included, information sharing, levels of comfort and service. Weaknesses were coded as vulnerability, information deficits, under-qualified staff, shame in research, and peer pressure. Opportunities themes included access issues, improvements in communication, inclusion and transparency. Threat-based themes were litigation, intimidation, harm or adverse effects, and compensation challenges.*

The parent themes reserved for organising the discussion were; Strength through the lens of support and rewards; Weakness was linked to disparity and shame; Opportunities

related the need for information and communication; Threats encompassed the themes of intimidation and loss.

Strengths

The two main themes to emerge in Strengths were supportive and rewarding. The respondents described positive experiences. CTPs welcomed research feedback, new information on managing conditions and positive reinforcement. Peer-to-peer support provided via online chats and forums was considered helpful, but contact information available only for internet troubleshooting emergencies was not. The support and interaction were not pre-existing expectations of the CTPs. They embraced the support and felt it increased their knowledge, feeling of safeness and some said the extra education and support helped them with the self-care to manage their conditions more effectively. CTPs that experienced this support reported being open to participating in future trials even when the experimental intervention was ineffective, or the trial was stopped. This pattern of response was constant across the self-reported severity of health condition and continued when CTPs reported facing a terminal diagnosis or participated in a high-risk trial.

> *"DA felt he got excellent care from the doctor running the trial and enjoyed being able to talk to him. He would if anything, have, liked more scientific information, even if it was hard to understand, to help him look into the press stories in more detail and understand how accurate they were*" [healthtalk.org].
>
> "*They gave two different lots of information. One for "J", the book was "J's" to read, which was designed really for the children to read and, and look at. And then they gave the adults other information, which went into it in more depth really. So, we were both informed of the same things but in different ways really*" [healthtalk.org].

Rewards reported as a result of trial participation exceeded any agreed expenses for remuneration. Rather, CTPs spoke about the satisfaction of taking part, that they enjoyed

hoping with others as a research community that the intervention was successful and they felt they were accessing the best available care.

> "*So, you know, the whole thing was a new, new experiment, but it was all done with using drugs that had been used at least, you know, for some time. So, I was always quite happy. I always felt I was in good hands and never really worried at all, you know.*" [Healthtalk.org]
>
> "*The trial improved my son, gave us hope, we would do it again*" [Twitter]
>
> *"I felt like, yes, I did feel like that if I could help someone and someone could have, you know, a much easier road to recovery because of something that I did, it made me feel a bit better about it and that my suffering, being sick was worth it for someone else*." [healthtalk.org].

Weaknesses

The themes that contributed to weakness in the trial were those that triggered a sense of disparity and shame. CTPs were frustrated with the disparity between themselves and other stakeholders. CTPs felt like objects mined for selective information if they were the "right" package. They imply human needs for validation, respect and care were unmet, and they contrasted this with sponsors who enjoyed a voice, profits, and prestige.

> *"Health disparities will persist until intent and methods and practice change.*" [PCORI Twitter-chat]
>
> "*Crowd-sourced to define the exclusion characteristics common in our specific disease; Listen and learn. The goal is to allow participants to answer only a few questions, but with those questions to eliminate a majority of trials for which they fail to meet eligibility criteria*." [Twitter-chat via Symplur]
>
> "*While they get a paycheck to live, we are paying with our lives*" As one volunteer aptly stated, "*Sponsors are making an investment from which they expect a return and staff is paid to make a living, their risk is small compared to ours, we gamble with our lives*." [LinkedIn]

CTPs expressed fear, desperation, shame and inner pain. The sense of exclusion and frustration was communicated.

> "*They only want perfect patients; if you have more than one thing wrong with you, you cannot get in a trial. In our MS group, we all tried, and none of us matched the inclusion criteria, we were all rejected*." [Boteh Twitter-chat]
>
> *"How do researchers expect treatment to work outside of the lab if they only take perfect patients?"* [F1000 Twitter-chat]
>
> *"If it were simple, we would just go to the doctor and get a pill, don't they understand our sickness makes us ill in other ways too".* [Regenerative medicine forum]

During a Twitter chat, one Parkinson disease (PD) patient and a veteran of multiple randomised trials gave an eloquent example followed by a video showing the gait freezing that comes when PD patients are off their medications for more than 24 hours. This happens because some trials need the patients to have their systems free from the medication that prevents gait freezing to prevent overlap with the effects of the experimental intervention. CTPs shared crossing the road or walking through a parking lot felt dangerous and humiliating. CTPs repeatedly requested admission to a clinic the night before and aides to help them navigate within the facility, but they said they were told this was not possible as it was "too expensive."

> *"A" is so keen to be involved in trials that he says sometimes he has worked very hard to persuade trial staff to accept him even if he does not quite meet the eligibility criteria. If they say no the first time, he will ask to be put on a reserve list and will keep ringing back*." [healthtalk.org]
>
> "*If the intervention is only effective for some of the people, we will all be denied the treatment in future;*" [blood cancer, emphysema and ALS online groups].
>
> *"We patients have all the skin in the game*" [LinkedIn].

CTPs shared how shame and fear heightened their sense of exclusion and disparity. They felt responsible for the trial and feared that reporting an adverse event might cause the trial to close. They were worried that this would destroy the hope of a "cure" for others. They admit they were ashamed to ask for help when they could not understand the directions. Others say they dropped out of a trial because they lacked funds to continue. It was common for CTPs to fear being labelled as difficult, blacklisted and banned from further trials. When asked on Twitter why CTPs do not report serious adverse events during trials the responses were:

Twitter

"*I'm afraid of getting kicked out*"
"Too sick to know what is a side effect and what is dying"
"*We were told it will ruin it for others if we say anything"*
Our doctors will be mad because they would lose "the recruitment reimbursement monies" and they will drop us as patients."
"If we withdraw from the trial, we have to pay for medical treatment to fix it ourselves or sue and we do not have the money."

Opportunities

The major themes were information and communication. CTPs wanted their input to be given equal consideration with that of other stakeholders and saw no reason why copies of their data could not be made available to them in a portable format. CTPs wanted to be informed ahead of the general public about trial results.

"*But patients are being harmed every day because of a lack of information sharing that could detect harmful side effects and drug reactions that would never be picked up by clinical trials. It is really this that we should all be working towards*" [Lily Twitter-chat].

"*First, they tell us any decent trial will be listed in http://clinicaltrials.gov and when people they don't like get approved, they tell us that trial is unethical, they keep changing the rules because they have a conflict of interest"* [LinkedIn]

"If you are upfront and explain to patients that there is genuine uncertainty about which treatment is best, they will understand the need for research. Greater public awareness would help." [healthtalk.org]. Participants wanted *"Helpful websites to learn about our conditions, find available treatments, and sign up for trials."* [LinkedIn]

Threats

The themes were intimidation and loss. CTPs were alarmed and angry that consequences for those that harmed them were non-existent. They wanted accountability from trial sponsors and investigators. Some CTPs state they were enrolled in trials by doctors but were treated only as participants and not cared for as patients.

One participant stated, *"I anonymously shared the terms of the contract they photographed on the Internet only to be tracked by the sponsor through an IP number and threatened"* (LinkedIn).

"*When I tried to report my problems to the FDA, it was way too complicated, and when I finally got someone on the phone from there, they made me feel stupid and like I was the criminal*" [LinkedIn].

CTPs wanted to know about adverse events or bad outcomes. They expressed concern trials staff were not adequately trained in their disease. They shared experiences of trials being closed without notice and not hearing about how the trial ended or what other research was completed as a follow-up to trials.

"*If they are going to research us shouldn't they know more about our needs and be better trained about the conditions. Sure, there are doctors in clinical trials but they are usually not there and the people that are do not have that training*?" [LinkedIn].

"*Shouldn't these organisations have an obligation to provide insurance coverage for study volunteers? I was truly shocked when I learned that a clinical trial sponsored by the NIH* (National Institutes of Health*) would do nothing to pay for long-term care needed as a result of serious trial-caused injury or disability"* [CISCRP-blog].

Discussion

The conversations of CTPs ranged from expressions of strength and support for trial personnel to harrowing accounts of shame and disparity. Similar results of variable quality in clinical trials were found in the PIRICOM[28] systematic review where authors focused on the degree and quality of Patient and Public involvement in terms of impact on all stakeholders although their research was published in 2010 many disparities and opportunities for improvement remain[29].

The identification of themes in weaknesses and threats can prepare researchers to consider these elements in the methodology they use for their trial. The themes of disparity and loss show experiences of rejection and exclusion are magnified through inadequate trials management. CPTs were emphatic about the need to make inclusion and exclusion criteria clear to prevent such negative experiences. Similarly, other studies report participants deal with significant financial loss and a sense of rejection when they are excluded from trials adding those who are excluded are less likely to participate in a future clinical trial[30].

Particularly shocking was the multi-faceted expressions of shame, intimidation and the fear of reporting adverse events which were confirmed in other research[28]. These concerns

are signs that not all participants feel ethically protected or psychologically safe in clinical trials.[29]. If these weaknesses and threats are not curbed, participation rates may continue to fall.[12] Ethics committee would do well to consider these weaknesses and threats as violations of good clinical practice and investigate when, where and under what circumstances these occur. These concerns were shared in US Congress and the National Institutes of Health grand rounds events by one of our volunteer content contributors[30].

Despite these challenges, strengths were also apparent and in synchrony with CPPs comments concerning research where patients regularly share knowledge and contribute to empowerment in clinical trials through the healthtalk.org website.[17] At Health Talk researchers serve as facilitators while patient interviews offer information and support. Healthtalk.org are recipients of multiple British Medical Association awards indicating that their positive influence spans disciplines and social groups[31].

Recommendations

I and my co-researchers on this project discussed recommendations for change in four areas; (1) reusable demographic trials data, (2) managing adverse effects, (3) participant profit sharing, and (4) self-recruited online participatory clinical trials.

As only a small number of excluded persons will go on to find another clinical trial for which they are a better fit, a registry to match participants to trials may reduce rejection of participants. This along with improved trial management in areas such as enrolment, consent and adverse events can lead to better participant experience.

Profit sharing for participants (the unpaid contributors who are bearing the most significant risk) might be considered in the principle of fair compensation. One argument against this is the potential for competing interests. The participation of citizen

collaborators as research partners may be the way forward. Engaging the public in all aspects of a clinical trial, including its design may well improve the quality of trials, lead to greater transparency and generate practical insights for clinical trials[4].

Strengths and Limitations

While this research offers the voices of clinical trials participants (CTPs), it is limited to a slice of history and to populations captured through social media during that era. Self-selection bias might have influenced the balance of opinions as it may be that people with strong emotional reactions (positive or negative) to their participation in a trial are more likely to comment on social media. These findings reveal the current meaning and experiences participants attach to clinical trials. However social construction is fluid and dynamic. The concerns expressed may change over time, while the methods are replicable, conversations around clinical trials are subject to change.

The original protocol for this study was built without using citizen research volunteers and was not usable. It was adapted with the help of citizen researchers, showing the value of piloting the process with the same population that will be involved in the research and that technical piloting with topic experts is not sufficient.

Limitations of the Population Sample

Social media and online commentary were used to capture the voice of issues that are expressed through online communications between patients, researchers and research participants. We have no way of knowing if CTPs (those who give interviews or comment on social media) differ from other less vocal or computer literate persons. The search was not limited by the severity of the condition, size of a trial or general population. This approach allows explorations of collective experience in clinical trials

across cultures, interventions and operations. The goal of this research was not to compare experiences of interventional versus observational research or to stratify for issues of engagement related to disease, socio-demographic influences, prognosis or treatment burden. It is expected these qualities will differ across trials and the aim was to explore common user experiences across trials. Social media collection allowed the research team to explore publicly available data that could be shared with our citizen researchers without incurring excessive costs or the data protection complications that would arise if we used clinic, hospital, or national health service records[31].

We acknowledge that the findings may exclude research participants who do not use the internet to communicate health or research information. However, exploring a broad overview of experience through online experience can expose areas worthy of future targeted intervention for public health research and online trials.

Conclusions

With an increase in life expectancies, more people with complex needs and limited mobility are likely to participate in clinical trials. Reduced costs, global access, and electronic data transfer tracking make online trials an attractive option where participants could enrol from home using an Internet connection. Participatory online trials could be adopted for citizen health science research particularly in fields of wellness, and self-management.[32] CTPs expressed concerns about data ownership, portability, and safety. Engaging the public in all aspects of research inclusive of trial design may well improve the quality of trials, lead to greater transparency and generate practical insights for all forms of participant populated clinical trials[33].

CTPs communication ranged from praise about support and acknowledgement about the sense of fulfilment trial participation brought them to the reality of facing disparities and loss that violated their rights. The participatory action research framework provided a safe space without power imbalances where professional researchers and citizen volunteers could work as equals rather than as researcher and objects of research[34].

Research Reporting

The Critical Appraisal Skills Programme (CASP) making sense of evidence: 10 questions to help you make sense of qualitative research[35] and GRIPP checklist [36] were used to report the study

Contributions

Amy Price (AP) had the original idea for this study. AP developed the methods section with guidance from Su May Liew (SML) and Mike Clarke, her supervisors. All authors contributed to the study; AP wrote the paper and SML and Mike Clarke critically reviewed the contents. All authors approved the submitted version.

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Mind the Gap Chapter Outputs

Price A, Liew SM, Kirkpatrick J, Price J, Lopreto T, Nelken Y. Mind the Gap Methods: Steps to making Participatory Action Analysis with Citizen Collaborators Work. *European Journal for Person Centered Healthcare* 2017;5(2):184-190.

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This work led to a keynote presentation at Stanford Medicine X and an online course that Professor Larry Chu and I co-instructed and co-produced with BMJ/Stanford/PCORI and was hosted by Stanford University. It is now available with CME credits and will be part of six course certificate for academic credit. Two of these courses I am co-instructing and building and they are in development. This chapter and the previous overview chapter also formed the basis for working with BMJ commissioned authors to help them bring public involvement and co-production into the work they developed for us.

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Chapter Four

SMOOTH: Self-Management Open Online Trials in Health | An Analysis of Existing Online Trials

Abstract

BACKGROUND
The growth of trials conducted over the internet has increased, but with little practical guidance for their conduct and it is sometimes challenging for researchers to adapt the conventions used in face-to-face trials and maintain the validity of the work.

AIM
To systematically explore existing self-recruited online randomized trials of self-management interventions and analyse the trials to assess their strengths and weaknesses, the quality of reporting and the involvement of lay persons as collaborators in the research process.

METHODS
The **O**nline **R**andomized **C**ontrolled Trials of **H**ealth **I**nformation **D**atabase (ORCHID)[1] was used as the sampling frame to identify a subset of self-recruited online trials of self-management interventions. The authors catalogued what these online trials were assessing, appraised study quality, extracted information on how trials were run and evaluated the potential for bias. We searched out how Patient and Public participation was integrated into the online trial design and how this was reported. We recorded patterns of use for registration, reporting, settings, informed consent, public involvement, supplementary materials, and dissemination planning.

RESULTS
The sample included 41 online trials published from 2002-2015. Trial quality was critically appraised as High (n=9), Medium-high (n=15), Medium (n=17), and low as (n=1). The reports for more than half the trials (23/41, 56%) contained insufficient information to replicate the trial, 19/41 did not report piloting the intervention. Only 2/41 studies were cross-platform compatible. Public involvement occurred mainly at the steering committee level.

CONCLUSIONS
This study catalogues the state of online trials of self-management in the early 21st century and provides insights for online trials development as early as the protocol planning stage. Reporting of trials was generally poor and, in addition to recommending that authors report their trials in accordance with CONSORT guidelines, we make recommendations for researchers writing protocols, reporting on and evaluating online trials. The research highlights considerable room for improvement in trial registration, reporting of methods,

data management plans, and Patient and Public involvement in self-recruited online trials of self-management interventions.

Chapter 4 Highlights

Tied to Objective 3 "*To establish what is known about best practice in conducting online trials through systematic identification of existing self-recruited online randomized trials of self-management interventions, analysis of their methodological strengths and weaknesses, and to review how patients and members of the public were involved in the research process*"

Problem: Barriers to replicability, knowledge transfer and future progress in online trials were identified because of unclear reporting of various aspects of the trial design and the methods used.

Take home points: Researchers in the methods and public involvement survey welcomed the development of protocol and reporting suggestions but were not in favour of adopting complex new frameworks that require extensive time, training, space, and funding. The development and implementation of a generic protocol for online trials that would contain embedded elements supported by relevant reporting guidelines could assist authors in writing up online trials, particularly those that use a participatory approach

Barriers to replicability, knowledge transfer and future progress in online trials were identified because of unclear reporting of various aspects of the trial design and the methods used. The barriers could be minimized through better reporting on the methods, dashboard design, data protection measures, software used for delivering the intervention and online materials used to train, test, and assess participants.

The technology needed for the different devices that would be used to access the interventions tested in online trials may be too recent, costly to develop, or insufficiently stable for widespread use at the time of the trial. Therefore, better reporting of the trial methods may provide a way for research quality and innovation to keep pace with emergent technologies in the future.

The sporadic use of different reporting guidelines in online trials at the moment prompts us to propose the development and implementation of a generic protocol for online trials that would contain embedded elements that are supported by relevant reporting guidelines to assist authors in writing up online trials, particularly those that use a participatory approach.

Word Count
Abstract (330)
Main Document: excluding tables, references, declarations, & appendices (4370)
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Registration and Protocol
Research Registry# 1986 http://www.researchregistry.com/browse-the-registry.html#home/registrationdetails/5856b9bd759db5ec4609d880/

Background

Modern digital technologies can provide health interventions through the use of mobile health apps, text messaging and telehealth video consulting, and provide an opportunity to conduct research solely over the internet in the format of online randomized trials. These trials can be conducted remotely over the internet using a computer, tablet, or smartphone without the need for face to face human interactions. Online trials continue to grow in scope and accessibility, and patients are becoming empowered to use these technologies to explore their health questions. However, the methods used for these trials raise specific benefits and challenges.

The benefits of using digital technologies for online trials include cost-reduction through the use of online rather than physical trial sites, ease of reaching multiple socio-demographic groups, the ability to use multiple languages with minimal cost and the inclusion of trial participants who have limited mobility but who can participate with access to an internet connection, through a computer, tablet, or smartphone [2]. These trials can also provide insights into the use of interventions outside of the lab or clinic, and online access has become affordable and accessible in low resource settings providing more equitable global access to research. Public health and epidemiology researchers in

low resource areas struggle with the challenge of accessing valid data on disease and population, where collection methods are inconsistent, culturally diverse, and subject to administrative delay[3]. Mobile device platforms might be designed for collecting valid health research data from the potential 5 billion unique mobile subscribers who account for 67-80% of the world's population as of May 2018 according to the GSMA intelligence calculator[4].

Online trials have unique methodological challenges including limited face to face interaction, limited to participants who are willing to respond online, reliance on self-reported outcomes, and the need for applications to work across different operating systems, be user accessible and compatible with aging technology and bandwidth variations [5]. Data protection breaches may be brought on by participants themselves through social media, or through health research data, purchased or stolen by third parties [6]. Inconsistent reporting of methods and Patient and Public involvement in online trials can limit opportunities for research replication, end-user experience transfer, and the development of strategies to build on previous work [7]. Therefore, research analysing current practice for these trials might help in developing strategies to improve recruitment, intervention adherence, participant retention, research methods, and reporting practices [8].

Writing protocols to conduct online trials and to report them requires robust methods, informed by best practice. To learn from previously published research, the *Online Randomized Controlled of Health Information Database* (ORCHID) was constructed to collect reports of online trials and methodology research about them [9], using a search strategy available in appendix-1. ORCHID was used to investigate reporting methods, and

the extent of public involvement in online trials and preliminary analysis showed that the number of online clinical trials was growing exponentially but with limited methodology research on validity and best practice of these trials [9].

In this research study, we analysed randomized self-recruited, self-management trials conducted over the internet. Self-recruitment is defined as the participants themselves enrolling in a trial online, via smartphone, tablet or computer without assistance by face to face contact with trial personnel. For this study, self-management or self-monitoring of health is the use of a medical device, intervention or process that, while it may be recommended by a physician or other clinician, can be used or undertaken without the assistance of a healthcare professional. For example, self-help, wellness, diet, activity, therapy online, an anticoagulation medication that is monitored and titrated by the patient or asthma medications with peak flow measurement recorded by patients are eligible, but interventions that are clinician dependent for interpretation such as radiological films or lab work are not. This study investigates factors affecting the conduct of online trials of self-management and identifies if, and how, these trials report the involvement of patients and public in their design [10,11].

Methods

Objective

To catalogue what can be learned about best practice in online trials from existing self-recruited online randomized trials of self-management interventions

Inclusion and Exclusion Criteria

Inclusions

Studies were included if they were randomized trials with online self-enrolment and used internet-based technologies, such as computers, tablets or smartphones, in the trial process. Interventions had to be related to health and well-being and could include educational or behavioural components; Trials were only included when there were self-reported outcomes.

Exclusions

Interventions in social care or education were excluded where outcomes were not health-related; where the population was exclusively health professionals, educators, or students; and the intervention was used for training purposes but was not a specific health intervention. Studies were excluded if clinicians or other health practitioners enrolled the population and when physician intervention was needed to measure primary outcomes. Non-randomized trials, cost-effectiveness research, and studies that were reported only as conference presentations or posters were excluded, as were aborted or withdrawn trials. (see appendix-1 supplementary files in the publication citation for the listing numbers and reasons for excluded trials).

Study Design

A systematic review of the methods of online randomized trials of self-management interventions. The **O**nline **R**andomized **C**ontrolled Trials of **H**ealth **I**nformation **D**atabase (ORCHID) [9] (updated in July 2016) was used as the sampling frame for identifying eligible trials.

Screening and Selection of Trial Reports

All citations were screened in RAYYAN which is an open-access tool for screening and appraising studies for systematic reviews [12]. Reviewers were not blinded to author, institution, or journal. Two researchers independently screened the title and abstract of all citations retrieved from ORCHID for those that met the eligibility criteria. Citations were categorized as include, unsure (without checking of full paper), or exclude. Full papers were retrieved for those categorized as “include” or "unsure." Exclusions were documented at this stage in the excluded studies table in the publication, appendix1 supplementary files . Full papers were stored and de-duplicated in Mendeley [13]. Two authors independently screened these full papers for eligibility and agreement was reached by consensus with a third author if they could not agree on inclusion or exclusion. Reasons for exclusion were documented. A PRISMA [14] flow diagram is included.

Sampling Rationale

Studies were grouped into the following strata after screening: feasibility or pilot studies and full trials, because scoping of the literature and consultation with experts in trials methodology showed that important choices about methodology and engagement might be detailed in feasibility or pilot trials but not included in the final trial report. Half the studies were then randomly selected from each stratum using a proportionate stratified sampling technique to provide an adequate number of studies to answer the research question within the available resources and timeframe.

Data Extraction

Two authors independently extracted key data for the randomly selected included trials. The data extraction form was piloted in EPPI reviewer [15] and adapted for best use of

resources and information quality. Results are presented using descriptive statistics and narratives. We catalogued what these online trials were assessing, appraised study quality, reported on how these trials were run and we reported the potential for bias. We also sought information on how Patient and Public participation was integrated into the design of the online trial and how this was reported and noted the use of reporting guidelines, accessibility of supplementary materials, protocol registrations, and whether plans for dissemination were reported.

Study Characteristics

Details for each included study containing the citation, study design, aims, objectives, study setting, health status of participants, demographics, sample size calculation, intervention details, outcomes, time–points and follow-up are available as an appendix-1, along with the list of excluded studies with reasons for exclusion.

Assessment of Methodological Quality

Included trials were quality assessed for methodological strengths and weaknesses by two review authors. Discrepancies were resolved by consensus, without the need for third-party consultation. The Critical Appraisal Skills Programme (CASP) "*11 questions to help you make sense of a trial checklist"*[16] was used, and each item was scored as yes, no, not sure/not reported. The aggregated "yes" count was used as a guide to quality across studies.

Assessment of Reporting

Reporting was assessed by including the number of trials that included a systematic review to justify the trial's testing of the intervention, a link to a registered protocol,

included a CONSORT flow diagram [17], used CONSORT eHealth [18] reporting guidelines, used CONSORT PRO [19] to report patient-reported outcomes and contained an intention to treat analysis. For studies using an online questionnaire, we reported whether studies used the CHERRIES [20] reporting guideline.

Assessment of Patient and Public Involvement

We report a summary of how, and at what stages, Patient and Public involvement occurred and whether the studies used GRIPP-2 [21] a Patient and Public involvement reporting guideline to report this involvement.

Risk of Bias

Two authors independently assessed the included studies using the Cochrane Risk of Bias tool categorizing risks as 'low,' 'high' or 'unclear.' Individual bias items were evaluated as described in the Cochrane Handbook for Systematic Reviews with modifications [22]. Risk of reporting bias (selective reporting of results) was adapted to not include prospective trial registration as criteria as some trials were initiated before the expectation that trials be prospectively registered. Performance bias arising from self-reported outcomes was not assessed because the eligibility criteria included self-reported outcomes.

Public and Patient Participation

Members of the public collaborated as research partners during this study, from editing the protocol to designing, analysing, contributing to the discussion and write up of the findings. A volunteer from Cochrane Task Exchange joined the research team (LV) and fulfilled the criteria accepted for authorship. The protocol was published in the public

domain [23] and the link posted on social media (Twitter/Facebook/LinkedIn /Research Gate) for comments.

Embedded research | Study within a Review (SWAR)

We conducted our embedded study within a review (SWAR) to learn how to train people better. When training a novice reviewer (or even an experienced reviewer) on a task online, it is challenging to know how much 1:1 support is needed and whether this varies across the reviewers or the tasks.

Assignments

An incremental design in which we moved the same set of eight reviewers through the interventions (4 to 1 to 2 to 3) across the three reviews above for screening, data extraction, coding, and analysis. Learners were assigned to one out of four support interventions for learning to do systematic reviewer tasks:

1) A single session of reviewer task training and written instructions
2) 3-5 sessions of task training and written instructions
3) 10 or more sessions of task training and written instructions
4) Written instructions alone (comparator)

Outcomes

The primary outcomes were task completion and number of support interactions and the secondary outcome was learner rated self-confidence.

Data Sources and Search Strategy

Analysis

Results are presented with descriptive statistics and narratives, using charts and tables for ease of understanding and visual comparisons. Characteristics of included studies are

presented in Appendix-1 with the citation, study design, aims, objectives, study setting, the health status of participants, demographics, sample size calculation, intervention details, outcomes, time–points and follow-up.

Results

Study identification

Figure 10 shows the flow of studies through this review.

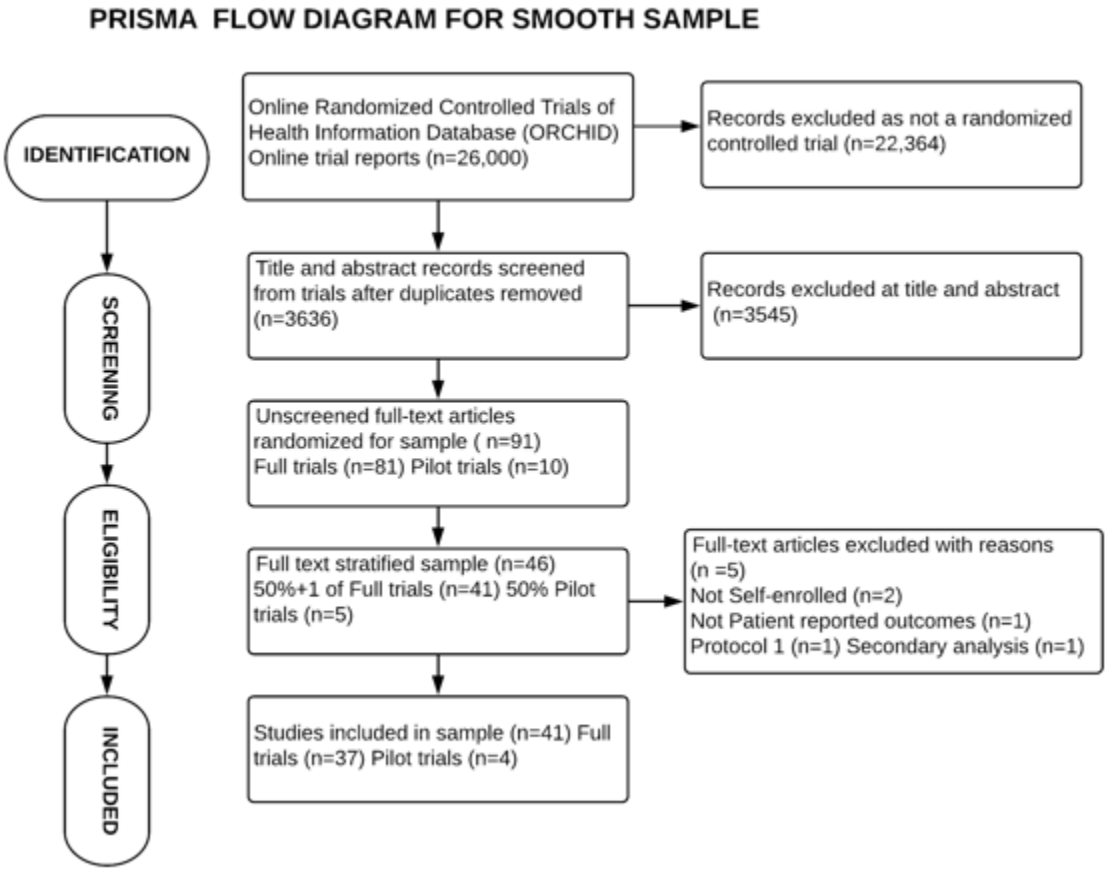


Figure 10 PRISMA Flow diagram

ORCHID contained 26,000 citations in July 2016. From these, 3636 de-duplicated citations were identified as randomized trials, and their titles and abstracts were screened for potential eligibility. Of these, 3543 citations were excluded, leaving 91 articles for full-text screening. These reports were stratified into full trials (n=81) and pilot trials (n=10), and the subsequent 50% randomly selected samples included 41 full trials and five feasibility/pilot trials (total n=46).

Studies Included for Full-Text Screening

The full-text screening of the 46 articles for eligibility, led to the exclusion of 5: not self-enrolled in trial (n=2) [24,25], protocol (n=1) [26], secondary analysis (n=1) [27] and not self-reported outcomes plus quasi-experimental design (n=1) [28]. All 41 eligible trials were included for data extraction and analysis.

Characteristics of Studies

Appendix 3 shows the characteristics of included trials [29,30,39–48,31,49–58,32–38] and excluded studies with reasons for exclusions [24–28]. There were 29,348 randomized participants in the 41 included trials, and we included data for 19,357 in the analysis. Trials ranged in size from 48 to 9919 participants, with the length of intervention varying from 1 to 104 weeks. All trial reports were available in English. Trials were hosted from nine countries with eight studies featuring multi-national collaborators (Table 1). Of the 41 trials, 30 were published between 2011-2015, eight from 2006-2010 and three between 2002-2005.

Trial Design

All 41 trials were coded as pragmatic rather than explanatory because each contained self-reported data with self-management interventions. Trial designs were parallel (n=32), factorial (n=1), waitlist controls (n=17), and pilot or feasibility studies (n=4). The participatory design was mentioned in 2 studies, but this PPI was restricted to consultation before trial preparation. Comparisons were assessed by waitlist controls (n=17), alternative interventions (n=19), current practice or standard of care (n=7), and dose-response (n=1).

Trial Origins and Funding Sources

Funding sources were reported in (34/41,83%) trials. Multiple funding sources were reported in 15 studies. Trials were funded by government (national funders and academic institutions) (n=25/41,59%), industry (n=3), NGOs (non-governmental organizations, trusts or charities (n=13, 32%). One trial was partially sponsored by advocacy groups who collaborated with the researchers on designing and running the trial. Information on funding was reported for 2 of the four feasibility/ pilot trials. No trial sought crowdfunding or was fully participant led and funded. All trials were initiated in high resource regions according to the WHO classification of low, middle, or high-income countries. (Table-4).

Table 4 Trial report and country of origin

Country of origin for Trials	**Number of Trials**
USA	18
Multi-national	8
Sweden	5
Netherlands	5
Australia	4
UK	3
Canada	2
Japan	2
Ireland	1
Switzerland	1

Recruitment

The included studies reported a variety of methods and sources for recruitment including various online and offline methods: use of websites, (n=5), healthcare centres (n=5), online-forums (n=4), bulletin-boards (n=4), Craigslist (n=4), other universities (n=4), advocacy organisations (n=4), communities (n=3), schools (n=3), social media (n=3),

newsletters (n=3), internet advertising (n=3), worksites (n=2), newspapers (n=2) and conferences (n=1/41). Smartphone advertisements, texting, use of professional recruiters, canvassing at large advocacy organizations, recruiting through massive open online classrooms (MOOCs), online clinical sites, or referral arrangements from other trials were not reported as sources of recruitment.

Intervention settings

In online trials, "setting" includes the platform and materials used to conduct the intervention. Computers were the primary devices (n=38/41, 93%), followed by smartphones (n=4) and tablets (n=2). The studies using smartphones and tablets did not report usability across operating systems or devices. Only one study reported using wearable devices to passively collect health data which participants reported on and used to adapt their lifestyles. In 23 (56%) of studies, the description of the settings is insufficient to facilitate replication of the intervention and in 19/41, 46% studies piloting, or testing of platforms went unreported. Online or offline data entry was available in 7 trials, but most 24 (56%) specified that data could not be entered unless participants connected to the internet. The option to share or download personal data was reported in 4 (10%) of trials. Automated password recovery was supplied for nine trials. Only ten trials reported the inclusion of methods for explaining data entry to participants.

Informed Consent

Digital signatures for informed consent were accepted in 24 (56%) studies, 5 required only computer text (typing in yes/no or accept/decline), multimedia packages were used in 3 trials, and 2 trials used interactive formats for consent or participation information sheets. Trials did not report testing for participant comprehension or having end users as

collaborators to develop patient information sheets and consents. In 7 trials, the method for obtaining consent was unspecified. There were no reports of biometric, multi-trial consents (such as those used in adaptable trials) or the use of participant downloadable formats.

Intervention and Outcome Types

We classified self-management interventions into the categories and outcomes in figure 11-12. All included trials measured behaviors. Trials could belong to multiple categories and contain more than one general outcome. Nine trials assessed knowledge in the general outcomes, while 29 trials (71%) assessed attitudes or behaviors.

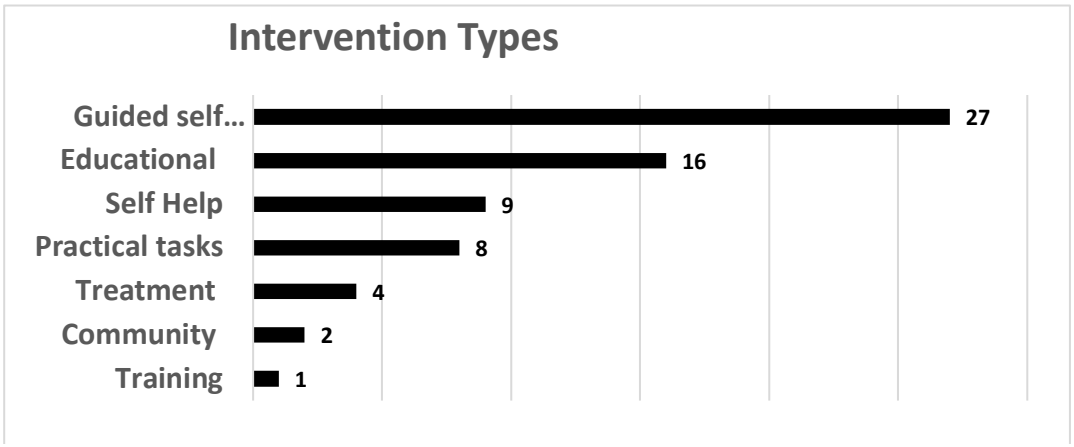


Figure 11 Intervention types

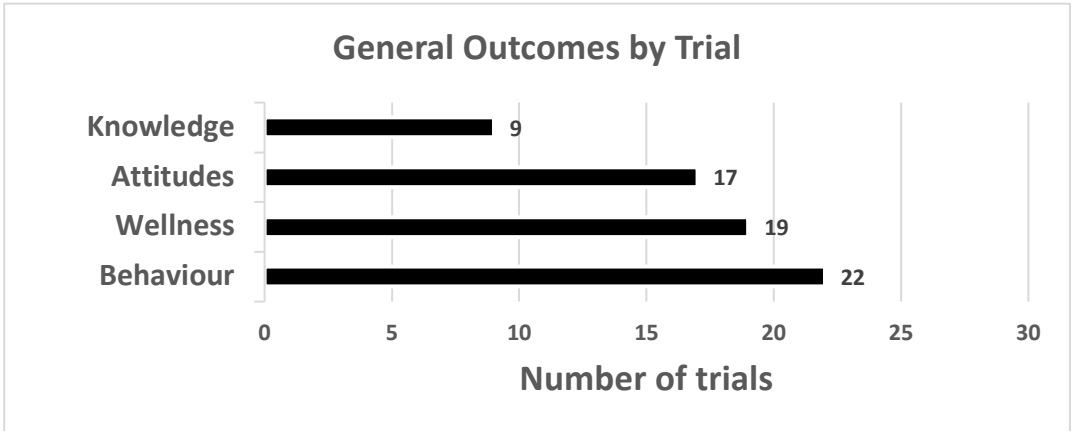


Figure 12 Interventional and general outcome types

Reminders and Incentives

The majority of trials used email for reminders (n=28). Platforms enabled participants to set reminders in 2 trials, and text reminders were implemented in one trial. Personalized, specific feedback was introduced as an incentive and later recommended by authors in 6 trials. Financial incentives ranging from US$25 to more than US$100 were offered over the course of the study in 17 trials (41%). Monetary incentives were available per task rather than as a lump sum in 10 trials. Bowen et al. [59] staggered the incentives per task and randomized half of the participants to higher payment for the last questionnaire. They found that increasing the incentive did not alter completion rates, which were similar for both groups.

Assessment of Methodological Quality

The Critical Appraisal Skills Programme (CASP) 11 questions to help you make sense of a trial [16] was used to appraise quality across the trials: High (n=9), Medium-high (n=15), Medium (n=17), and Low quality (n=1). No trials achieved a CASP score of Very-low, as a focused question and randomization (items 1 and 2, respectively) were required by our inclusion criteria. The appraisal was based on the trial's publication without supplementation from personal correspondence with the original authors (Table-5).

Table 5 CASP RCT Quality Appraisal

CASP (How to Make Sense of a Trial) [16]	**Total of 41 Trial Reports**		
Questions 1-11	***Yes***	***No***	****?***
1. Clearly Focused Question?	41	0	0
2. Randomized?	41	0	0
3. Patients accounted for?	35	4	2
4. Was blinding reported?	13	11	18
5. Have groups similar demographics?	37	0	4
6. Groups treated equally other than intervention?	37	2	2
7. Treatment of effect size measured?	27	8	6

8. **Estimate of treatment effect/confidence intervals?	20	12	9
9. Do results apply to the local population?	22	1	18
10. Were all clinically important outcomes considered?	20	6	15
11. Are the benefits worth the harms and costs?	35	2	4

**? It was not reported, or the reporting was unclear or incomplete. **Yes = with confidence intervals. No = reported narratively or without confidence intervals*

Assessment of Quality of Reporting

Eligible studies were searched for a relevant systematic review or meta-analysis to justify the trial and were found in 33/41 trials. Protocol registrations were reported in 15 trials. The CONSORT flow diagram was used in 18 trials with two including an intention to treat analysis. Piloting of the trial or platform was reported by 19 trials. Although the 41 trials included studies contained patient-reported outcomes and 40 trials contained an online questionnaire, none used the CHERRIES [20] reporting guideline for online surveys or CONSORT Pro [19] for reporting patient-reported outcomes. Four papers used the CONSORT E-HEALTH [18] reporting guidelines. However, several of the trial reports preceded the publication of reporting guidelines, including the 2010 update of the main CONSORT statement [1].

Assessment of Reporting Patient and Public Involvement (PPI)

PPI (defined as involvement in the research other than as a trial participant) was reported in 10 trials and forms the participatory element in online trials. Face to face PPI and email were the most common forms of interaction with PPI. There was participation in steering groups, community sessions, board meetings, focus groups, pilot testing sessions, computer iteration labs, dashboard design, surveys, or interview design. In some trials, advocacy groups were used as a proxy for individual patients or the public. Four reports included PPI activity in the acknowledgments section. Trials implemented PPI for advisor

roles (n=9), design of a trial interface and user materials (n=9), usability testing and piloting (n=9), recruitment (n=3), selection of outcomes (n=2), setting the research question (n=1) and translation (n=1). The ten trials reporting PPI did not cite the GRIPP-1[60] or GRIPP-2[21] guidelines for reporting, but, again, some of the trials pre-dated the publication of those guidelines.

Study within a review (SWAR) Results

An incremental design in which we moved the same set of eight reviewers through the interventions (4 to 1 to 2 to 3) across three reviews for screening, data extraction, coding, and analysis. Learners were started with written instructions alone (intervention 4) but none of them completed the tasks and errors could not be assessed. Improving the written directions was not enough to change these results. All learners without exception expressed their lack of confidence. An instructional session was then added (intervention 1). After this intervention, learners expressed appreciation for the help and initial confidence. Six out eight attempted but did not finish tasks. The two that did complete the tasks had unacceptable error rates. All reported losing confidence when faced with completing the balance of tasks without support.

Intervention 2 (3-5 instructional sessions and written instructions) was then introduced and proved to be the most successful with reduced error rates with 2 or less errors across all tasks as compared to 3 errors or more per task, all tasks completed and improved reviewers reported much improved confidence levels but this was not formally assessed.

When we tried to improve this further to reduce errors rates and hasten time to completion by offering intervention 3 to 4/8 reviewers (10 sessions and written instructions), we found

no increased benefits for confidence levels, error reduction or independent task completion beyond that noted in intervention 2. The superior results of interventions 2 and 3 with these eight participants made it impractical to continue using interventions 1 and 4. The intervention benefits and failings were constant across tasks in this review and in others.

Risk of Bias

The risk of bias from the generation of the random sequence was generally low because most studies used computer generated algorithms for randomization. Attrition (incomplete outcome data) and blinding of outcome assessment might be problematic for online trials as only 11 trials showed the low risk of bias for this domain. For the blinding of participants or personnel, 12 trials were assessed as low risk of bias. As already noted, analysis by intention to treat was reported in only two trials. The prevalence of reporting bias in online trials was at least as high as in conventional trials [61]. (Figure-13)

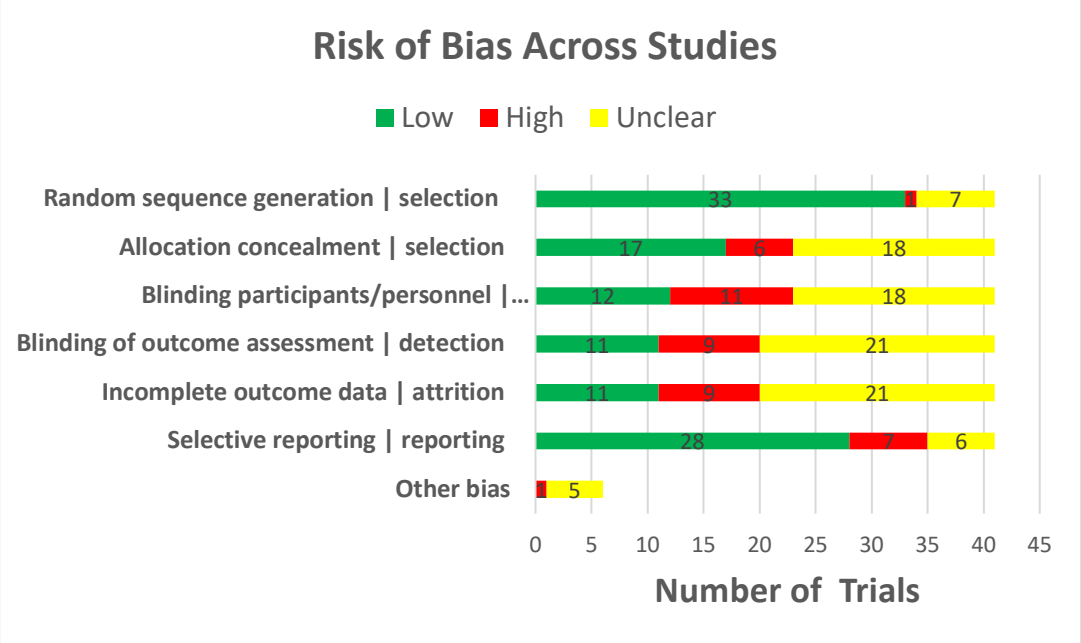


Figure 13 Risk of Bias across trials

Discussion

Quality was consistent or comparable to that of traditional trials. There were, however, gaps central to the success of online trials and we suggested recommendations to bridge these gaps in table-7. In 38/41 studies computers were the only resource available for entering study data, and this is in contrast to the growing number of individuals, particularly in low resource settings who have smartphones or tablets as their primary vehicle for online usage. Compliance and intervention engagement per session and over time were not systematically reported in the 41 trials in our sample but could be seen in part by viewing the CONSORT flow diagrams, where higher adherence was common in waitlist control groups. This suggests the engagement with interventions over time were not optimal.

Comparison with Other Studies

To the best of our knowledge, this is the first review of the quality of a sample of online self-management trials, but similar reviews exist for more conventional trials. This study and those earlier studies show that these online trials face some of the challenges of face-to-face trials regarding validity, data security, viable methods and the challenge of providing valid self-reported outcomes [62]. These may be greater challenges for online trials because of the lack of face-to-face interaction to troubleshoot participant interaction or assess validity. About PPI, our findings are similar to those reported by others [63,64]. However, given the speed of the development of the internet and of devices that interface with it, the 41 trials in our sample might not reflect the current situation for online trials because of advances in methods and technology since the cut-off date for articles in ORCHID.

Implications

Challenges for Online Participatory Trials

Our application of the CASP appraisal criteria identified only 1 of the 41 trials as low quality. The higher risk of bias scores may be due to features that online trial researchers are powerless to change, such as the use of self-reported outcomes. However, as with conventional trials, we found substantial barriers to replicability and progress due to the lack of clear reporting, for example about the setting where participants engaged with the intervention. Within online trials, settings can be particularly influential when one considers attrition in online trials that might arise due to unresolved technical difficulties. Designing, piloting and monitoring all interfaces with end-users could increase the durability, stability, and usability of the resources needed to complete the intervention and the trial, from enrolment of participants to follow-up. PPI collaborators in this study highlighted the importance of automated password recovery, plus online and offline data entry across devices. They identified a preference to access, manage, and share their research related data but also raised concerns about how research data might be shared for a fee with third parties without their specific consent. It would be useful for researchers doing online trials to consider these concerns. Behavioural interventions and waitlist controls featured in 17 trials. The use of a comparative intervention in a parallel design may produce more reliable results because the use of a waitlist control design might artificially inflate intervention effect estimates [65]. The mechanism for this inflation may be the participant's determination to comply, so they will not miss out on the "real" intervention [66].

Reporting challenges

Inadequate reporting may not reflect a poor-quality trial [67] but incomplete reporting and research without public input into the design can impede replicability and might lead to the unnecessary repetition of research, waste of resources, and unnecessary complexity [68,69]. Reporting shortfalls may slow the redesign or implementation of existing interventions [70] and are not limited to online trials. Initiatives such as the "All Trials" campaign for registering all trials and reporting all results may help to redress some of these problems about the access to trial findings [71], and uptake of the TIDieR guidance should improve the reporting of trial interventions[72]. An additional limitation is that technology across devices may be too recent, costly to develop, or insufficiently stable for widespread adoption. The trial sample was published from 2002-15, and some studies in the sample were designed several years before this, in a time when computers (rather than mobile phones or tablets) were the primary interface for the internet.

Supplementary materials

Supplementary materials were not always accessible for the trial reports. This is a particular problem if the article is downloaded for offline use. Details of the software used in online trials were reported using static screenshots leaving insufficient information on models, coding structure, or usability for replication. We recognize that the sample of trial reports was published from 2002-2015 and earlier papers may have been written for print journals without an option to store supplementary files, models or software. Furthermore, even current online journals may be restricted by the file structures their platforms can process. However, researchers might be able to comply with the FAIR standards (findable, accessible, interoperable, re-usable) by using responsive multi-file open access

repositories such as Zenodo, Dataverse, or GitHub and putting links to the files in their publication [73].

Dissemination

If the main report of a trial is not published open access, free-to-view dissemination of its findings can still take place through, for example, blogs, social media, and teaching. It is also increasingly possible for researchers to provide free access to pre-publication versions of their manuscripts through institutional repositories. Dissemination strategies are not adequately addressed within existing reporting guidelines or protocol templates, leaving researchers with insufficient guidance on how to report or highlight their dissemination strategies (other than, perhaps, within the relevant sections of their applications for funding).

Study Limitations

Identifying relevant online trials presented a challenge given the lack of specific search terms that are available in bibliographic databases such as MEDLINE and Embase. To help mitigate this, the design of ORCHID (from which we sampled the included trials) was underpinned by research on search strategies and filters to establish the optimal trade-off between exhaustiveness and precision; and, so, we believe that we have a representative sample of eligible trials from the early 21st century.

As with other assessments of trial quality [65], our analysis was dependent on what authors reported, which may differ from what they did, and we were not able to access additional potentially relevant information that is stored in inaccessible formats, contained in related papers, or is unreported. However, our analyses reflect the information that is readily

accessible to users of these trials and, therefore, is valid as a description of what can be easily found by users of online trials.

Future Directions and Conclusions

The SMOOTH (Self-Management of Open Online Trials in Health) analysis highlights the importance of consideration being given to good practice and reporting as early as the protocol planning stage for an online trial. Reporting of trials was generally poor. In addition to recommending that authors report their trials in accordance with CONSORT guidelines, we make the following recommendations (Table-6). Trialists should cover when reporting, and readers of trials should evaluate when reading, an online participatory clinical trial (some of these may also be applicable to non-online trials): There are items included in a protocol that will not be reported in the final manuscript. These might be described as aspirational, whereas the manuscript reports what took place. For example, a protocol could have a backup plan for recruitment when the sample size is not reached or for alternative equipment if technology fails, however, this is unlikely to be reported in the published manuscript. Also, there may be handbooks, software algorithms, and models that will not be part of a short protocol document, but they are trial documentation that is needed to replicate the work. This is why links to protocol registrations and other relevant trial documentation need to be reported in the published report.

Table 6 Protocol and reporting suggestions

Checklist Item	Research Recommendation for Online Participatory Trials
Trial title and registration	The trial registration is reported, prospective, and has IRB approval. Include in the title the fact that the trial was online
Study Design	State design, describe arms, report number of participants in each arm, report if control group will have access to the intervention post-trial, report online components if the trial is not fully online.

Public and patient research involvement(PPI)	Report at what stages and in what form members of the public were involved in the research as part of the research team. Report in what ways they contributed to the design, oversight, running, analysis, and writing up of the trial report. We suggest PPI be reported in the methods section with a link to other sources if applicable where PPI was reported. For a checklist of what to include and report in an online participatory trial, we suggest the GRIPP-2[21] short form reporting guidelines.
Questionnaire Inclusion	40/41 of the studies analysed contained a questionnaire or survey. We recommend using and citing the Checklist for Reporting Results of Internet E-Surveys (CHERRIES)[20] for best research practice.
Randomization	The point at which randomization takes place, e.g., before or after collection of baseline characteristics (we recommend that it should be after collection of baseline characteristics to minimize attrition rates),
Flow diagram	Consider including a flow diagram to show the path of the participant through the intervention.
Recruitment	Report methods used for recruiting and for validating that the data has come from a participant.
Pilot or Feasibility	State how the study was piloted. We recommend piloting with people not only using computer models or people familiar with the platform. Pilots need to be completed by fully online participants representative of the population in addition to any other platform testing that takes place.
Informed consent	Describe online informed consent methods, their validation and how participants could contact study personnel given the lack of face to face communication. Convey to participants the time resources and risks of contributing. Assess participant understanding and their knowledge of the purpose of the study.
Setting	Describe in detail the software and algorithms used in the trial and the launch date of the online site. Include the period for which the online site remained open for recruitment, and in what timeframe the online site remained open for data input.
Patient Reported Outcomes	We suggest reporting how the outcomes were informed by patients and if patient or public volunteer assessments of the outcomes were carried out before launch. Specify parties, including patient contributors, who developed PRO content. For other areas of reporting patient outcomes, we recommend adopting the SPIRIT PRO extension[74].
Replication	Include access to all materials and settings needed to replicate the research.

	Include explicit statements about platform downtime or failures even if none occurred, as this may explain some loss to follow-up and the stability of the setting
Compliance and loss to follow-up	We recommend building on and reporting consistency and completeness checks at each stage of the intervention process as this contributes to best practice and replicability.
Data protection	Outline how personal information was collected and protected. Include methods for password storage and recovery if applicable.
Data Sharing	Policy on retention and use of already collected data, if a participant withdraws from the intervention or control (we recommend that data collection should be used to optimize the information available to the study and that participants should be aware of this in informed consent) State who has access to the data during and post-trial including third parties and how this was consented. State whether participants will have the option to download personal data collected during the trial
Contributory statement	Online trials may be run across countries and cultures with not all team members having access to the raw data. Stating who contributed and to what extent increases transparency and accountability
Competing interests	We recommend financial and personal competing interests be declared by all parties within the research team including members of the public or advocacy groups.
Supplementary Materials	If not supplied by the publisher, we suggest authors establish ways that the supplementary materials can be linked to the primary paper and in a file format that is accessible to readers. Multi-file type open access repositories can be used such as Zenodo, Dataverse, or GitHub[72].
Dissemination	Consider building and reporting on a dissemination plan for reaching non-professionals. This could be through social media, blogs, the trial website, through the public report to the funders, and in conferences and training venues.

The SMOOTH (Self-Management of Open Online Trials in Health) analysis reported here highlights the importance of consideration being given to good practice and reporting as early as the protocol planning stage for an online trial. Although online trials are still an emergent field, careful application of new findings for best research practice could improve the quality of online trials.

The researchers' insights into ways to improve interventions or trial design were rarely discussed in publications even when authors used interventions repeatedly across conditions and populations with minimal difference in effect [75,76]. Online trials could benefit from the practicality and cost savings of applying methodology research within the context of a functioning trial, nesting Studies Within A Trial (SWAT) [77] in host trials and by making use of the Trial Forge initiative [78]. For example, in this analysis the results from a study within a review (SWAR) were used to guide the development of this research and also the Delphi and Overview of informed consent where it helped resolve uncertainties about the right balance of training and support for review teams. A similar study within a trial (SWAT) [77] could be used in online trials to train research teams.

Following the sporadic use of reporting guideline in these reports of online trials, we propose the development and implementation of a reusable online protocol that follows good practice for reporting these trials. An adaptable protocol template could provide strategies for data management plans, reusable interactive consent, patient and public involvement methods and a checklist to verify what to report from available guidelines when conducting an online trial. We also suggest that researchers might improve the uptake of their interventions by partnering with patients to improve access, usability, quality, and dissemination.

Differences between protocol and review

The preliminary protocol was amended following public feedback and input was incorporated into the data extraction process. We had hoped to include an investigation of online research impact, but this was not reported or easily measured for all 41 included trials.

Dissemination

The results were distributed to clinicians, researchers, industry, and members of the public using blogs, open access online classes, and as a keynote address in one conference, with results shared in two other conferences as part of a workshop.

Contributions

AP led the research and managed the team, designed the analysis, coding scheme and data extraction forms with feedback from all authors, EPPI Reviewer staff, CerQual and from volunteers. Anne Brice built the database with support from AP and Professor Amanda Burls (AB). AP, AB, and Lenny Vasanthan (LV) extracted data extracted. AP and LV independently coded the reviews. AP acquired and trained the volunteers. AP and LV analysed the anonymized data with feedback from other authors SL and MC. AP drafted the manuscript. All authors interpreted the results and contributed to the writing of this manuscript.

Acknowledgments

We thank all the volunteers, including Caroline Struthers, Dr. Denis English, Ryan Price and those who commented on the protocol for this study and improved it but preferred to remain anonymous. We are thankful for the volunteers' thoughtful edits and contributions to the discussion. We are indebted to software developers from RAYYAN [12] and Mendeley [13] who contributed to the research by customizing their products as open access for use with citizen researchers. Finally, we appreciate the feedback from the JCE editors and reviewers who encouraged us to improve the structure of this report and sharpen its focus.

Methods and Public Involvement Survey of Corresponding Authors of Existing Online Trials

Abstract

BACKGROUND
The Self-Management Open Online Trials in Health (SMOOTH) survey reports methods as well as researcher preferences in online trials and explores to what extent public and participant involvement in online trials occurs. This survey queried researchers' experience in online trials and their perceived value of Patient and Public research involvement. The preparation, consideration, and publication of research involvement require the use of resources by the authors. The survey explores whether authors consider resources to be sufficient or useful to improve online trials about self-management of health.

OBJECTIVE
To identify the present state of public research involvement in online trials concerning health self-management and to explore the needs of researchers when contemplating the building and writing up an online trials protocol.

METHODS
The ORCID database of online trials was used to survey corresponding authors concerning trial methods and preferences including the frequency, format, and quality of citizen involvement in online trials about health self-management.

RESULTS
Blended trials were reported as online trials. Remote recruitment and communications were less common than local recruitment even when participants signed up online. Research volunteers helped more with recruitment and as advisors than with trial design, analysis, or outcome setting. Forty-seven percent of Corresponding authors report that an online trial was the best way of answering their research question

CONCLUSIONS
Detailed reporting of online methods and volunteer researcher involvement was hindered by role confusion between research volunteers and trial participants. Respondents were responsive to the development of protocol and reporting suggestions but were not in favour of adopting complex new frameworks that require extensive time, training, space, and funding.

**Protocol available: Research Registry# 1986 http://www.researchregistry.com/browse-the-registry.html#home/registrationdetails/5856b9bd759db5ec4609d880/*

Introduction

The use of participatory research for public involvement and self-management methods in online clinical trials brings unique methodological challenges and benefits[3]. A systematic overview of Patient and Public involvement in trial design was conducted with reporting on the quality of methods used and the ways PPI was reported in the literature[4]. This research was followed by *the **S**elf-**M**anagement **O**pen **O**nline **T**rials in **H**ealth: An Analysis of Existing Online Trials (SMOOTH)* [1]using *The **O**nline **R**andomized **C**ontrolled Trials of **H**ealth **I**nformation **D**atabase (ORCHID)*[5] The overview and the analysis provided insights for the improvement of online trial methods and ways that are used to engage members of the Public and Patients as research volunteers, however areas that could illuminate author preferences and observations are used in developing the Delphi questions for the Participatory Lab for Online Trials in a later thesis chapter.

It is reported that research volunteers add value to the research and can reduce collateral expenses in the design and the running of trials[6]. There are, however, many gaps in reporting on methods and public involvement in clinical trial design [7] as we found in our analysis of *The BMJ* Patient and Public involvement declarations[8], research that will be addressed in more detail in the next chapter. .Mandatory declarations and explanations of the methods used for public involvement are increasingly expected by funding bodies and dutifully supplied by researchers and yet the peer-reviewed record of this involvement is sparse[9]. It seemed prudent to initiate a survey with corresponding authors of online trials in order to search out answers to these areas that were underreported and to explore ways that this situation might be remedied. Respondents were invited to comment on the

usefulness of qualities to include when designing and reporting on a participatory online trial.

Methods

The research was reviewed by and received ethics clearance through, the University of Oxford Central University Research Ethics Committee MS-IDREC-C1-2013-174.

Sampling

The sample was a convenience sample from studies in the ORCHID Database. Respondents were authors who are principal investigators who published online trials of health self-management.

Questionnaire Administration

This was a two-part survey. Part-1 reports author's insights and preferences about online trial methods and Part-2 explored areas of Patient and Public participation in trials. The survey was administered online without geographical restrictions and used the validated Survey Monkey software to collect and store responses in a data secure setting.

Survey Data Entry

This study used CHERRIES[10] reporting guidelines as a check for good practice in administering surveys. Survey items were managed with JavaScript programming for consistency and completion checks before the questionnaire is submitted. For instance, a question missed will be highlighted so the person has the opportunity to complete that question. Unique identifiers stop participants from filling in the survey more than once.

Data Security

The survey platform met ethical requirements of the institutional review board and the data protection act. All survey data were treated confidentially and IP addresses were not collected. The maintenance of confidentiality of information is subject to normal legal requirements. Responses will be presented in aggregate form; no individuals will be named. Any identifiable information that is obtained in connection with this study remains confidential.

Informed consent

Participants were emailed an information sheet outlining the reasons for the survey, how the data will be stored, used and disseminated. They were informed the survey will take less than 15 minutes of their time. Consent was embedded within the survey and respondents who did not agree were exited from the survey and thanked for their time. Responses to queries about consent or other challenges were answered within two working days.

Development and pre-testing

The survey was hosted on Survey Monkey which is a validated and secure online survey site that meets the standards for the data protection legislation in the UK. The survey was developed by the researchers. The survey was piloted with 8 volunteers to increase accessibility, usability and to reduce ambiguous questions, the survey was then amended according to volunteer feedback.

Adaptive questioning and Respondent Burden

Adaptive questioning is where certain items, or only conditionally displayed questions

based on responses to other items) are used to reduce the number and complexity of the items. Questions were distributed over multiple pages with a progress bar so respondents could see their progress. Completion rates are noted to be higher when the burden on the participant is low.

Completeness check

Automated consistency or completeness checks are managed by the software before the questionnaire. All items provide a non-response option such as “not applicable” or “rather not say”, “I don’t know” or “I cannot remember” or “other” so participants will not have difficulty completing due to being unable to answer a survey question. No question responses were mandatory and respondents could choose to exit the survey or skip any questions they chose not to answer.

Analysis

Descriptive statistics and qualitative narratives were used to address the distribution of key outcomes. The data were used to describe author response patterns and frequencies across research manuscripts. The weighting of items or propensity scores was not needed to adjust for a non-representative sample as the purpose of the study was descriptive and exploratory and not to validate a measurement.

Public Research Involvement

Members of the public, patients, students. researchers, editors and peer reviewers were invited to contribute to survey question formation and edit questions for readability and usefulness. They were invited to comment on the protocol as it was posted on PeerJ [11] and on social media (Facebook and Twitter. Volunteers were invited to comment on the

analysis and the readability of the final document. Patients, advocates, and students made themselves available to review the research manuscripts of those who participated in the survey to give feedback to these authors on their Patient and Public involvement methods as they requested.

Results

Sample

Among 337 corresponding authors invited to participate, we received 32 (9.5%) responses. Fifteen additional authors emailed or phoned citing security concerns and two offered to be interviewed.

Part One: Your experiences of running an online trial

Corresponding authors were asked to share their previous trials experience. Table-7 shows that (n=3/31) had worked only on online trials prior to the survey, the rest had experience with other forms of trials.

Table 7 History of corresponding authors work on trials

Have you ever worked on clinical trials that were not conducted online	Responses (n=31/32)
Yes, before the online trial	20
Yes, after the online trial	13
Yes, in parallel with the online trial	9
No, I have only worked on an online trial(s)	3
I have worked on multiple trials online and person to person and there can be overlap but the trials are not always connected	3
Not applicable	3
Other (please specify)	2
No, but I worked on a direct person to person clinical trial with others	1

When corresponding authors were asked, “Are you working on or have you applied for funding for a trial that includes public involvement?” (n=10/32) replied yes, (n=8/32) no.

Only (n=4/32) had done PPI in the trial they were asked about but (n=14/32) engaged 1-3 persons in PPI and (n=12/32) reported more than 4 individuals per project were added for PPI. When asked if an online trial was best to answer the research question (n=14/32 or 47%) agreed, although (n=4/32) stated the trial was blended rather than online.

Corresponding authors were asked if patients or members of the public were involved in the online trial as members of the research team other than as research participants and 11/32 said yes but 16/32 replied no. The open responses indicated some struggled with this question and other corresponding authors felt PPI in the design was not needed other than through feedback from participants or as expert consultants on the patient condition. There were sentiments expressed that formal priority and outcome setting and workshops for research redesign added to resource costs without increasing value for the study.

> *"Prior experiences of users have played a large part in intervention design, but not with any formal input. In my view, this is a far more effective means. It also includes pilot testing and modifications based on feedback".*
>
> *"Engagement is critical to proving useful feedback, in my view, much of the participant engagement stuff is pseudo engagement*".
>
> "*Our methodological trials did not include patients or members of the public"*

Two corresponding authors stressed the need for recognizing and capturing successful patterns for each trial and stated a template approach concerned them as they felt it might take away from the importance of treating each trial as individual. They learned through failures that expecting what worked in one trial to work in another even if it was a different population but the same intervention was not wise and urged researchers to look at trials like human relationships where there are some common rules for engagement but individual attention and adaptation is required.

Part-2: Who Included PPI in the Trial

Corresponding authors whose trials included PPI were (n=16/32)

Recruiting

Recruiting methods for their research included an online screening questionnaire (n=4/16), telephone (n=4/16) or face to face meeting with the trial team and then signing up online (n=5/16) and (n=3/16) responded other.

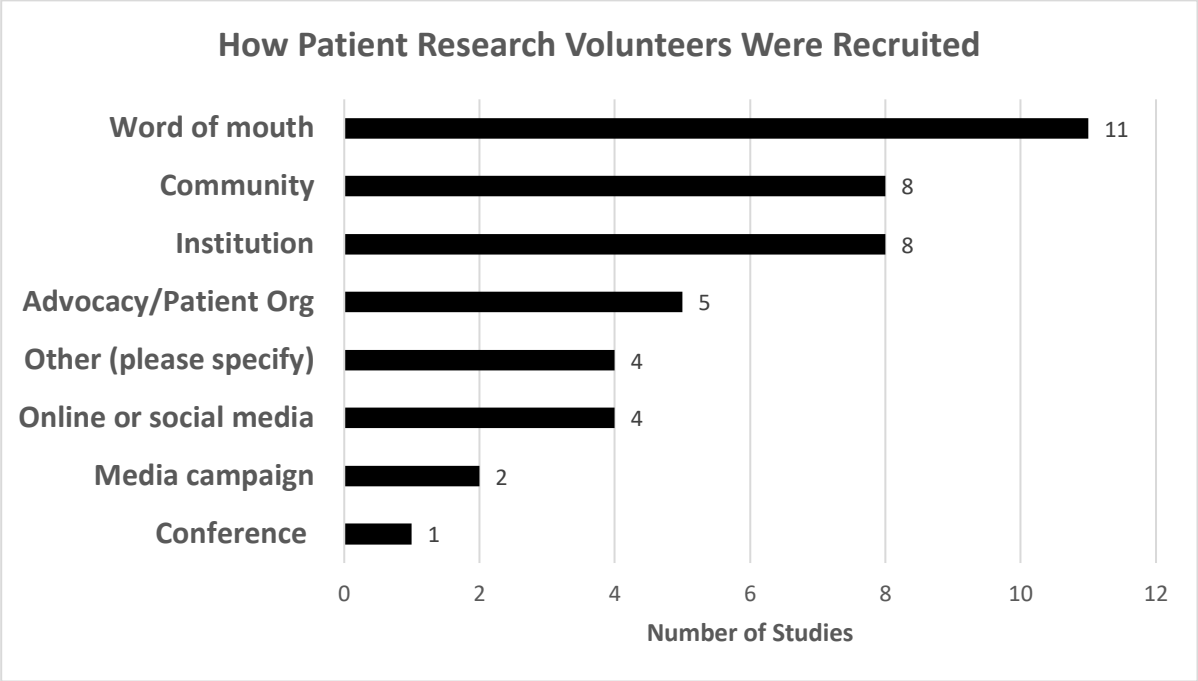


Figure 14Methods by which patient research volunteers were recruited

Participants were less likely to be recruited remotely even though they would be enrolled in an online or blended trial (n=31) versus remote recruitment via media campaigns or social media (n=8). For ways patients were recruited see Figure-14

Where PPI Occurs in the Research Process

PPI was more likely to occur in designing recruitment strategies (n=8/16), and as advisory board members (n=7/16) or in assessing the burden of the intervention on participants

(n=6/16). It was least likely to be a part of the analysis (n=3/16), ethics, or grant proposals (n=3/16).

Table 8 Types of PPI used throughout a trial

At Which Stages of the Research Did PPI Occur	***Number of Responses***
Answer Choices	
The design of recruitment strategy	8
Advisory boards or steering committees	7
Assessing the burden of the intervention (where applicable)	6
Development of the research question	5
Interviewing or collecting feedback from trial participants	5
Selection and or development of outcome measures	4
Decisions for data acquisition	4
The review of patient information documents	4
Dissemination or presenting research	4
Grant writing and/or ethics applications	3
Analysis and/or interpretation of study results	3
Other (please specify)	3

Communication between researchers and volunteers

Email and in person were the most popular ways of communication (n=7/16) for researchers and volunteers. This was followed by telephone(n=6/16). Facebook and WhatsApp were not used in these trials(figure-2).

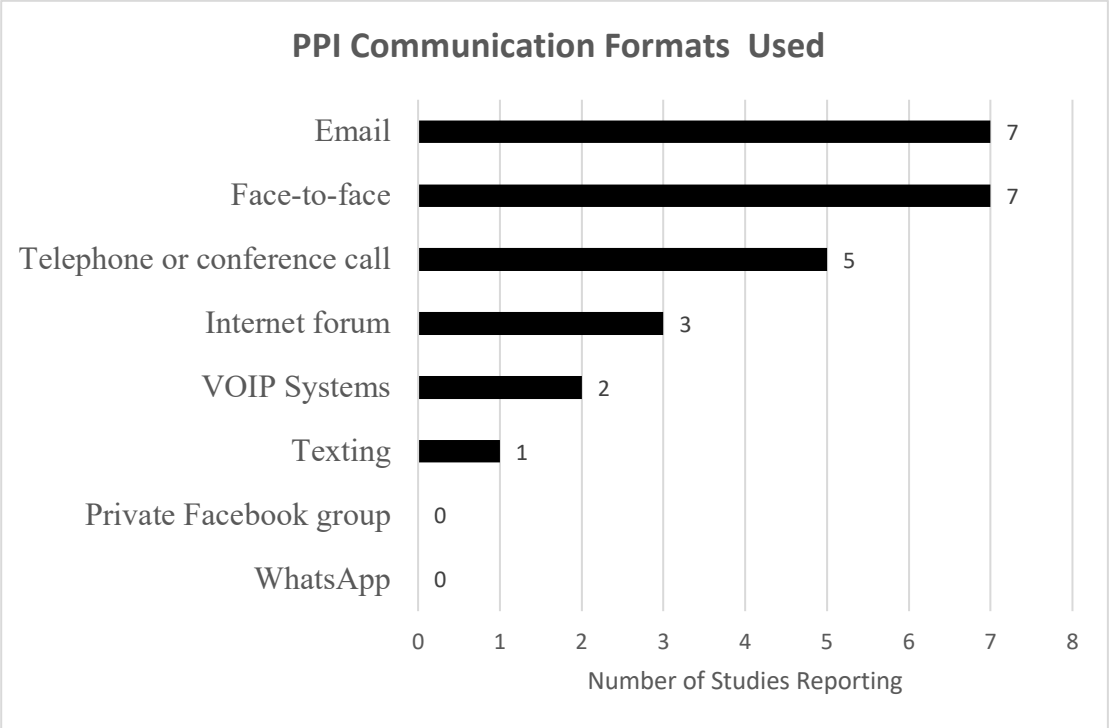


Figure 15 The ways researchers chose to communicate with PPI volunteers

How were PPI volunteers reimbursed?

In (n=4/16) trials PPI volunteers were paid in addition to expenses, in (n=5/16) the expenses were met and in (n=2/16) trials no reimbursement was offered.

PPI in writing up research and sharing the results

Although (n=7/16) corresponding authors did not include PPI in writing the manuscripts, there was substantive involvement in other areas. PPI was used in the dissemination strategy especially for the design aspect (n=6/16). Patient collaborators were acknowledged in (n=6/16) studies but this was most frequently in the acknowledgment s section and not by name (Table-9).

Table 9 PPI activities and acknowledgment of PPI in writing up and dissemination plans

PPI within the research writing process	**N=# of Trials**
No contributions	7
Reading drafts of the manuscript	4
Revising drafts of the manuscript	3
Writing sections of the manuscript	2
Final approval of the manuscript	4
PPI in the Dissemination Plan	**N=# of Trials**
Designed dissemination strategy or materials	6
PPI in Dissemination to patient groups or communities outside of the trial	4
Disseminating results to participants (peer to peer)	1
How was PPI acknowledged in the Manuscript	**N=# of Trials**
Acknowledged but not individually named	6
Named advocacy groups	2
Named individuals	5
It was not acknowledged	2
Where was the PPI acknowledged	**N=# of Trials**
Authorship	4
Contributorship Statement	4
Acknowledgement section	7
An additional paper was written to report the Public Involvement in the trial	1
Public Involvement was not acknowledged	1

Part-3 Future Plans for PPI

Additional guidance for building an online trials protocol was queried and 20 /28 favoured guidance to build the full protocol plus financial conflict of interest statements. Survey reporting help was the area where the fewest corresponding authors wanted guidance 13/28, although every online trial included in the sample reported containing a survey or questionnaire. The areas of interest can be seen in (Figure-16).

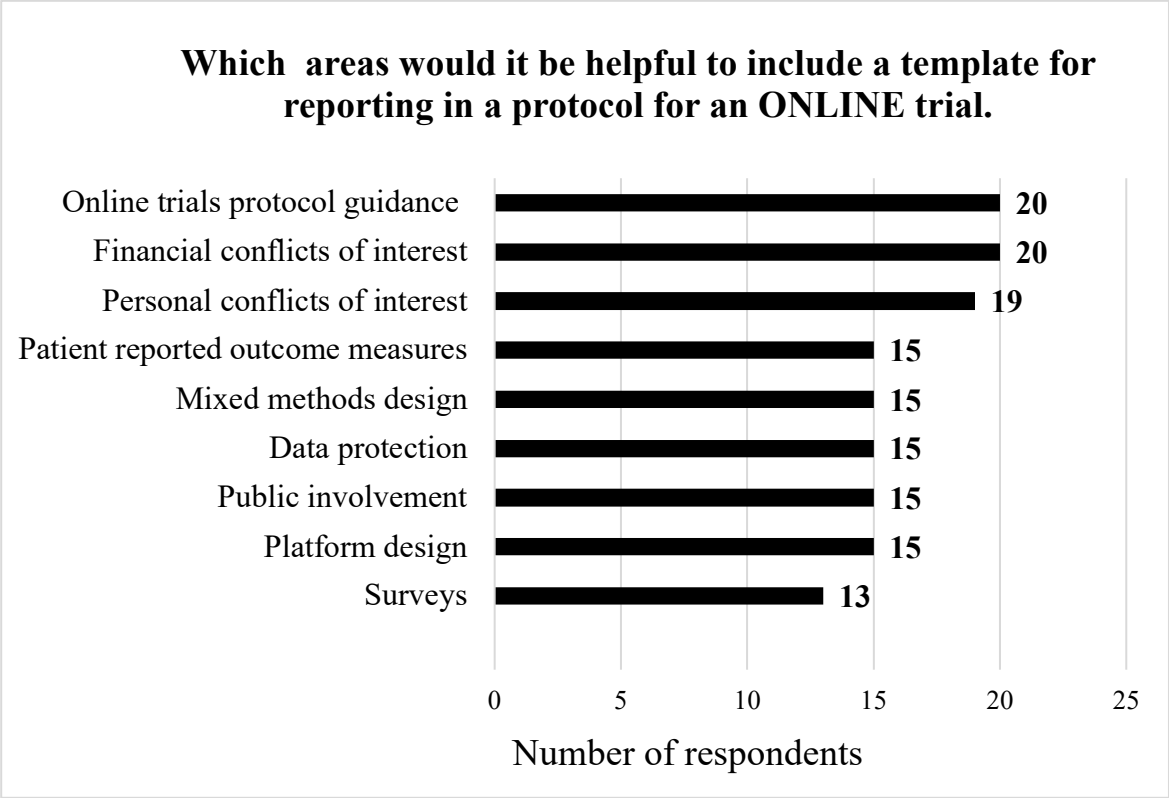


Figure 16 Results on queries for where additional reporting guidance would be helpful

Corresponding authors commented that any trial needed these areas identified and that the priority for inclusion was dependent on the research question. Only one author commented on the unique needs of an online trial and the need to adapt methods to make them viable. Others identified "*Safety considerations for a mental health trial (e.g., backup in the case of suicide ideation or intent)".* They recommended reporting "*How the site would be sustained over time*" They also suggested "*There should be more standardized information on technology and exact content of protocols that are used in online trials (e.g. the flow of a participant through an online trial protocol is very different from face-to-face trials*" Another point made was "*there is also great diversity between online trials - in order to be able to compare between trials we need standardized criteria/information*".

In planning for their next trial (n=13/32) Corresponding authors would like to introduce more PPI and (n=13/32) wanted PPI to stay about the same, (n=0/32) favoured no or less PPI. The comments indicated those not responding felt the term and definition used for PPI lacked clarity. When asked if a modifiable protocol template would be useful for planning a trial, (n=13/32) corresponding authors responded affirmatively, (n=5/32) did not think this would help and (n=11/32) did not know. The question *"What would better help you to report research involvement of patients and the public?"* generated several *"I am not sure"* responses along with other selective quotes from corresponding authors.

Suggestions for Improvement

"Easier access to volunteers and a better response rate without having to chase people down!"

"More substantive involvement of the public with regard to the design and the research protocol and manuscript writing".

"We make a point of in our press communications and have narrative stories with pictures of our partners"

"I think it's important to include patients in as many aspects as possible and to also think more about asking patents to create the questions of interest. I do think that we need to think about the best places to include patients, though, and let the goals of the work drive inclusion"

"PPI gives value to our research. we also learn a lot of reality about patients".

Corresponding Author Concerns

"Has inherent challenges, but can be meaningful"

"It can be valuable if protocol design can anticipate and exclude bias".

"The more we can involve the public the better but it's very challenging to do so in a mutually beneficial way"

Comments for Journals and Funders

"A protocol template and journal partnership for Public Involvement materials"

"APC reimbursement from university for unfunded PPI research, better provision from funders, or a waiver from the journals"

Comments on Reporting

"There could be a reporting checklist".

"More and more guidelines (e.g., PCORI in the US) are helping with this"

"I guess I would have to report it if it would be recommended or compulsory"

Discussion

What was Found

The objective was to identify the present state of public research involvement in online trials concerning health self-management and to explore the needs of researchers when contemplating the building and writing up an online trials protocol. This was complicated in that corresponding authors may not include volunteers or lay research partners by name. This raises wider questions about how personal unintentional conflicts of interest in PPI volunteers or intentional influence by industry funded advocacy and how this may influence reporting[12]. Lay researchers may belong to multiple advocacy organisations and if the lay volunteers are not named, there will be no conflict of interest statements required from them. Some authors report writing dissemination plans and PPI activity into funding protocols but state there were no requirements for reporting them. There was confusion about how roles of the participant and the patient research partner differ. This was indeed

a common finding in systematic reviews about PPI and undoubtedly has hindered reporting efforts[4,13,14]. Authors state their concerns and need for support and welcomed reporting guidelines in terms of protocol design and ways to concisely report their work in terms of PPI. They suggested adequate funding, help with author processing costs and standardized methods could improve quality and free up resources for PPI inclusion in their research.

One purpose of the SMOOTH survey was to capture knowledge the SMOOTH Analysis may have missed as it assessed only the trial reports, and to increase knowledge by including the full sample of these trials. The quantitative information remained constant however open comments reveal corresponding authors struggle with public involvement methods and the writing of protocols for these trials. The resistance and power struggles cited by other publications[15] was not evident in this sample. Respondents readily shared their willingness to engage but report their uncertainty about how to start. Some share the survey questions got them thinking about how they could add patient involvement for future work. All respondents reported PPI as relevant to online trials of self-management interventions.

Strengths and limitations of the study

The survey presents previously unreported information from a small sample of corresponding authors of online trials for self-management interventions and enabled sampling from experiences, values, and preferences of the corresponding authors. More than ½ the sample was unopened (n=190.51.6%) and only (n=53/14.4%) clicked on any link. There are concerns that the survey was blocked by institutional spam filters as this was the case for several of our pilot testers. In addition, multiple authors emailed or

phoned us and remarked on the quality of the questions and then said they had data theft and privacy worries about filling in any online survey at this time and they mentioned multiple data breaches that have taken place. Of the 53 authors who did click on a link 32 of these submitted responses and an additional 2 authors preferred to be interviewed for a total of 64%. The survey may have benefitted from providing more detail on how PPI is defined and by providing for blended (partially online trials) although spontaneous comments about blended trials were elicited by the open-ended questions.

Unanswered questions and future research

Mandatory declarations and explanations of the methods used for public involvement were commonly expected by funding bodies and dutifully supplied by researchers, however this may not be reported in the research paper[9]. More work will need to be done to address the wider questions of how personal unintentional conflicts of interest in PPI volunteers may influence reporting and how this can be mitigated. Methods are not transparent if they remain unreported and this, in turn, limits the construction and adaptation of successful strategies as they are not accessible from trial reports. It also reduces the scope for external validation or reporting of impact[17].We could find no existing similar or larger survey that addressed the research question(s). This limits representativeness of the population, however, the field is emergent and this sample provides information that could be used in a Delphi process and to guide online trial protocol development. Studies within a trial or survey (SWATs) could be used to test what works in to improve the methods used in future research.

Conclusions

Detailed reporting of online methods and volunteer researcher involvement was hindered by role confusion between research volunteers and trial participants. Respondents were responsive to the development of protocol and reporting suggestions but were not in favour of adopting complex new frameworks that require extensive time, training, space, and funding.

In the next thesis chapter, we will address other areas where partnering with patients could occur and that may be of importance for online trials including, partnering with patients, what might be done with supplementary materials, questions around patterns of dissemination, and a survey of Patient and Public reviewers from two journals[8,18–20].

Dissemination

All Corresponding authors could opt in to receive a link to the full paper. The results were used in teaching sessions and presented at conferences. The public was invited to comment on the results through social media.

Contributions

AP designed the study and drafted the questionnaires. AP extracted the samples of authors and reviewers from the ORCID database. Anne Brice built the database with support from AP and AB. AP managed the surveys on SurveyMonkey and acquired the volunteers. AP analysed the anonymized data with feedback from other authors SL and MC. AP drafted the manuscript. All authors interpreted the results and contributed to the writing of the published paper that originated from this manuscript.

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SMOOTH Chapter Outputs

Published Protocol:
Price A, Burls AJ, Vasanthan, *et al.* Self-management open online trials in health [SMOOTH] an analysis of existing online trials [Protocol]. *PeerJ* Published Online First: 2017.

Primary Publication:
Price A, Vasanthan L, Clarke M, May S, Brice A, Burls A. REVIEW SMOOTH: Self-Management of Open Online Trials in Health analysis found improvements were needed for reporting methods of internet-based trials. *Journal of Clinical Epidemiology* 2019;105:27-39

Supplementary Survey
Price A, Vasanthan L, Clarke M, et al. Self-Management Open Online Trials in Health (SMOOTH): Methods and public involvement survey of corresponding authors of existing online trials. *European Journal for Person Centered Healthcare* 2018;6(3):372-378.
Embedded Research
Price, A SWAR 09 *Use of 1:1 Sessions for training and supporting novice reviewers in the conduct of online systematic reviewing tasks* https://mistral-itn.eu/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWARStore/

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Chapter Five | Reporting and Publishing Gaps, Growth, and Methods in Patient and Public Involvement

Chapter Five highlights

Meets Thesis objective 4 To investigate how mandatory public involvement reporting, Patient and Public reviewers, the use of supplementary materials, and current dissemination practices impact the reporting and publishing of Patient and Public involvement.

Take home points: We found that mandating declarations increases the reporting of PPI. This helps researchers, readers, patients and clinicians understand how PPI can be used to co-produce research with non-academics and when co-production is not possible. Information gained from co-production can influence future implementation, end-user satisfaction and use in practice.

Introduction

The chapter uses condensed versions of four research manuscripts[1–4] that relate to methods, reporting and implementation of Patient and Public involvement (PPI) in research. The research emerged from developing journal policy at *The BMJ* [5–7] to encourage authors to succinctly report PPI as a declaration within the methods of the paper[8]. Authors, readers, reviewers, publishers and patient panel members queried us about how to manage data storage and ownership to address ethical concerns and the preferences of researchers, clinicians, and end-users. The journey brought learning points for integrating and training public reviewers within a peer review system. It is clear that research planning and co-production with lay research partners at the protocol stage could improve study methods and research reporting[9,10].

Section 1

We analyse BMJ research manuscripts before and after the mandatory inclusion of PPI declarations in The BMJ[1]. We include a 2018 follow-up audit using a convenience sample of 50 BMJ Open research manuscripts and protocols following their change in policy to include mandatory PPI reporting. The objective was to determine whether mandatory PPI reporting increases the number of papers that contain PPI.

Section 2

This report looks at the timeliness and responsiveness of Patient and Public (P&P) reviewers as compared to Peer reviewers, and goes on to assess the needs and preferences of P&P reviewers by surveying them about their needs.

Section 3

Simple PPI declarations provide insufficient content for replicating PPI methods. When those methods are disambiguated from the primary paper they are not visualized as occurring within the research. It was suggested that we urge BMJ authors to store their PPI methods and data within the supplementary materials and we assessed what barriers could prevent the implementation of this process.

Section 4

We evaluate the benefits, restrictions, and problems inherent in dissemination and access to data as this may shape PPI, health literacy and the willingness of the public to become involved with research.

Each report contains an objective, background, results, and points to consider. Patient and Public Involvement for all sections is combined and reported at the end of the chapter along with a summary of the conclusions, acknowledgements and papers published as a result of this research.

Section One | Frequency of reporting on patient involvement in research studies in two BMJ Journals

Objective:

The BMJ asks submitting authors to include a declaration in the methods section to report on how they involved patients or members of the public in their research. The objective was to explore the declaration's early influence on PPI reporting, frequency, and practice following the introduction of a mandatory PPI section.

Background

The BMJ introduced an innovative policy instructing submitting authors to report if and how they involved patients in their research.[1-4] This policy is intended to foster increased researcher/patient collaborations by shifting cultural expectations about the importance of reporting PPI. [5–7] Authors of research papers are required to include a PPI declaration in their methods section under a subheading called *Patient Involvement*. [8] Authors of all research paper submissions are required to state if and how patients were (or will be) involved in developing the research question and outcome measures, designing and conducting the research, assessing the burden of the intervention (where applicable) and disseminating the results to patients. Authors are also instructed to thank patients involved through the contributorship statement, acknowledgments or both. Where authors have not

involved patients, they are asked to report this explicitly in the paper. Research describing studies without patient involvement are not rejected solely for this reason. At the point of article acceptance, editors check that information about PPI activity is recorded in the manuscript and request that this be added if it is absent.

To assess the influence of this policy, I worked with colleagues to compare published research papers in *The BMJ* before and after its introduction to explore how researchers are involving patients and the public in research, whether the policy lead to an increase in reporting of PPI, and whether infrequent documentation of PPI information in research is a reporting phenomenon or is indicative of an absence of PPI activity.

Methods

We report a before and after comparison of published research papers to assess whether rates of reporting will reflect increased involvement of PPI in research or better documentation of this involvement[1]. Three researchers independently data-extracted research manuscripts and protocols accepted for publication in The BMJ and in BMJ Open. We reached consensus for incidences and types of PPI across two 12-month samples in the BMJ and in the 2014 and 2018 consecutive convenience samples of 50 papers each from BMJ Open for these time periods. There were no study designs exclusions as PPI is possible with studies that have no direct contact with participants such as systematic reviews or registry studies. The consecutive sample of 50 research papers published in *BMJ Open* during 2018 and the earlier sample in 2014 were selected for audit following the introduction of a policy to have authors write a mandatory declaration of public involvement in research and protocols. In the *BMJ Open* sample, the PPI declarations were categorized as complete, adequate, incomplete, indirect (PPI was provided outside of the study by a third party) or missing (Table 10)

Table 10 PPI Declaration Classification for Quality

Classification	PPI Declaration Descriptors of Classification
1. Complete	Authors followed BMJ guidance and included study specific detail about the PPI.
2. Adequate	Authors followed the BMJ template but without reporting on the presence or absence of PPI in study specific areas such as the research question prioritization, study design or conduct or outcomes.
3. Indirect	Indirect or third-party declaration of PPI
4. Incomplete	Incomplete declarations or one with misperceptions: PPI was not described, what was described was not PPI or authors gave inadequate or misleading rationales for not including PPI
5. Missing	No PPI declaration was provided

Results

Between 01 June 2013 and 31 May 2014, *The BMJ* published 189 research papers, and only one (0.5%) of these included some information on PPI activity (Table 2). Between 01 June 2015 and 31 May 2016, following the introduction of the PPI policy, *The BMJ* published 152 research papers, and 130 (86%) of these included a PPI statement in the methods section, with 16 (11%) of the 152 papers reporting some PPI activity (Table 2). This was a more than a 10-fold increase in the proportion of papers reporting PPI compared with pre-implementation, but still only a small proportion of the total number of articles published. In the *BMJ Open* sample, the papers containing PPI activity was much higher with 16/50 papers or (32%) reporting some PPI. The types of PPI contribution across the samples are reported in Table 11.

Table 11 PPI Contributions of Patient and Public involvement in manuscripts before and after introduction of mandatory PPI statement in BMJ and BMJ Open

The BMJ and BMJ Open Short audit for Frequency and Content of the Public and Patients Involvement Declaration				
Areas of the research process where PPI was included by number of studies	***Before BMJ (2013-14)***	***After BMJ(2015-16)***	***Before BMJ Open (2014)***	***After BMJ Open(2019***

Study design	0	0	0	6/16
Contributions to the grant application and or study protocol	0	3/16	0	5/16
Help to set the research question or commenting on its importance	0	4/16	0	3/16
Ensuring the development of, or choice of, outcome measures were informed by patients' priorities, experience, and preferences	0	7/16	0	4/16
Study conduct	1/1	6/16	0	2 /16
Involved in the study steering group or a member of the research team	0	8/16	0	5/16
Recruitment and implementation of the research	0	4/16	0	0
Patient/public communication materials, for example, patient information sheets	0	1/16)	0	2 /16
Analysis (contributed to data analysis interpretation of study findings)	0	2/16	0	2 /16
Drafting of the manuscript contributions to editing, revising and or writing the manuscript	1/1	3/16	0	1/16
Patients listed as co-authors	1/1	1/16	0	0
Dissemination direct involvement of patients led by the research team including the development of materials for dissemination and choosing the most appropriate method of dissemination	0	3/16	0	1/16
Indirect involvement through dissemination to patient charities, and groups that may, in turn, involve patients in the process	0	3/16	0	1/16
Patient representation informing the content of dissemination materials on a general advisory board for the use of the data used in research	0	3/16	0	2/16†

Note: Responses are not mutually exclusive. For example, if a patient was on the steering group, this will be indicated in the relevant box and the box about the implementation of the research. However, not all those involved in study conduct were members of steering groups.

** The denominator only includes studies where there was an intervention, i.e. excludes systematic reviews, population-based studies, secondary analyses, etc*

† This includes three papers from the QResearch team with identical statements about some aspects of PI in dissemination, but this PI was specific to the QResearch database, not the individual published studies, and it is not clear how much patients were involved in the individual studies reported.

Papers across samples included information in the *Patient Involvement* section that did not describe PPI, and it was sometimes difficult to distinguish valid PPI from qualitative data collection (e.g., capturing patient's perspectives from active participation in the research process). This motivated us to categorize the quality of reporting in a convenience sample of BMJ Open research papers. In the *BMJ Open* sample, we categorized the quality of reporting and of 50 papers assessed, 48 (96%) of papers contained PPI declarations; 15/50 (30%) of all papers were protocols and 45/50 (70%) were research manuscripts. Of all papers, 32/50 (64%) stated that they did not do PPI and in 16/50 (32%) authors reported that PPI occurred. In 5/50 papers (10%), this PPI was indirect. No BMJ Open manuscript reported patients or members of the public as authors. The details of the quality of PPI reporting in the declarations is illustrated in Table 12.

Table 12 Appraisal of quality of BMJ Open PPI Declarations

Quality of Patient and Public involvement declarations	**BMJ Open 2018 N=50 (%)**
Declarations for studies reporting at least some patient and public involvement	16 (32)
Good or adequate reporting	12 (32)
Third party involvement	*4 (8)
PPI declarations for studies reporting no patient and public involvement	29 (68)
Good or adequate reporting	9 (18)
Third Party	1 (2)
Incomplete or inappropriate (*e.g., reported we did a meta-analysis, and it was not possible to involve patients or members of the public in this research*)	20 (40)
No PPI declaration provided	2 (4)

.

**Note: these categories are not mutually exclusive because, for example, authors may report a combination of indirect PPI and direct PPI within a study*

Points to Consider

- Based on this analysis of published research papers in *The BMJ,* and *BMJ Open* a higher proportion of papers reported PPI activity after mandatory PPI reporting was introduced.
- PPI occurred at multiple stages from grant applications and study design through data analysis, editing, writing of final manuscripts, and post-study dissemination.
- The frequency of reporting PPI in studies published by *The BMJ* and *BMJ Open* is different from current research practice, and these differences may be exaggerated by the active policy of reporting involvement and promoting patient partnership
- BMJ Open's policy on PPI declarations covers research manuscripts and protocols. The addition of protocols can be beneficial as authors are stating their plans ahead of the research, which is a commitment in print and may provide examples others can learn from as well as provide opportunities for editors or PPI reviewers to shape the PPI research development.
- PPI may not be practical in studies of research methods, or statistical reviews, and in this case, authors may appreciate knowing that a journal is interested in PPI or the absence of PPI being reported (for example for journal-related audit and research purposes).
- Authors and editors might need help to distinguish indirect third-party involvement from direct involvement, qualitative research from PPI and to provide meaningful PPI declarations at an appropriate point in the manuscript.
- Infrequent documentation of PPI information in research appears to be partially a reporting phenomenon as PPI increased when reporting was mandatory, however

the increased rate of PPI was 32% or less which may be indicative of an absence of PPI activity.

The second brief report evaluates Patient and Public (P&P) Reviewers versus Peer Reviewers at The BMJ in terms of how often reviewers are invited to review research manuscripts, the percentage of those who go on to review, and the completion rates of these reviewers from 2014 to mid-2018. We noted completion rates declined slightly across P&P and Peer Reviewers. We invited P&P reviewers to comment on what they needed to become proficient and confident while completing a P&P review.

Section 2 | The Self-Reported Needs of Patient and Public Reviewers at The BMJ

Objective

To evaluate the editorial review flow and needs of Patient and Public reviewers for constructing the optimal workflow for critical appraisal and PPI review of BMJ research papers while respecting barriers that reviewers face. Although *The BMJ* lists resources for Peer review in the general guidance for reviewers, P&P review has a different scope than Peer review as far as the context and content requested. P&P reviewers are asked to assess the effect of the intervention on the end-user, they are asked to evaluate the quality and scope of PPI within the manuscript and for their insight on the success of the intervention for use in daily practice. P&P reviewer training is not widely available and it became essential to ask reviewers how we might meet this need.

Background

The BMJ was the first open access, and open peer review large general medical journal to invite Patient and Public (P&P) Reviewers to review alongside Peer Reviewers and this represents a landmark shift in the concept of peer review at journals, reflecting a desire to ensure research is appropriate and relevant to end users.[7] With open peer review, authors and reviewers know each other's identities, as reviews of published articles are published online besides the article for readers. P&P reviewers could experience unwanted personal exposure should they be identified as patients.

While some P&P reviewers can comment on research methodology, this is not a priority; however critical appraisal skills are helpful for any BMJ reviewer. With P&P reviewers,

their collective strength is to address the relevance and importance of the research to patients and carers, and whether the treatment or intervention studied was practicable and acceptable to patients. They can identify challenges patients and carers face; whether the outcomes measured in the studies described are essential to patients and carers and if other findings or issues could be considered. They will suggest ways to strengthen papers to make them more useful for shared decision making. Contributions will vary according to the background, skills, and experience of the patient and public reviewer, as it does with academic or peer reviewers. Some patients and carers may comment on the relevance of a study for a particular group, while those with academic training and research knowledge might comment on methodology. Others may focus on the clarity of the reported research and its interpretation to a lay audience. All these contributions and others have the potential to enhance the quality of the research and its uptake in practice. How these roles are distributed is mapped in Figure 17 which presents the review process of a paper from submission to acceptance.

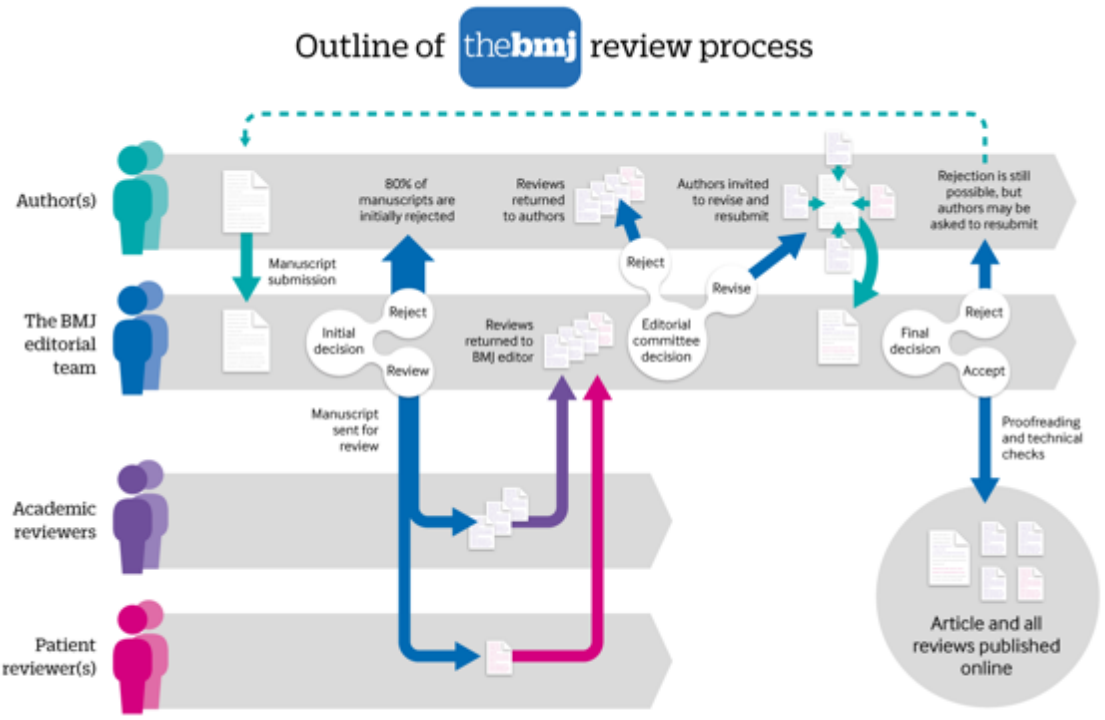


Figure 17 Will Stahl-Timmins, Guidance for BMJ Patient and Public Reviewers | The BMJ

Methods

Information in the tables was extracted and updated from Scholar One, the publishing software used by BMJ and the associated journals. We surveyed P&P reviewers listed in *The BMJ* Scholar One database.

Results

The number of P&P reviewers increased from 223 in 2014 to more than 775 in 2018; the increase slowed in 2017 as the publishing system sign up was challenging for P&P reviewers and there was insufficient staffing to accommodate individual enrolment. The number of papers sent for review to one or more P&P reviewers has grown from 14-85% in 2014-2018 with the caveat that some papers are not suitable for P&P review, so the number will never reach 100%. The number of reviews completed has also grown from

85-214 reviews per year in 2014-2017, figures for 2018 are from January to the first of August only. (Table 13)

Table 13 P&P Reviewer activity at the BMJ 2014-2018

Registered Public & Patient Reviewer Activity by year					
	2014	**2015**	**2016**	**2017**	**2018 to Aug**
Number of P&P reviewers registered on S1*	223	476	692	759	775
Proportion papers sent for review where ≥ 1 P&P reviewer was invited to review **	117/833 (14%)	186/695 (27%)	412/636 (65%)	483/619 (78%)	352/413 (85%)
Total reviews completed by P&P reviewers	85	120	258	214	115

Agreement to review has dropped substantially for Peer and P&P reviewers with the rates of completion and days needed to review a paper remaining constant from 2014-2018. The Peer reviewers show a slight advantage in completing reviews while the P&P reviewers take about two days less to review the paper (Table 15)

Table 14 Comparison of Peer and P&P reviewers at The BMJ

Invitation agreement and time to completion rates | Peer Reviewers and Patient & Public (P&P) reviewers										
Year	**2014**		**2015**		**2016**		**2017**		**2018 Jan-Aug**	
Reviewers	**Peer**	**P&P**	**Peer**	**P&P**	**Peer**	**P&P**	**Peer**	**P&P**	**Peer**	**P&P**
Agreement rate	41%	53%	40%	48%	40%	40%	36%	33%	35%	30%
Completion rates	83%	79%	84%	81%	84%	77%	85%	77%	82%	80%
Days to review Mean (SD)	13.8 (7.9)	10.7 (6.8)	13.7 (7.6)	11.9 (5.9)	13.5 (7.6)	10.8 (6.1)	13.6 (7.5)	11.8 (6.7)	13.6 (7.1)	11.7 (6.3)

For the survey, the response rate was 74% (122/164) for those BMJ P&P reviewers who had previously reviewed and 38% (51/133) for those who had not yet reviewed. Reviewers described wanting to bring patient voices into the research process, influence healthcare standards and meet the needs of patients. Of the 122 who had reviewed, (82%) would recommend being a reviewer to other patients and carers. (91%) Thought more journals should adopt patient and public review. Only (3%) of reviewers reported concerns about open review. They worried they might be wrong in their review and were concerned about being perceived negatively by others because of a medical condition. Concerns included breaches in patient confidentiality, misuse of personal information, implications for future job applications and administrative challenges for receiving disability benefits.

When asked to rate support materials 63% of the P&P reviewers found existing *BMJ* materials '*extremely*' or '*very helpful'.* When asked what they disliked about reviewing or why they declined to review, they said it was a struggle to manage family and workload conflicts with tight deadline for completing a review. Some dislike open peer-review and they find the online manuscript review system unmanageable. Other reasons reviewers declined to review included a lack of experience or interest in the topic, the irrelevance of the question for patient and public review in general, and not understanding the paper.

P&P reviewers' suggestions included adding online resources and training to improve reviewer skills and to provide more time to review. They recommended improving ongoing communications and the building of a user-friendly submission process. P&P reviewers requested how to review guidance using videos and online courses. They stressed the importance of matching papers to reviewers' experience and providing review

samples and targeted feedback on the usefulness of reviews they completed. They wanted a sense of community among reviewers and the opportunity to share with others, the advantages of patient and public review. There are further details in the open-ended comments (Table 15). The BMJ has since incorporated many of the helpful suggestions P&P reviewers have supplied to guide implementation.

Table 15 Patient and Public Reviewer Suggestions to The BMJ

Public and Patient Reviewer Suggestions to The BMJ
Access to more information
Online access to articles on specific topics of relevance.
Access to other BMJ Journals
Training
Relevant training & attendance at meetings/conferences
Online resources, tools, tips to encourage excellent standards
Mentoring and peer to peer training
Communication
Improved & more frequent communications
newsletters
More support
Named person to contact and mentoring peer to peer or by staff
More info about the review process and path of a paper from submission to acceptance
More time to review
Targeted personal feedback so reviewers could learn and replicate what was useful
Community
Establish a supportive network of patient reviewers
Patient reviewer tweet-chat led by BMJ staff
Lay BMJ conference – to meet other reviewers
Articles on patient reviewers & the value of patient reviewer contributions to the journal
Rewards
Two-year subscription or rolling access to online journal subscription
Add reviewers' names to the acknowledgment section of published articles
Printable online certificate of acknowledgment and acknowledgment by Publons

Points for Consideration

- A free online certificate class for P&P reviewers that could be co-produced might benefit not only P&P reviewers but also journals without the resources to train P&P reviewers

- P&P reviewers could work in small teams with an assigned mentor to build community
- P&P reviewers might be invited to write Opinion blogs on articles they have reviewed
- Reward P&P reviewers and authors who have co-produced content with a distinctive logo recognizing co-production

Section 3 | The Role of Supplementary Material in Journal Articles: Surveys of Authors, Reviewers, and Readers

Objective

In the following study on supplementary file usage and preferences, we address the feasibility of storing PPI methods and data within the supplementary files of a journal and what this might mean for reviewers, authors, and readers. To do this, we report the partial results of an extensive survey of 17 *BMJ Group Journals* and consider the data for learning about the implications and the practicalities of the supplementary materials as a home for PPI methods and data.

Background

Many journals allow or require authors to submit supplementary material along with their manuscript. These materials might prepare the article for review and publication (such as checklists for reporting guidelines) or provide additional information for readers who wish to delve deeper into the findings or replicate the research. The materials can improve initiatives such as FAIR (Findability, Accessibility, Interoperability, and Reusability) Data Principles with the automatic finding and use of scientific data,[11] and the wish to facilitate automation in the systematic review process.[12] However, the requirements and attitudes of journals for supplementary material vary, its use during and after submission and publication is patchy,[13] and its perceived value to stakeholders involved in producing, assessing and using it is unclear. Here we investigate the consequences for PPI development, for example, the research editorial team at *The BMJ* and the publishers of *BMJ Group* who host BMJ specialty journals suggest that Patient and Public involvement

materials be stored within the supplementary materials. This brings questions about the appropriate use of patient data and PPI methods if the supplementary materials are not peer-reviewed and may not lend itself to reuse[14]. Furthermore, and as reported elsewhere in the thesis, these materials may not be accessible with the downloaded PDF of the paper[10]. Therefore, the findings of this survey also investigated the practicalities of PPI stored in supplementary materials and queried how they might be accessed.

The Role of Supplementary Material in Journal Articles: Surveys of Authors, Reviewers, and Readers

This survey and the nested randomized controlled trial are registered at ClinicalTrials.gov ID: NCT03021863. The research was reviewed by, and received ethics clearance through the University of Oxford Central University Research Ethics Committee MS-IDREC-C1-2013-174

Methods

We queried the perspectives of authors, peer reviewers, and readers of journal articles. Among authors and peer reviewers of research submissions to 17 BMJ Publishing Group journals, we randomized two-thirds of each group to receive an author or reviewer survey, respectively. The remaining third of each group received a reader survey. Participants completed an online survey in November 2016 from the perspective of their allocated role to provide information about their use of specific types of supplementary material (study protocol, data collection or extraction forms, data tables and figures, completed reporting guideline checklists and flow diagrams, interview transcripts, raw study data). Survey questions asked about who the material is most useful to; the expected use of materials by authors, reviewers, and readers; the preferred option for accessing supplementary material;

and if and where supplementary material should be published. Select findings relevant to PPI reporting and review are presented below.

Results

From 20,340 surveyed authors and peer reviewers, we received 2872 (14%) responses (819 [12%] from authors, 1142 [17%] from peer reviewers, and 911 [14%] from those responding as readers). Additional data tables were the most common supplementary material type submitted or seen (authors, 74%; reviewers, 89%; readers, 67%). The table below which shows overall and individual group results for two forms of supplementary material: additional tables and reporting checklists. A majority of respondents indicated additional data tables were most useful to readers (58%-72% in each group), fewer reported they were most valuable to peer reviewers (19%-34%) and journal editors (3%-4%). Patterns were opposite for reporting guideline checklists where only (14%) perceived them as useful to readers. All three groups favoured publication of additional data tables and figures on the journal's website (80%-83%), with less than 4% of each group reporting that these were not needed.

These findings also show that using supplementary files to store PPI methods and materials may not be practical as these are unlikely to be accessed or peer-reviewed and the PPI methods are not contained solely within tables or figures which are the formats survey participants prefer to access (Table 16).

Table 16 Author, Reviewer, and Reader Perspectives on the Value of Additional Tables of Data and Completed Checklists for Reporting Guidelines by Group [a]

Group	No./Total No. (%)*		
	Most Useful to Journal Editors	Most Useful to Peer Reviewers	Most Useful to Readers
Additional tables of data			
Authors	29/819 (4)	187/819 (23)	564/819 (69)
Reviewers	32/1142 (3)	384/1142 (34)	662/1142 (58)
Readers	25/911 (3)	172/911 (19)	659/911 (72)
Overall	68/2872 (3)	743/2872 (26)	1885/2872 (66)
Completed checklists for reporting guidelines			
Authors	365/819 (45)	291/819 (36)	96/819 (12)
Reviewers	453/1142 (40)	414/1142 (36)	186/1142 (16)
Readers	340/911 (37)	394/911 (43)	117/911 (13)
Overall	1158/2872 (40)	1099/2872 (38)	399/2872 (14)

*Percentages do not sum to 100% because of missing data

We identified four existing areas where supplementary materials might be adapted to include PPI methods and data, the study flow diagram, in the research reporting guidelines, within data collection materials, and in study protocols. The most promising areas are within the study protocol and the research reporting guidelines. These findings show us that research reporting guidelines are likely to be found or accessed by only 14% of readers, but that protocols might be accessed in supplementary materials by 38% of readers. (See Figure 18)

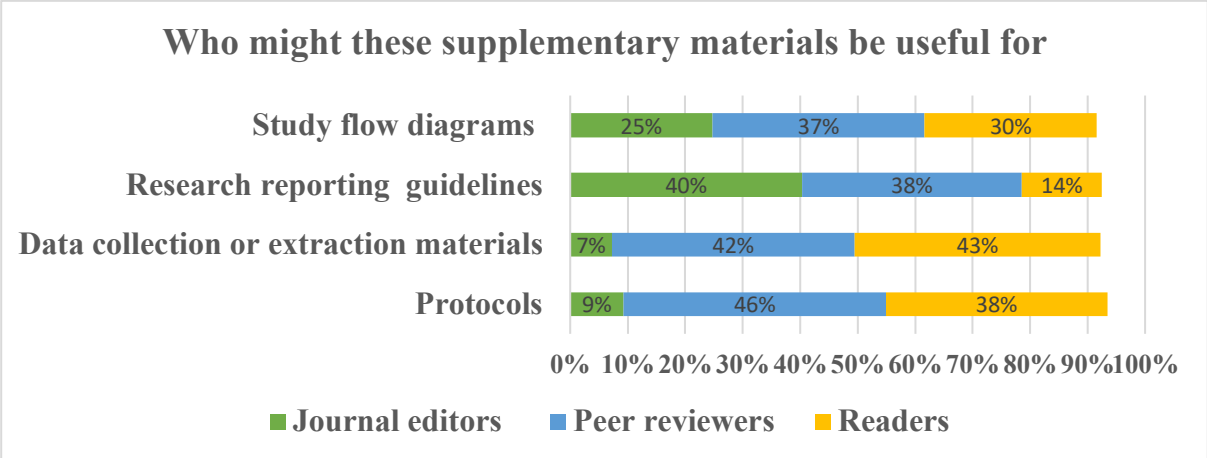


Figure 18 Views by group on the value of PPI relevant supplemental materials Open-Ended Survey Comments

Participants commented that supplementary materials could be briefer, better organized, and more accessible, and exempt from paywalls. They noted materials can become separated from a paper during downloads. Respondents from all groups commented that when existing software was part of the study, they preferred software access rather than screenshots. Some who identified as authors expressed concerns that as the volume of supplementary materials increased, the costs might be passed on as author processing fees. Other concerns were that these materials can span hundreds of pages and yet they are without peer review. Thoughts were that they could be a burden to reviewers and readers as well as a potential source of litigation for publishers and journal editors. There were no indications from the open comments that groups would welcome PPI materials or any additional methods reporting in the supplementary materials.

Points for Consideration

- Supplementary materials are free, but they can be disorganized, separated from the main article and not peer-reviewed (is this the ideal location for emergent PPI methods?)
- Additional data tables were the most common supplementary material type submitted or seen by authors, 74%; reviewers, 89%; readers, 67% and yet it is unlikely PPI methods would be stored in this location
- Publisher software is limited to what files can be displayed.
- The study protocol is the likeliest target for including P&P methods in the supplementary materials and these could contain an embedded research reporting guideline.

Section 4 | How Frequently are Research Trial Results Disseminated to Participants and in What Format? A Survey of Trialists

Objective

To survey authors of clinical trials to determine the frequency, format and perceived barriers of research dissemination including the sharing of personal and aggregated data to research participants and advocacy organisations.

Background

Dissemination is the planned process where study results and sometimes individual and aggregated data results are communicated to the stakeholders of the research.[15] One challenge is that researchers report receiving minimal guidance in how to communicate findings to participants and advocacy groups and some researchers state that patient-centred dissemination and policy orientated work may be poorly rewarded by academic institutions.[16] Traditionally, dissemination has targeted healthcare professionals, policy makers, and academics through journal publications and conference presentations, however, optimal knowledge translation depends on disseminating results to all stakeholders including patients and end-users.[17] The other area of interest is in sharing individual and aggregated data results with participants who argue that objective data about their individual responses to an intervention offers them and their clinicians the knowledge to make more informed choices about future interventions.[18] The sharing of individual study results is actively encouraged although little is known about the extent to which study results are shared with patients. Furthermore, there is no consensus on what dissemination to patients or members of the lay public means, what is the most effective

dissemination process and whether research results should be disseminated to relevant patient groups and the wider public as well as the patients who took part in the studies.[19] This study surveys authors of clinical trials to determine the frequency and format of research dissemination to research participants including the sharing of personal data with participant and the sharing of aggregated data to patient groups. In this survey we share researcher self-reported challenges, barriers and benefits in the planning and implementation of dissemination.

How Frequently and in What Format Are Research Trial Results Disseminated to Participants

The survey and nested randomized controlled trial are registered at ClinicalTrials.gov ID: NCT03021863. The research was reviewed by, and received ethics clearance through the University of Oxford Central University Research Ethics Committee MS-IDREC-C1-2013-174

Methods and Design

On 24/01/17 we surveyed first authors of clinical trials published in English in 2014/15 and indexed in PubMed. We asked Authors if they shared results with trial participants and patient groups, the format of what was shared, and how often PPI was used to determine the format, content, and extent of dissemination materials.

Study Results

Surveys were emailed to authors of 19,824 trials; 3127 responses were received (16%). Of the 3127 trials, 2690 had human participants, and 1818 enrolled individual patients. Among the 1818, 498 authors (27%) reported that they had already disseminated results to participants and another 238 (13%) planned to do so, 600 (33%) did not plan to, 176 (10%) were unsure, and 256 (14%) responded with "other" or did not answer. Of the 498

authors who had disseminated results to participants, 198 (40%) shared academic reports, 252 (51%) shared lay reports, 111 (22%) shared both, and 164 (33%) provided individualized study results (Table 18).

Table 17 Dissemination Findings

	Dissemination Findings N (%) of trials		
Type of information	**Completed=498**	**Planned n=238**	**Combined n=736**
Prepared for an academic/clinical audience	198 (40)	105 (44)	303 (41)
Full study report	56 (11)	24 (10)	80 (11)
Journal publication(s)	139 (28)	67 (28)	206 (28)
Academic summary	74 (15)	47 (20)	121 (16)
Prepared materials specifically for lay readers	252 (51)	114 (48)	366 (50)
Participants sent a lay summary	170 (34)	82 (35)	252 (34)
Lay summary posted on a website	48 (10)	39 (16)	87 (12)
Trial participants invited to attend workshop or meeting	82 (16)	23 (10)	105 (14)
Included materials for an academic/clinical audience and lay readers	111 (22)	61 (26)	172 (23)
Shared individual study results, such as outcomes, scores, or analysed data	164 (33)	49 (21)	213 (29)

**Note: authors could indicate multiple options*.

Of the 1818 trial reports, 577 authors (32%) shared or planned to share results with patients outside their trial by direct contact with charities/patient groups, 401 (22%) via informal patient communities, 845 (46%) via presentations at conferences with patient representation, 494 (27%) via mainstream media, and 708 (39%) by publishing lay

summaries online. Of the existing dissemination plans, public involvement was more frequent in those that planned dissemination than in those that did not (Table 18).

Table 18: Public involvement in the dissemination of the research

Public involvement in the dissemination |of the research	**N=1818 (%) of trial reports**			
	Completed	Planned	No PPI plan	Maybe
Interpreting study findings & potential impact of the study	183 (10)	88 (5)	1172 (65)	126 (7)
Developing the content of the materials for dissemination	178 (10)	127 (7)	1105 (61)	151 (8)
Contributing to writing or commenting on manuscript drafts	117 (6)	52 (3)	1259 (69)	122 (7)
Selecting the most appropriate dissemination method	155 (9)	140 (8)	1072 (59)	178 (10)
Presenting / sharing results with other patients or the public	211 (12)	155 (9)	998 (55)	187 (10)

**Note: percentages do not sum to 100% due to missing data.*

Relatively few authors of the 1818 trials reported that dissemination to participants and patient groups was suggested or recommended to them by institutional bodies. For example, authors report that research funders 314 [17%] suggested dissemination to trial participants, while in 252 [14%] papers, funders recommended dissemination to patient groups), and in 333 [18%] of reports the ethical review boards suggested dissemination to trial participants and 148 [8%] recommended dissemination to other patient groups (Table 18) .

Open Comments

In the open comments, Authors describe numerous barriers to dissemination that varied by the clinical context and nature of results. These include limited resources for dissemination, trouble locating participants and ethical issues about contacting them after the trial. Researchers share that participants die, move, or become incapacitated. Some

researchers worried about finding the time to explain the trial again to relatives and did not know how much to share with families. Researchers may have left the team or institution where the data were collected, and will have no access to the data. Others report data were corrupted between collection, publication and storage.

Researchers were concerned that negative findings might be premature and could distress their participants and they did not understand how to communicate the clinical results other than in research terms. They worried that media sources would twist the findings and this could be used against them professionally and hurt participants and their families. Some commented they were concerned that participants might share results prematurely on social media and by doing so confound the results in a multi-phase trial.

Points for Consideration

- Fewer than half of respondents disseminated or planned to disseminate their results to participants and only half with public facing plain language summaries.
- Motivation to disseminate materials was intrinsic to the team dynamics rather than being mandated from institutional bodies.
- Participants value information about data collected about them, and they want to understand the implications of the findings even when they are exploratory and non-conclusive.
- In online participatory trials, a participant might only communicate through the internet, and the only tangible shared asset is their data. Perhaps barriers to the sharing of individual study results could become more widespread as individual results were shared with participants only 33% of the time.

- When access to their research data and the aggregated data of others is restricted, participants can feel excluded, patronized, and used, as was found throughout chapter three in the Mind the Gap studies.
- Dissemination concerns and recommendations were added to the Delphi process for consideration in building an online participatory trail protocol.
- Participants could benefit from greater understanding about the rationale for harm in vulnerable populations and the reluctance by researchers to disclose exploratory findings as results, especially when they could needlessly generate fear, hype or false hope. Mutual understanding, collaboration, and co-production of policies for dissemination might facilitate wider, more effective dissemination of research.

After discussion, it was decided that authors could add this content to the supplementary materials and mention it in the PPI declaration if they chose to. There is no mechanism in the submission software to identify and link this content other than naming the file and pointing readers to the supplement. It was not possible with the present system for *The BMJ* to offer a dedicated DOI for the materials and the file types the publishing and reviewer system supports are limited and do not include what is needed to run live models or active software support. *The BMJ* is taking up these matters and others with the submission software developer.

Section Series Conclusion

This series of sections outlines complexities a researcher might face when writing a Patient and Public declaration, how a protocol template can meet some of these requirements and why it is desirable for a journal to mandate the PPI declaration. We found that mandating declarations increases the reporting of PPI. This helps researchers, readers, patients and clinicians understand how PPI can be used to co-produce research with non-academics and when co-production is not possible. Information gained from co-production can influence future implementation, end-user satisfaction and use in practice.

P&P reviewers review papers, grants and conduct audits with minimal guidance while reviewing the work from the perspective of the end-user and assessing the implications for implementation. P&P reviewers may lack research backgrounds and they value training in critical appraisal, receiving targeted feedback and building community. A free access online training course for P&P reviewers could fill these objectives and make it more practical or smaller journals to make use of P&P reviewers.

We found that storing PPI content only in supplementary materials limits the replication of these methods as few readers will find, download, and read them. The most widely seen and read supplementary materials are extra tables and figures, and these are unlikely containers for the PPI methods. As supplementary materials are not peer reviewed, their validity and reliability may be questionable. PPI methods uploaded as supplementary files could be linked if they contain a DOI.

It was found that although dissemination sounds like the moral and responsible option there are many contexts where dissemination is difficult or undesirable and methods to improve this process and to facilitate the secure return of data to trial participants might be addressed in the study protocol.

**The findings in this chapter were used to develop the Delphi in (chapter 7) and the planned use of these results will be to build a prototype for a participatory online trial.*

Public and Patient Involvement and Acknowledgments

Section 1:

Sarah Foster (BMJ intern) helped with data extraction. BMJ Patient and Public Reviewers Melissa Hicks and Rebecca Harmston, (co-authors) were involved with the interpretation of the results, editing and preparing the manuscript for publication and were involved with the dissemination plan for the paper which included presenting a poster at the 2017 Peer Review Congress.

Section 2: Public and patient reviewers were involved in multiple stages of the research. Three Patient and Public reviewers Andrew Demaine, Jim Elliot and Rebecca R Harmston, are co-authors on this paper we wrote from this as they were core members of the research team and substantially contributed to the development and refinement of the questionnaire, interpretation of results and manuscript revision. These three patient partners coproduced an abstract and poster of the findings with us for the 'NIHR-INVOLVE' Conference 2018 to aid dissemination of the research to academic and industry research professionals, patients, policy makers, editors and advocacy groups. We pretested the questionnaire with a further four BMJ patient and public reviewers (outside of the research team) and refined the questions based on their feedback.

Section 3: Forty-five volunteers piloted the surveys and shared valuable feedback to make the questions clear and unambiguous. These volunteers were community members, physicians, researchers, patients and teachers.

Section 4: We thank the three BMJ P&P reviewers for their comments on the survey content and editing of the manuscript as well as the 15 volunteers who pilot tested the survey to help us improve the survey questions.

Contributions

This chapter was written by Amy Price, who conceived, planned, structured and edited the document with feedback from her supervisors Professor Mike Clarke and Professor Su May Liew. The data from Scholar One used in section #3 was accessed by Dr. Sara Schroter at *The BMJ* as the level of Scholar One permissions was not available to Amy Price. The graphic in Figure 14 is used by permission from *The BMJ.*

Relevant Publications Linked to This Chapter

1. Price A, Schroter S, Snow R, et al. Frequency of reporting on patient and public involvement (PPI) in research studies published in a general medical journal: a descriptive study. *BMJ Open* 2018;8(3):e020452.
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3. Price A, Schroter S, Clarke M, McAneney H. Role of supplementary material in biomedical journal articles: surveys of authors, reviewers and readers. *BMJ Open* 2018;8(9):e021753.
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5. Richards T, Schroter S, Price A, Godlee F. Better together: patient partnership in medical journals. *BMJ* 2018;3798(September):k3798. 2. Chu L, Price A. *Partnering with Patients and the Public in Medical Research*. Stanford; 2019.

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Chapter Six | Informed Consent in Randomized Controlled Trials: An Overview of Systematic Reviews

Abstract

Background

Informed consent is how a potential participant learns about and understands the purpose, benefits, and potential risks of clinical trials and then agrees to participate in the trial. When participants and the investigators decide the participant sufficiently understands the risks and benefits of participation, the prospective participant will sign a document attesting to this, and this is the basis of a mutual contract between them. This overview will investigate what methods could improve informed consent methods in terms of delivery, comprehension, safety and data reuse.

Methods

Six databases and gray literature were searched without date or language restrictions for systematic reviews of informed consent in clinical trials design. This systematic overview of informed consent included 23 reviews from which areas of good and bad practice were identified. Informed consent strengths, weaknesses, opportunities and threats were explored through use of meta-narrative analysis.

Results

Inclusion criteria were met by 23 reviews. Confidence in the findings was assessed using CerQual, Nice-H, and CASP systematic reviews. Review quality ranged from high (n=7), medium (n=9) to low (n=3). In 12 reviews ethical compliance were not reported for primary studies. Challenges identified a lack of clarity within common language and cultures; Measures used to validate findings or assess quality of the intervention as well as the responses to the intervention were missing; Retention was variable for consent information especially in vulnerable populations with co-morbidities; Data ownership and security were concerns. Logistical needs include validated outcome measures, extra time and training for researchers and participants and the funding this would require.

Conclusions

Advances in technology and an increase in research complexity make data "containers" that house informed consent no longer fit for purpose and this creates a window for finding ways to improve informed face to face and digital consent.

PROSPERO Registration:

Amy Price, Mike Clarke, Nia Roberts, Su May Liew, Amanda Burls. Informed consent for randomized controlled trials of health care: an overview of systematic reviews . PROSPERO 2018 CRD42018085076 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018085076

Chapter Six Highlights

Meets objective 5: To identify uncertainties around informed consent and to systematically review the evidence on this to inform an online Delphi.

Challenges are:

- Develop standards to assess consent quality, how well communicated it is as measured by researchers and end-user responses
- Retention was variable for consent information especially in vulnerable populations with co-morbidities
- Data ownership, third party use, and security were uncertain risks.

Take home points: Advances in technology and research complexity make data "containers" that house informed consent no longer fit for purpose and this creates a window for finding ways to improve informed face to face and digital consent and reporting of the same.

Introduction

Informed consent is the process by which a potential participant learns about and understands the purpose, benefits, and potential risks of clinical trials and then agrees to participate in the trial. When they and the investigators decide the participant sufficiently understands the risks and benefits of participation, the prospective participant will sign a document attesting to this, and this is the basis of a mutual contract between them. This

overview will investigate what methods could improve informed consent methods in terms of delivery, comprehension, safety and data reuse.

Without accurate knowledge, decision-making is not informed. Development and delivery of informed consent materials for participation in research is part of this process. In online trials, the opportunity for face-to-face signed consent with researchers may not be an option, so we need to find other suitable alternatives to develop and deliver this information. Consent acts as a safeguard for participants and researchers that full disclosure occurred. Informed consent materials inclusive of signed participant information sheets provide a record between researcher and participant of the roles and agreements they share and adequate documentation is evidence against any false reports of coercion. People can become hardened to the importance of consent as many contracts are now online, and it is possible to click agree without reading or understanding of the contents. In a clinical trial, this habit could put a participant in the position where the consent was not informed and where the participant might not understand the intervention.

The age of comprehension that researchers are encouraged to aim for is that of a nine-year-old. According to existing research[1], only 6% of consents and participant information sheets are written below an eighth-grade level of comprehension; 54% of participants with an 8th grade level education only partially understood the consent with figures rising to 72% of partial understanding for participants with higher than 8th grade educations. Gaps in bridging knowledge and presentation need improvement. The deficits ranged from misunderstandings about risk, side-effects, adverse effects reporting, a participant's right to withdraw, confidentiality and even the purpose of the trial. This systematic overview of systematic reviews was undertaken to gather research into a single

document to identify available evidence and best practice for developing and delivering informed consent materials in clinical trials[2]. It summarizes what has been found and reported; identifies the context, methods and processes that facilitate consent; and promotes the uptake of effective strategies to improve informed consent in research and reduce the harms that might result from ineffectual informed consent.

Why it is important to do this overview

Research in this field varies in quality, scope, size, and focus, making a systematic overview a practical option[3,4]. The overview enables comparison and critical appraisal of choices made across reviews. Informed consent, data reuse, data ownership and access were overarching concerns amongst learners, during the presentation of the Stanford/BMJ/PCORI online course "*Partnering with Patients in Medical Research*"[5]. Also, standards are evolving for Findability, Accessibility, Interoperability, and Reusability (F.A.I.R) data liberation [6], shared informed participant ownership of data for data reuse [7] and appropriate methods for safe sharing of individual patient data.[8] Data hacking technology and scientific advances in artificial intelligence [9] provide the ability to classify disease using facial recognition [10]. These advances have made data "containers" no longer fit for purpose [7]. Advances and the consequences open a window to improve informed face to face and digital consent [11] and data reuse.

Research Question

What can we learn from existing systematic reviews about the best methods for developing informed consent materials for clinical trials?

Aim

To undertake a systematic overview of systematic reviews about the methods, usage and reporting of informed consent in clinical trials.

Objectives

To identify gaps for reporting informed consent in clinical trials and examples of what worked, what did not, and what is still needed to identify good practice for the development of informed consent methods.

Methods

Research for consideration

Systematic reviews and overviews published in any language that reviewed informed consent materials for clinical trials were eligible. A review could include quantitative or qualitative or mixed methods studies. Reviews of methods used in informed consent materials for clinical trials were eligible if they searched a minimum two databases, appraised the included studies, provided summary findings and included a synthesis of the data and the information retrieved[12].

Outcome measures

The outcome of interest was to examine methods of informed consent employed in clinical trials and to report the quality of the informed consent materials for participants.

Data Sources and Search Strategy

The following databases were searched from 1995 until January 2018: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) [1946-present], EMBASE (OvidSP)[1974-present], PsycINFO (OvidSP) [1967-January week 3 2018], Science Citation Index (Wed of Science Core Collection, Thomson Reuters) [1945-present], Cochrane Database of Systematic Reviews (Cochrane Library, Wiley) [Issue1 of 12, January 2018] Library, Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley)[Issue 2 of 4, April 2015], PROSPERO (https://www.crd.york.ac.uk/prospero). There were no restrictions on language or

publication status. The general search terms for MEDLINE were reviewed by the authors and a medical librarian and adapted for each database.

The PRESS checklist[13] was used to ensure inclusion of essential elements in the search strategy. IRIS AI[14], Epistemonikos[15], reference lists and search terms of reviews captured by the initial searches were searched for additional reviews. Topic experts were contacted about knowledge of other reviews. We searched Prospero for recently published reviews or overviews from existing protocols.

Public Involvement

Individuals from the Cochrane Task Exchange, Stanford Medicine X and Think Pink Bahrain co-produced the study design and were active in screening, data extraction, analysis, prioritizing what to report, and editing tasks. They are co-authors.

Screening and Selection of Reviews

All citations were screened in RAYYAN[16], a free online tool that allows the use of unlimited volunteers, tracking and blind review. For screening accuracy, retrieved citations were screened by one author (AP) and then rescreened by her four weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[17]. A random sample of 6% of titles and abstracts were double screened (JS, LV). Full papers were retrieved for articles that appeared eligible or potentially eligible based on their title and abstract, and for a 1% random sample of those judged to be ineligible to check for the correct exclusion[17] (AP, JS, LV). Reviewers were not blinded to author, institution, or journal.

Paper Retrieval

Full papers were downloaded to a shared folder and de-duplicated in Mendeley[18], where overview authors could write and share notes, add questions, and additional data. Two authors (AP, JS) screened the retrieved full papers independently to match them against eligibility criteria. Papers were categorized as include, exclude or unsure. Papers classified as unsure were discussed and agreement at all stages was reached by consensus of three authors.

Data extracted from included reviews

Three review authors (AP, JS, LV) independently extracted key data for included reviews, using a data extraction form in EPPI reviewer[19] that was piloted on a small sample of reviews. Data on informed consent materials used in clinical trials were extracted, covering exploration of roles, reporting and methods used. All findings were reviewed and discussed by members of the author team until consensus was reached.

Review Reporting Completeness Assessment

The CASP[20] checklists for systematic reviews[21] were used as a preliminary screening tool when assessing systematic reviews for eligibility. The first three questions are general and can be used to include or exclude a review. The NICE Quality Appraisal Guidelines for Qualitative Studies Appendix-H form[22] was used to determine whether the research question(s) and theory underpinning reviews were appropriate for the outcomes sought. The following domains were included when assessing quality: aims, methodology, search quality, data collection, data analysis, reflexivity, ethical considerations, findings, and research contributions. For quantitative systematic reviews AMSTAR[23] was used to evaluate review reporting quality. Each review was searched to determine if Benefits, Risks, Alternatives and do Nothing (BRAN) were reported[24]. In addition, the reviews

were searched for inclusion of a registered protocol, the PRISMA[25] Flow chart and whether risk of bias and conflict of interest were reported.

Risk of Bias

Confidence in the Evidence from Reviews of Qualitative Research (CERQual)[26 27] was used to summarize confidence in the findings of the reviews. This is based on four components: limitations of methodology, relevance to the research question, coherence, and the adequacy of the data presented. CerQual enables ratings of "high", "medium", "low" and "very low" (although this final rating was not needed because such reviews were not eligible). The starting point of 'high confidence' reflects that each review finding is a reasonable representation of the question of interest and is downgraded if there are factors that would weaken this assumption[26]. After assessing all four components, authors agreed on overall confidence in each review finding and the relevance to the Informed Consent Overview.

Composite Reporting Completeness and Bias Assessment Figure

CASP, AMSTAR, NICE and CERQual (methodology, relevance, coherence, adequacy) numbers/scores were converted to a numerical scale from 1-3, (1=low, 1.5=medium low, 2= medium, 2.5= medium high, 3=high) to make what was reported and bias assessment visible at a glance. Mixed methods studies were assessed with AMSTAR and NICE and these were averaged for one score. The lowest minimum that could be scored across all measures was six and the highest achievable score was eighteen. This method was used in Price and colleagues 2017[28] Reporting completeness and bias assessment is not sufficient to assess the value of the review as the review may be for scoping purposes, may be narrative, methods based, or a review that assesses implementation or the use of

frameworks. Such reviews may "score" poorly with a reporting quality tool, however they may still be useful for the planning, replication and implementation of research.

Other Items Reported

Consent ethics, media used, consent administered by, participant feedback method and Patient and Public involvement were reported in tables, figures, and narratives.

Thematic Analysis

A strength, weakness, opportunity, and threat (SWOT) framework was used to analyse the review findings and classify the data into themes for coding. The SWOT makes it possible to identify and agree on methods with positive or negative effect on understanding consent materials in clinical trials and to identify research gaps not obvious in a quantitative format. The SWOT approach is used in healthcare research[29,30] including systematic overviews[28] to help teams analyse data individually and then reach consensus on how to present their findings. Coding is individual without access to any other coder's findings. Following coding completion, the findings are reviewed by all coders, agreed, and written up. An additional member of the research team is available to mediate any code that is not reconciled and agreed. Because writing up these findings may be interpreted as subjective, two additional coders not involved in the initial coding were reserved to agree the coding and the interpretations. They served as a fresh set of eyes.

Results

Search Report

Figure 19 uses a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to outline the process of study selection [23]. Our search of 6 databases yielded a total of 3841 records.

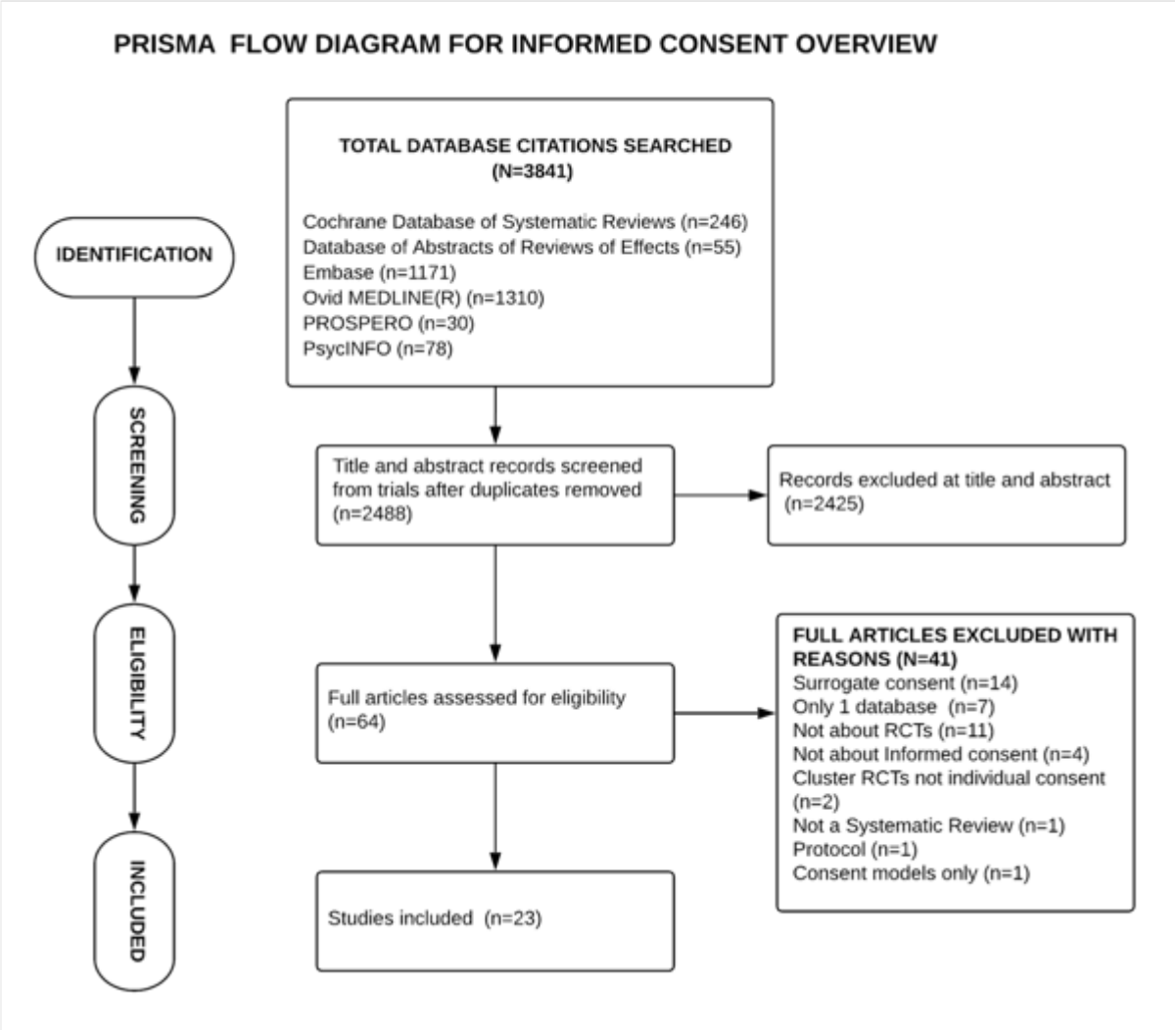


Figure 19: Diagram for Informed Consent Overview PRISMA

Title and Abstract Screening

After de-duplication, 2488 records remained. To improve screening accuracy, retrieved citations were screened by one author (AP) and then rescreened by (AP and AB) 4 weeks later. This method was described in a published review of systematic reviews of treatment for intracranial aneurysms[13]. A random sample of 6% of titles and abstracts were double screened by (AP and LV) and for a 1% random sample of those judged to be ineligible to check for correct exclusion. Full papers were retrieved for articles that appeared eligible or potentially eligible on the basis of their title and abstract. Reviewers were not blinded to author, institution, or journal. The agreement was 100% before discussion and 2425

records were excluded leaving (n=64) potentially eligible articles for full-text screening.

Full-Text Screening

Three authors, (AB, JS and AP) independently checked the full text of (n=64) articles for eligibility, (n=41) of which were excluded. Reasons for exclusion were; surrogate consent (n=14), used only one database (n=7), not about RCTs (n=11), not about informed consent (n=4), cluster RCTs rather than individual consent (n=2), protocol (n=1), models of consent (n=1) and not a systematic review (n=1). (Appendices, Table-S1 Excluded Studies). Twenty-three reviews met inclusion criteria for data extraction and analysis. Interrater agreement prior to discussion was considered to be very good Kappa= 0.938 (SE = 0.031; consensus was reached by discussion.

Table of Included Reviews

Table 19 shows the first author, year of publication, citation number, number of included studies, research question focus, findings and funding support type for each included review.

Table 19 Table of Included Reviews

Author, year Country (n=studies)	Focus of review	Finding(s)	Funds*
Afolabi 2014 (n=29)[31] Gambia	Comprehension African settings	Tools to define and measure comprehension need to be built with the community to be accurate, sensitive to cultural needs and to build trust	Multi
Cohn 2007 (n=23)[32] USA	Improved comprehension	Deficiencies exist in comprehension measuring/assessment tools	NR
Edwards 1998 (n=14)[33] UK	Best consent method Clinical Trials	Minimal evidence that information improves understanding and reduces anxiety	Gov
Farrell 2014(n=29)[34] UK	Audio visual media	Adjusting for reading age improved recall, satisfaction or anxiety	Acad
Fitzpatrick 2016 (n=56) [35] Australia	Indigenous community methods	Tribal elders to decide approach for indigenous communities	Multi
Flory 2004 (n=30)[36] USA	Comprehension of interventions	Multimedia enhanced consent understanding but not as much as using one-to-one educators	Gov

Gillies 2015 (n=2)[37] Scotland	Decision aids within clinical trials	There was insufficient evidence to compare the efficacy of decision aids to standard consent forms	NGO
Gobat 2015 (n=52)[38] Wales	Consent perceptions of critically ill	Third-party, deferred, and waived consent models are acceptable to stakeholders but gaps in methods for use in emergency research settings were found	Gov
Johnson 2016 (n=48)[39] USA	Consent in alternative high schools	Active consent was most effectual	Multi
Kao 2017 (n=9) [40] Australia	Comprehension in Clinical Trials	Methodical limitations for use with cancer patients, consent ability could change across time and	NR
Kinnerslee 2013 (n=65) [41] UK	Interventions to Promote Consent	Enhanced consent improves patient knowledge	Multi
Kirkby 2012 (n=14)[42] UK	Participant preferences	Participants prefer tailored/individual consent information	Gov
Montalvo 2014 (n=26) [43] USA	Research comprehension	Viable consent requires working within health literacy, reading levels, culture	NR
Moore 2017 (n=26)[44] USA	Mobile research kit app methods	Unregulated settings, standards needed	NR
Moreira 2016 (n=19)[45] Canada	Comprehension and recall in adult dental patients	Patients report understanding yet have limited comprehension and recall	NR
Mukherjee 2016 (n=80)[46] USA	Implementation for adult dental care	Substantial knowledge gaps exist between the understanding and implementation of consent procedures in adult dental care	Gov
Nievaard 2004 (n=30)[47] Netherlands	Factors that influence trial decisions	Informed consent decisions are influenced by uncertainty, randomization, placebo, the information methods used and study quality	NR
Nishimura 2013 (n=39)[48] USA	Comprehension by intervention	Improves with enhanced consent forms and extended discussion (included meta-analysis with (n=22) of these studies	Multi
Palmer 2012 (n=20)[49] USA	Multimedia aids and comprehension	Multimedia was effective across populations but not with consistent results	Gov
Schellings 2005 (n=50)[50] Netherlands	Randomized consent design	Random consent designs seldom used and quality is inconsistent: Trials with incomplete-double design consent associated with significantly higher rates of non-compliance	NR
Soininen 2014 (n=32)[51] Finland	Participant Perceptions of coercion	Coercion perceived when eligibility was manipulated, during recruitment, and through flawed data collection	Multi
Sugarman 1998 (n=99)[52] USA	Understanding in elderly	Consent methods might need to be adapted to accommodate for declining and impaired comprehension	Multi
Tam 2015 (n=103).[53] Vietnam	Longitudinal comprehension	The proportion of participants who understood informed consent had not increased over 30 years.	NR

** Type of funding is classified as multiple (Multi), Non-governmental organization (NGO) governmental (Gov), academic (Acad), or not reported (NR).*

The total number of studies for the 23 reviews was 895 (range: 2-103; mean: 39; median: 30). In (n=16/23) reviews the final search was updated two years or less before publication.

The number of participants in studies and the use, reporting and definition of grey literature was variable and not consistently quantified. Multiple funders were reported in (n=7/23) reviews; (n=6/23) reported government funding; (n=1/23) NGO funding; and (n=1/23) for academic funding; no review reported being researcher funded; and (n=8/23) reviews did not report funding sources. It was not reported if academic, private/public foundations, government departments or researchers were indirectly funded, employed or working on behalf of industry partners. No review sought crowdfunding or was fully participant led and funded (Table 1). The general focus of the reviews as reported by the authors was to (n=11/23) explore consent relationships, (n=5/23) examined what works in different settings, (n=5/23) reviews scoped the literature to date, and (n=2/23) reviews were to review and describe aspects of consent.

Reporting Completeness and Risk of Bias for Included Reviews

Research transparency in reporting may reduce research waste by leading to replicable research as it is challenging to learn from what remains unreported. Review protocols were registered and reported in (n=4/23) reviews [54–57]. A Prisma flow chart was included in (n=14/23) reviews[31,39,42,48,51,54–62]. The risk of bias in primary studies was reported in (n=6/23) Farrell et al. 2014; Fitzpatrick et al. 2016; Moreira et al. 2016; Gobat et al. 2015; Gillies et al. 2015; Kao et al. 2017; reviews and conflicts of interest declarations were recorded for primary studies in (n=9/23) reviews. [27,28,30–34,39,40]

Further completeness of reporting can be observed in Figure 20 and consists of composites of CASP for systematic reviews, AMSTAR for reporting quantitative reviews, The NICE Quality Appraisal Guidelines for Qualitative Studies Appendix-H form[22] Confidence in the Evidence from Reviews of Qualitative Research (CERQual [26,27] was used to summarize confidence in the findings of the reviews based on four components: limitations of methodology, relevance to the research question, coherence, and the adequacy of the data presented. The term completeness is used rather than quality as a scoping review or a review on frameworks would not be expected to report on some areas and that lack of reporting is not indicative of the review quality.

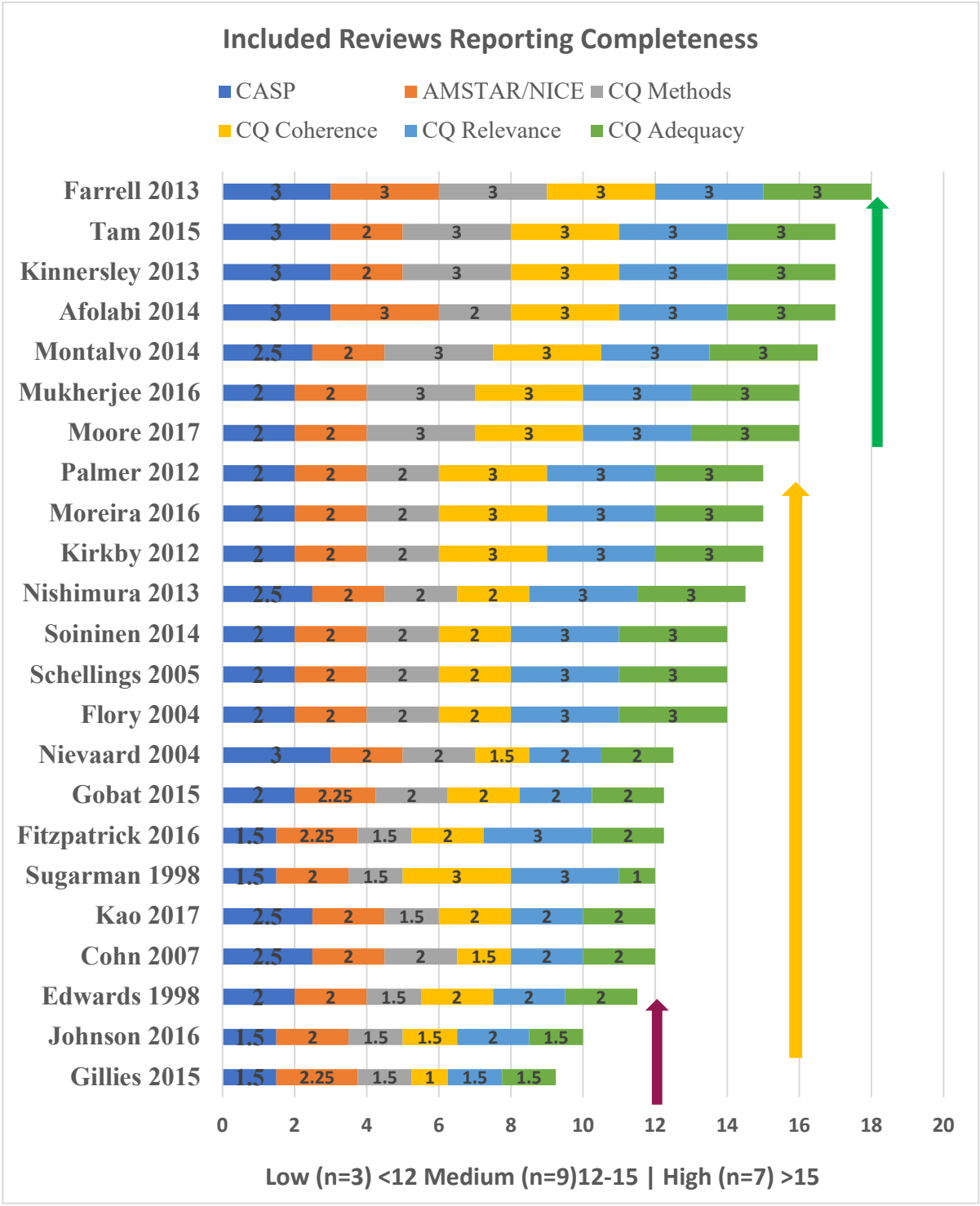


Figure 20 Included reviews and their reporting completeness

In included reviews, consent was administered by a principal investigator in (N=7), by study personnel or educators (n=11) and online self-administered in (n=4) reviews. In (n=10) reviews it was not reported who administered consent, (n=2) reviews were clinician consented, (n=1) was peer to peer consented (n=1) was parent administered.

The media for consent used was reported in reviews as text (n=15), face to face consent (n=14), interactive (n=13) multimedia (n=11) and digital (n=9) Biometric, multi-trial permissions and downloadable consent was reported in (n=1) reviews each and (n=7) reviews did not specify the consent medium. There was not sufficient information or clear enough terms to determine the number of primary study consents that contained internet only options for informed consent.

Table 20: Ethics compliance reporting in informed consent

Where reviews reported the ethics compliance in primary studies	Number of reviews
Ethics were not reported	12
Described risks and benefits	10
Description of research	9
States participation is voluntary	6
Therapeutic misconceptions	6
Describes how to withdraw from a study	4
Withdraw at any time but data retained	4
Alternatives to Participation	3
Compensation	3
Ownership and/or 3rd party data usage	3
Contact for PI listed	2
Contact for IRB listed	2

Third party data reuse was queried in (n=3/23) [31] [59] [44] reviews. Only one study [39] reports the use of Patient and Public Involvement methods to conduct the review, although (n=2/23) other reviews suggested community involvement could improve the informed consent process [31] [59]. The reviews were searched to determine if Benefits and Risks (n=10/23), Alternatives (n=3/23) and doing Nothing (n=6/23) (BRAN) [24] were reported for informed consent. In (n=12/23) reviews ethics were not reported. Therapeutic misconceptions were reviewed and then reported in (n=6/23) reviews (Table 20).

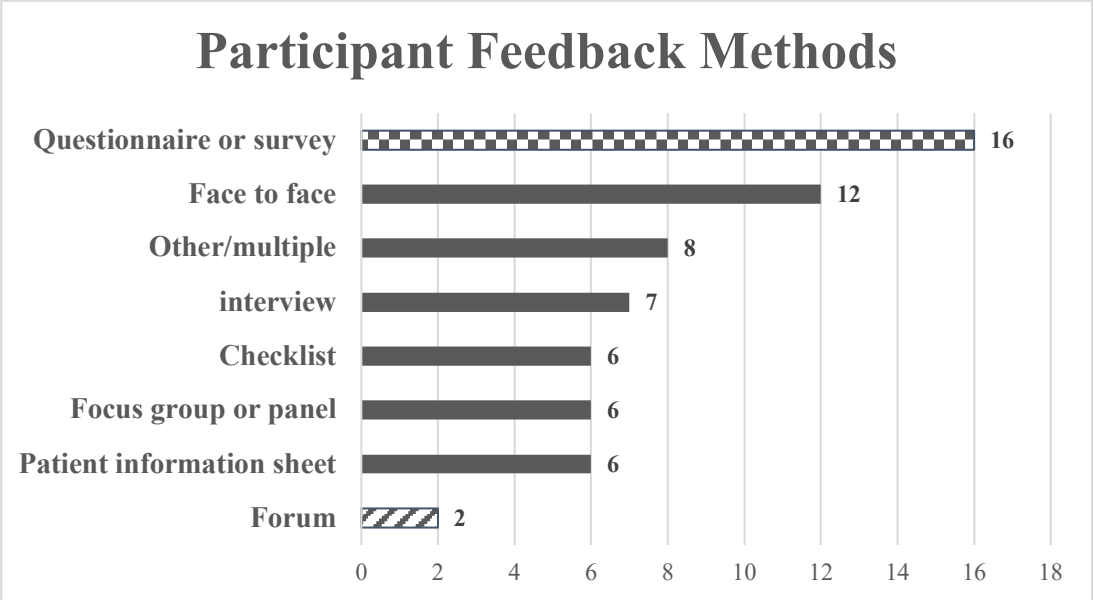


Figure 21: Participant feedback methods

Multiple participant feedback methods were reported with questionnaires being the most common form of feedback (n=16/23) and forums as the least (n= 2/23) (Figure 21).

Table 21: What consent aspects the reviews reported

What Areas Reviews Reported On	Number of Reviews
Understanding of consent	22
User satisfaction with consent	15
Consent Anxiety	15
Placebo understanding	11
Randomization	11
Coercion	9
Knowledge testing	8
Reported the number of times or participants that needed help with understanding consent	5
How many times consent materials accessed	2
Time to complete consent	2
Consent for reuse of data	2
Links about consent clicked	1

A majority of reviews (n=22/23) gathered data on understanding, satisfaction (n=15/23) and anxiety (n=15/23) along with understanding placebo (n=11/23), randomization (n=11/23) and coercion (n=9/23) There was overlap in included reviews where authors

referenced the same primary studies and cited other reviews containing these studies in their introductions and conclusions. This might be problematic for interpreting the effect size of a result across findings. However, there was a basic agreement in the interpretation of the same content. The factors that would be measurable in online consent were seldom reported, such as frequency of consent material access (n=2/23) consent for data reuse (n=3/23) and consent information links clicked (n=1/23) (Table 21).

Themes and SWOT Framework

The themes contributing to the strength, weakness, opportunity, and threat (SWOT) analysis are comprehension, methods, ethics, data reuse, recommendations, limitations and dangers (Figure 22).

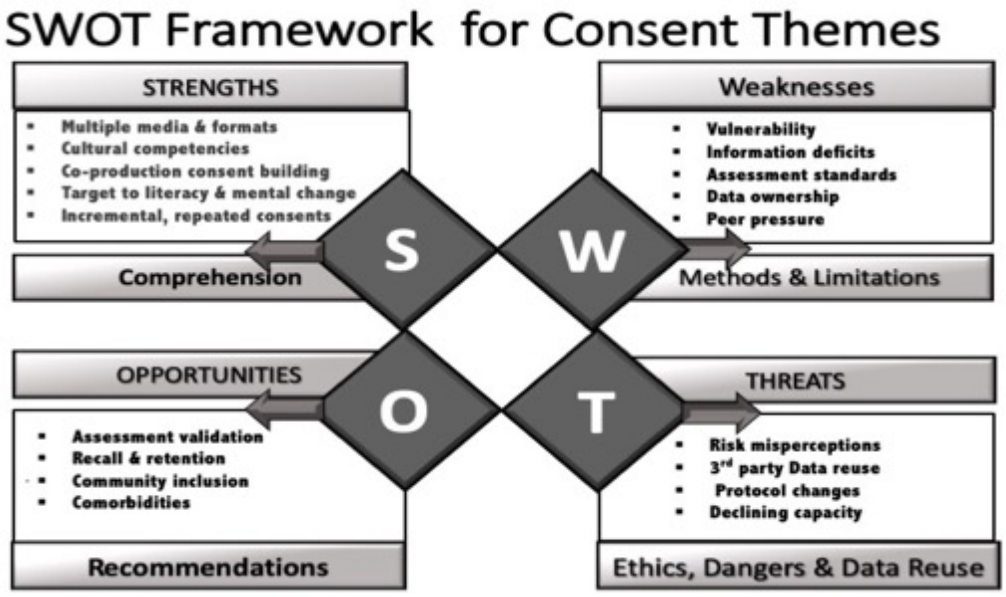


Figure 22: SWOT Framework

The themes were individually coded and aggregated by AP and JS. The codes were then further refined by LV,MM, and UG and agreed by all coders. Elements of the SWOT are applied to individual themes . For example, in coding the themes of danger and limitations, strengths were not found. The total number of codes was 293. The number of codes per review and by theme are seen in Figure 23.

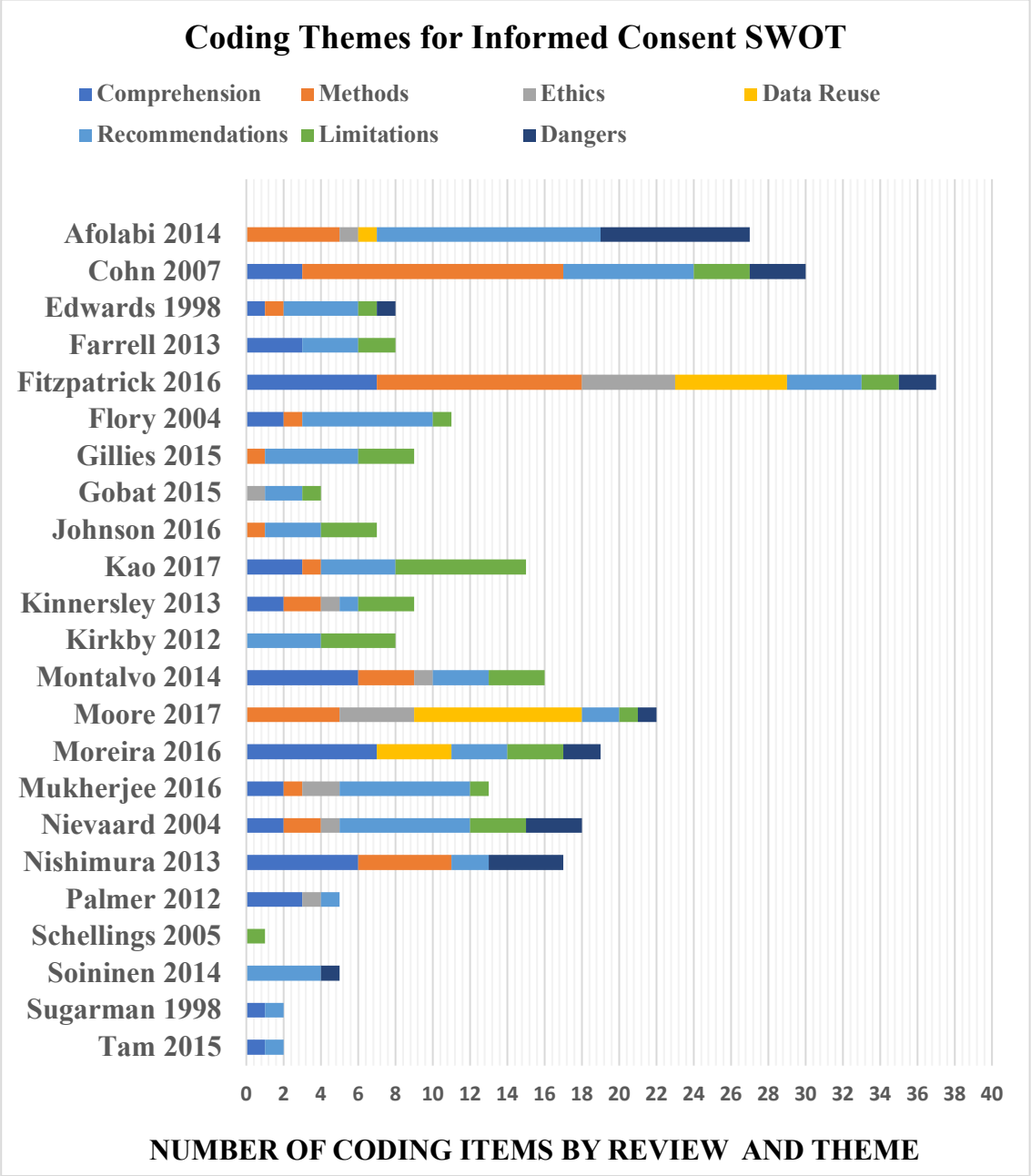


Figure 23: Coding themes for informed consent

Comprehension Theme

Knowledge, understanding, retention, cultural variance, the use of varied media approaches, and informed consent strategies were encompassed in this theme. Information in consent is optimally presented with sufficient information so the risk is understood and retained, but not so much that the consent forms cause anxiety or information

overload.[33]Comprehension levels were compounded by factors such as education level, disease state, age, health literacy, culture, and consent presentation.[40,43,48,49,]

Strengths

Review authors suggest that comprehension was enhanced when media was targeted to participant reading age as well as presented with a comprehension assessment multiple times especially during longer studies where mental status might change.[43] Using oral and written consents together improved understanding.[33,34] Comprehension was associated with multiple opportunities offered over time to interact with the written or media consent and the research staff [35] No single strategy was consistently associated with improved comprehension.[32]Multimedia and enhanced consent were found to improve both retention and recall [32,34] [36]Multiple formats using tables, slide presentations, simulations, auditory presentations, discussion and multimedia improved engagement and comprehension, especially when used in conjunction with one to one interactive discussion with research staff .[32,43,47,48] Informed consent when combined with shared decision making and co-production can orientate clinicians to face the informed choice process as an opportunity for teaching participants how to weigh the risks and benefits for the current and future health care decisions and potentially increase health literacy and relationships with clinicians and their patients or trial participants.

Weaknesses

Medical jargon presented barriers [35,43] as would be expected. However, this challenge was multiplied when working with translators in low-resource settings where translators had to decipher jargon, translate content so it was culturally acceptable and attend to end-users. Juggling these complex tasks presented multiple opportunities for misunderstanding and assumptions.[31]When comprehension abilities shift so consent can no longer be “informed”

participants should be given a choice about who should consent on their behalf with the option for a proxy decision maker even when patients are conscious.[38]

Opportunities

No single strategy was consistently associated with improved comprehension.[32] and results for enhanced and multimedia consent were mixed, although Farrell, Flory, and Cohn [32,34,36] report multimedia and enhanced consent can improve both retention and recall. Using multiple formats like tables, slide presentations, simulations, auditory presentations, discussion and multimedia improved engagement and comprehension, especially when used in conjunction with one to one interactive discussion with research staff .[32,41,43,47,48] Importantly, it was suggested that consent is a communication process and this process of building consent should include the community.[31]

Threats

Multiple systematic reviews found that tools used to measure and define comprehension were not standardized and that therapeutic misperceptions were common, specifically concerning receiving treatment versus participation in an experimental intervention.[31,41,43,47,49]

Methods Theme

In this theme strengths, weaknesses, opportunities and threats are reported with the aim of providing practical information to improve informed consent methods

Strengths

The use of simple print media and a consent educator together improved comprehension [32]Initial consent with video achieved comprehension in 74%. Addition of the consent educator yielded 90% comprehension. In one primary study, cited by Nievard et. al. 2004 [47] only 44 of the candidates wanted to participate in the trial when randomization was

raised however the number of participants rose to 68 when extra information on randomization was provided by trial staff. About one-third of mobile apps surveyed (9/26, 35%) have already implemented summative evaluations to test participants' understanding of key concepts contained in the consent. [44]

Weaknesses

Afolabi notes time intervals between the informed consent process and the assessment of comprehension may occur more than 14 months after trial completion, in addition, there was insufficient information about the assessments in order to determine their validity. The use of close-ended questionnaires allows respondents to guess the answers or provide socially acceptable responses. Another key point is that the "performance" of participants was measured but the communication skills of the researchers were not queried. [31]

"*This may represent an asymmetry, where researchers ask why participants do not comprehend' but do not ask why are we not good at explaining crucial information to our participants?"* (Afolabi et al)

Single encounters about participation in a trial may be overwhelming. Research information spaced over multiple encounters with sufficient time to review research information and address participant questions could enhance understanding, comprehension and retention.[35] In addition, there is a need to understand and refine the focus of complex information, with attention to consumer perspectives. [40] MMSE and MacCAT (mental status testing tools) are validated capacity assessment tools but they are time-consuming to use and insufficient to determine the degree of participant consent capacity.[46]

One challenge was that when broad consent was sought, participants did not realize the implications of broad consent. It is essential to establish ethics committees with

Indigenous members to monitor and approve future medical research projects because there is little protection in national and international law about genetic sampling protecting people.[35]

Opportunity

The use of mobile platforms is increasing and provides opportunities for multiple types and volume of data collection within a highly scalable, delocalized framework.[44] Tiered and broad consent might be written into the protocol and obtained for future research in local, multi-site, and in remote online research.[35,44] Due diligence is even more important for extended, longitudinal research.[35] and where data reuse is anticipated by third parties. Guidance needs to be clear, transparent and informed as opposed to a checklist or waiver where the implications and risks are not clear to participants [35,44] Another area for consideration is that aged participants were reported as not specifically consenting but deferring to their perceived wishes of the physician.[32]

Consent information and interpreters need to be provided in the participants language of preference.[35] It is suggested that the integration of tables, clearly defined and understood symbols and visual aids might aid comprehension. Participant self-reports and forced answer questionnaires produced falsely increased perceptions of clinical trial consent comprehension specifically related to trial aims, eligibility to participate, risk to the participant, and compensation for an injury, when compared to vignette or narrative measurements of comprehension.[32]

Using continuous assessment as a formative evaluation provides opportunity to enhance participant understanding when correct information about the study is provided when incorrect answers are given by using a test, retest strategy.[35] Informed consent requires the assessment of health literacy, reading level, and comprehension of research participants

using validated assessment tools and methods.[43] Consent could be integrated with advance care planning and shared decision making, to address susceptibility to declining capacity.[46]

Threats

The standards used to measure comprehension and retention are inconsistent in quality and measurement. For example, participant response but not consent content was evaluated, and measurement of the quality of the researcher responses to participants was not captured. Also, time to recall or measure of comprehension was measured retroactively and on occasion with extensive delays of beyond a year, at which point, memory would degrade. Review authors point to these factors as confounders for evaluating comprehension, retention and recall.[32,40,43]

Limitations and Dangers to Informed Consent

In this theme, reporting strengths and opportunities are not possible as solutions were not available in the coded data. For coherence, we combined areas of weakness and threats.

Participants feared being denied medical care should they leave a study. In low resource settings cultural pressure can be used to enhance enrollment[31] The review by Afolabi cites studies where 51% of participants understood study risk and 31% understood confidentiality, participants did not understand how or where their medical records were stored. The distinctions between research participation and seeking medical care were blurred.

For indigenous people, English may be the second, third, or fourth language making it difficult for them to comprehend the "foreseeable risks" to which they are consenting.[35] Some languages do not have standardized writing formats, making the instructions to

write informed consent in a participant's native tongue unrealistic. Despite regulatory scrutiny, deficiencies still exist in participant comprehension, and there are inconsistencies in comprehension measures and assessment. [32]One review stated that multimedia interventions might be useful as a way of standardizing disclosure and that even if multimedia interventions do not improve understanding, at least all research participants in a study are exposed to "required information".[36] Coders classified this as a threat or danger since exposure is no substitute for comprehension and would make any "standardization" meaningless. Kao et al. note that when a trial is the only treatment option, hope for extending survival may result in a patient ignoring the experimental nature of the clinical trial or the burden of participation.[40] Also, the patient or guardian comprehension of the informed consent process may be incomplete and violate a minor participant's right to informed consent.[45]

Guidelines for broad consent of participants for future research are unclear and leave the future use of data open to the interpretation by the researchers, which historically, has not resulted in an ethical solution. [32]A clinician or researcher is not always a disinterested stakeholder, the project may be his or her research, or there is a financial allowance attached to the inclusion of participants in a sponsored trial.[47] The knowledge that Phase I studies are designed to test only safety and often use dosages too low for therapeutic effect was not conveyed to participants and clinicians were reported as believing that this would benefit their patients.[32]

Data Reuse

In data reuse, the strengths, weaknesses, opportunities and threats are intertwined with a strong emphasis on transparency in sharing and the risks of data misuse by third parties.

Mobile research can simplify the return of data and results to participants, although the risk of safely returning data is a concern.[44]

In the Human Genome Diversity Project, the methods of data collection use and distribution were considered to be disrespectful to the cultural values of Indigenous people.[35]

"*Beyond consent, the issue of ownership of research findings requires consideration. With advances in biotechnology, there are implications about intellectual property rights, where companies are patenting genetic material of research participants for commercial value"* Fitzpatrick [35]

Identification of ownership of data is critical. For example, in the USA, blood samples were collected for diabetes research in 1990, and these samples were re-used over subsequent years without the community's knowledge. They were using the tribe's genetic material to examine links to schizophrenia as well as conducting other studies which the tribes felt questioned their sovereignty.[35]

Moore et all outlines these useful areas of disclosure.[44]

"Required Disclosure" *includes informing participants of possible sharing of data with US federal agencies, such as the US Department of Health and Human Services, and the institutional review board (IRB) or other ethics committee (J).*

*"**Commercial resale of data"** addresses whether the participant is informed about the possibility that the data they have donated for research may be sold to third parties for advertising or other commercial endeavors; where disclosures are found; as well as how they will be made available*

"Open data sharing for scientific discovery" *to describe whether the research app has any data sharing outside the primary investigator.*

" Where and to whom consent will apply" *for example, what kind of data sharing the participant may consent to: with researchers within the institution of the primary research, with researchers at other institutions, or with qualified researchers worldwide including cross-border data transfer.*

Because of the diversity and volume of data collected, participants are potentially more easily identifiable. It may be impossible to de-identify an individual's mobile phone data, the standard way of protecting personal privacy in research. Further, a number of the apps surveyed use a backend data collection service other than the primary research sponsor thus providing both a security risk and an economical solution for hosting and storing large amounts of collected data.[44] The use of third parties can increase the risk of hacking and data collected through app-mediated research is collected in the context of a particular disease or condition, such as Parkinson Disease, Melanoma, Autism, or Cardiomyopathy, potentially compromising a participant's confidentiality through reidentification. The multitude of potential mishandling of data makes a strong case for participants to be informed of these possibilities.[44]

Recommendations

Recommendations focus on how to manage complex information, language and information. Montalvo et al. assert informed consent requires the assessment of health literacy, reading level, and comprehension of research participants using validated assessment tools and methods.[43] There is a need to understand and refine the focus of complex information, with attention to individual and community perspectives.[31,35,40] including the perspectives of students, nurses, and researchers in alternative high schools who face participation challenges and exclusions when active consent is used .[39] In addition, placebo arms produced barriers to participation when placebo interventions was described as being 'no treatment' but responded more positively when randomization and placebo were explained clearly.[32,43,47]

When patients are recruited to clinical trials soon after diagnosis, or as a result of disease progression they may be unprepared to deal with complex information about trial

treatments, processes and procedures and could need additional time to clarify questions and concerns regarding trial participation. Preferably this could take place across several clinical visits in the presence of family while explaining the clinical trial and then allowed to decide about informed consent together as this has positively influenced participation.[40,47]

Farell suggests that the development of core outcome sets (sets of endpoints reported as a minimum in all trials) for informed consent could help by ensuring that the same outcomes be consistently reported with standardized measures.[34] Future studies could focus on decisional comfort or regret, along with participants' physical or psychological distress as key variables for the development of effective consent interventions[40] Flory et al. recommends a randomized controlled trial of test-to-train feedback interventions meant to avoid the rote-memorization methodological problem. Researchers also suggest that unrealistic consent simulations are impractical measurement tools.[36] Electronic information may be one way to address different information needs by offering access to varying levels of information.[42]

Discussion

This systematic overview found 1/3 of reviews on informed consent were unfunded. The qualitative reporting was consistent with the quantitative findings, all of which pointed to gaps in technology, methods and reporting tools and participant preferences. It was surprising that review information from tribal networks[31,32,35] is consistent with what other countries with high technology use in research are grappling with. Data reuse (Moore and Fitzpatrick) and declining cognition or disease states (Montalvo) continue to be a concern and shared decision making and co-production are emergent concepts that may be helpful

but are not yet accepted general methods.[32,37,44] Even in multimedia testing, the quality of the media was not considered, and yet participants were measured on their ability to recall and retain informed consent information.[32,35,43] The overview was intended to inform future study on ways to translate the requirements of informed consent in a paper-based context to one where documentation is electronic. The disadvantages are that click through without reading is problematic but could be mitigated by comprehension questions. The advantages are easy linked recall of materials, and the opportunity to provide in-depth explanations of terms and procedures used that participants could access as desired on an as preferred basis. Interactive forms and media might be useful as tools to improve participant understanding and better document their comprehension and consent. There are many levels of risk and baseline comprehension amongst participants and interventions. This research adds knowledge of the contexts where electronic informed consent might be used and the rationale for face to face consent when needed. It may also be that studies could benefit from a hybrid method. Interactive online forms and media might be built by partnering with patients and the public to better understand and implement informed consent that balances time and resources while providing fully informed consent.

Limitations of this Overview

The overview shares the limitations of the reviewed research. Standards for measuring and reporting informed consent are inconsistent with heterogeneous information. It was found that participant knowledge skills were measured but not the research staff's ability to deliver that information. There is representation from African nations and other parts of the world but no reviews originated from India or China where 2.8 billion of the 7.6 billion of the world's populations reside. Internet technology, mobile phone research usage and data sharing are progressing rapidly within multiple fields, and it is possible that

methods, systems and behaviors could change, and these changes may produce significant changes that are not reported due to the time it takes a review to be completed.

Conclusions

The information in this review is useful for seeing the state of play for informed consent, but there are many inconsistencies. For example, many review authors suggest shared decision making and community involvement but only one review, Johnson et.al reported implementing Patient and Public involvement in the review they authored.[39] Many of the aims and intentions of informed consent remain unfulfilled. Gaps remain between understanding and presentation. The deficits have varied only slightly over the last 30 years, even though literacy has dramatically increased (Tam et al., 2015).[53] These deficits or gaps ranged from misunderstandings about risk, side-effects, adverse effects reporting, a participant's right to withdraw, confidentiality and even the purpose of the trial.

This systematic overview of systematic reviews was undertaken to gather research into a single document to identify available evidence and best practice for developing and delivering informed consent materials in clinical trials[2]. We need to identify the context, methods and processes that facilitate consent; and promote the uptake of effective strategies to improve informed consent in research to reduce the harms might result from ineffectual informed consent. We recommend shared ownership of data for data reuse [7] and appropriate methods for the safe sharing of individual patient data.[8] We advocate for transparency and full disclosure concerning the technology and scientific advances in artificial intelligence in terms of data scraping used in health research.[9] We acknowledge that classification of disease by facial recognition[10] tied to personal health information have made data "containers" no longer fit for purpose[7] and that this creates a window for

finding ways to improve informed face to face and digital consent[11] and responsible FAIR data reuse.[6]

Contributions

This chapter was written by Amy Price, who conceived, planned, structured and edited the document with feedback from her supervisors Professor Mike Clarke and Professor Su May Liew and from Professor Amanda Burls who also extracted data. Julie Sprakel, Michel Mittelman, Urvi Gupta, Lenny Vasanthan, co-produced the coding. All authors will contribute to the published manuscript. I would also like to thank Task Exchange volunteer Ingeborg van Lubeek translated the German language review for us.

Relevant Projects Linked to This Research

1. The Delphi in the next chapter (8) made use of this evidence to determine how and what questions to develop concerning informed consent for online trials.
2. The research in this chapter will be published as a systematic overview and is currently in review
3. A collaboration with HUGO health, Yale and Stanford University to develop an intelligent consent application that gives participants control over their data for use in ongoing trials
4. Methods training for Stanford University Publishing School and Summer Program

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Chapter Seven | Protocol Lab for Online Trials Delphi (PLOT-D)

Abstract

Background

Participatory clinical trials conducted online are growing in numbers without a specific research reporting framework to guide the building of protocols or development of best methods. This study aimed to find consensus on which core items to include when building a protocol for or reporting online participatory trials.

Methods

The preparation to inform the consensus process consisted of writing two systematic reviews of reviews of the literature, a qualitative social media analysis of user perspectives of online trials, an analysis of methods and practice used for online trials and surveys on dissemination, supplementary material usage and an analysis of the current state of the publication of public involvement statements in The BMJ. The Delphi process consisted of two rounds of meetings online and consultation with an advisory group

Results

The Delphi participants represented three stakeholder groups. The numbers of participants completing the two rounds were 415 and 385 respectively. 57 items were presented with consensus of 19 items in Round-1 and 7 items in Round-2. Consensus was reached for 26 of 57 items.

Conclusions

Consensus was established across stakeholder groups and with minimal effect on the methods of information presentation. Interest was high and consensus was sufficient for the development of a research reporting guideline and a multi-use customizable protocol template.

Ethics Registration in compliance with University of Oxford, CUREC # MSD IDREC-C1-2013-174 and R58550/RE001.
Protocol Registration: Clinicaltrials.gov registrations with nested studies NCT03498690 and NCT03498690 and the SWAT Repository

Chapter Seven Highlights

Meets objective 6 To conduct an online Delphi using a participatory action research approach to develop a post thesis research reporting guideline and a multi-use protocol template to use in writing protocols for participatory self-recruited online trials.

Take home points: Full Consensus was achieved in 26/57 items. In other items respondents cited their lack of knowledge as limiting factors in rating items highly. A surprising finding was the lack of consensus for supporting the declaration of personal and competing interests by patients and members of the public. In areas where substantial information was available over many years as to why the item was important and how to include it in reporting, the consensus was high. Support for a research reporting guideline and a multi-use protocol template were high.

Introduction

Our findings show gaps in the building and reporting of online trials. To narrow this gap, I conducted a Delphi to seek consensus on what items would be valued for reporting an online participatory trial. These findings and the information from earlier chapters can inform the construction of a protocol lab for online trials (PLOT) where adaptable reusable templates can be used to construct protocols and to report online participatory trials so they are replicable. This research employs nested studies to explore Delphi methods and find the methods and declarations that are useful for inclusion when building and reporting online trials and in involving the public as research collaborators. Research findings completed in previous chapters were used to build the Delphi for the protocol lab for online trials Delphi (PLOT-D). (Figure 24)

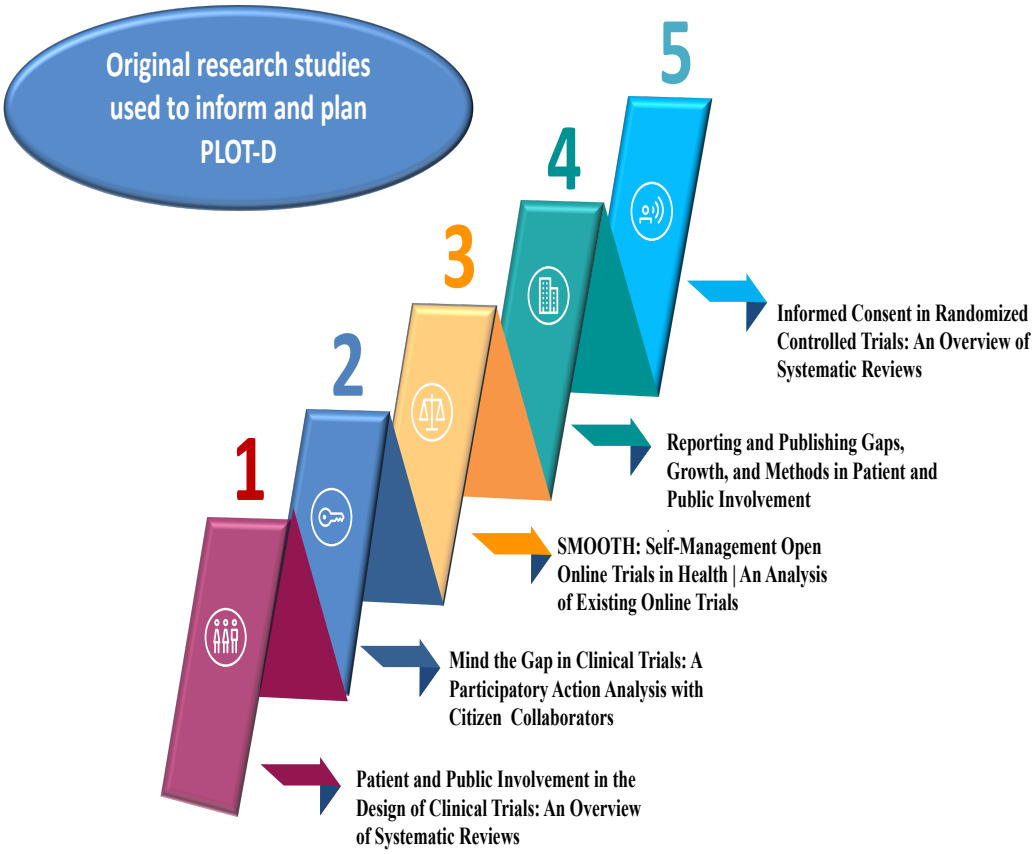


Figure 24Delphi research review

Rationale for using the Delphi Method

An online Delphi is a structured communication tool developed through multiple rounds of questions presented online for evaluation by participants. The online Delphi in combination with consensus meetings is presently used in achieving consensus in the construction of core outcome sets. As of 2014, 75% of COMET core outcome set consensus research projects successfully used this method[1]. Delphi research is increasingly used to develop core outcome sets across diagnosis, intervention, effectiveness, and public and patient involvement and methodology research[2,3].

The Delphi method has been used to build reporting guidelines for PPI research[4], to establish guideline recommendations for inclusion of patient-reported outcomes in clinical trial protocols (the spirit-pro extension)[5] and has been modified for use in developing

clinical practice guidelines for traumatic brain injury[6] Researchers are using Delphi methods to develop community involvement in healthcare policy and research, clinical practice guidelines and patient information materials[7] A Delphi can serve as an interactive consensus tool, a forecast of emerging opinions, as an assessment for gaps in research,[8] and as a shared decision–making method[9].

The participants answer questionnaires in a minimum of two rounds. Following each round, the panel are provided with an anonymous summary of inputs from the previous round. The participants are invited to revise and prioritize their earlier answers in view of the other panel members responses. The range of variation tends to decrease until common ground is attained. The theory underlying this method is the assumption that forecasts, consensus or decisions from a structured group of participants will be more accurate than those from unstructured groups[10].

Participatory Action Research in the Delphi

This research conducts an online Delphi using a Participatory Action Research (PAR) framework to build the prototype for an online trials protocol with PPI. PAR without Delphi inclusion is change-oriented[11] and can be designed to promote participant involvement at every project stage; it is also subject to the limitations imposed by trade-offs between power relations, group domination, and a safe place for involvement and confidentiality[9]. An Online Delphi allows collaborative consensus building and problem solving which is informed, and participatory.

The online Delphi offers involvement and confidentiality thus sidestepping the complications of power imbalances and undue influence as respondents contribute anonymously. Delphi participants can be culturally diverse, geographically separated but

participating with respondents who are engaged in potential application of Delphi results[12]. We hope to elicit a series of recommendations to help others navigate good practice for participatory online trials research methods, research reporting, and PPI inclusion.

Embedded Research | Trial Within a Delphi

Two SWATs were nested as randomized controlled trials within the online Delphi. The first SWAT assessed the effects of population compared to purposive sampling for reaching consensus in an online Delphi. The Delphi method of engaging panels of experts from specific interest areas has been widely utilized in the development of research reporting guidelines, core outcome sets, clinical medicine, nursing practice, medical education and healthcare services. An assessment undertaken by Atkins and colleagues in 2005 reported that a small panel of similarly trained experts can develop reliable criteria that inform judgment and support effective decision-making.[13] Despite the wide applicability of the Delphi methodology, it is not understood how the number of participants or their similarity as a stakeholder group influences results in an online Delphi. The second SWAT assessed the impact of using different groupings to provide aggregate feedback to participants in an online Delphi study. The SWAT investigated how working with all stakeholder feedback aggregated together, within one's own group only or with the knowledge of what responses each group provided influences prioritization and decision-making. A similar assessment was done in the development of a core outcome set in trials of mechanical ventilation in critical care (COVenT).[14]

Methods

Research Question:

Which items are beneficial to include to when constructing protocols for building and reporting online trials as well as involving the public as research collaborators?

Aim:

To develop robust and practical methods for building participatory online trial protocols.

Objectives:

1. To reach consensus on items ranked by stakeholders as critical for robust trial methods and PPI inclusion.
2. To identify the top three disparities and similarities in ranking between stakeholder groups (this may identify common ground as well as potential barriers for later problem solving).
3. To explore how ranking is influenced by the method of feedback provided in the Delphi.

Study Design

To achieve the study aims and answer the research questions we used a DELPHI method with a mixed-methods sequential participatory action research (PAR) approach[15] involving researchers, clinicians, industry, policy-makers, and the public to develop a prototype for research collaboration in online clinical trials. The Delphi was conducted online over the internet, and the sources included primary investigators or first authors of articles published in PubMed in 2013-2017, Linked in, Facebook, Twitter and related

snowball sampling. We aimed to reach a broad representation from the current research culture, rather than a narrow pool of experts.

Multiple Round Delphi

This Delphi was limited to three rounds to minimize resource costs to participants, reduce attrition (people dropping out) and because research shows there is only minimum change beyond three rounds. The rationale for time between multiple rounds is to reduce concerns that participants could be manipulated to a snap judgement or would perceive their accountability to be reduced because they are unnamed contributors. The other limitation with using one round or short multiple rounds in the same 24 -hour time frame is that consensus or conformity may feel forced with little room for beneficial alternative or outlying opinions[16,17].

Advisory Group

An advisory group agreed on the original item questions and troubleshot comprehension issues in the way the material was presented in the first round of the Delphi. Because of involvement in the study design and the possibility of swaying the outcomes due to knowledge gained in planning, the members of the Advisory Group did not participate in the Delphi exercise. Instead, their role was to guide the design and implementation of the Delphi and to take part in any final consensus meeting without overriding the Delphi consensus.

Research Teams

The primary research team consisted of academics, students, librarians, researchers, publishers, clinicians, and citizen volunteers. The advisory group was representative of the panel groups.

Delphi is limited to three rounds to minimize resource cost to participants, reduce attrition (people dropping out) and because research shows there is only minimum change beyond three rounds. The rationale for time between multiple rounds is to reduce concerns that participants could be manipulated to a snap judgement or would perceive their accountability to be reduced because they are unnamed contributors. The other limitation with using one round or short multiple rounds in the same 24 -hour time frame is that consensus or conformity may feel forced with little room for beneficial alternative or outlying opinions[16,17].

The Panels

Panels are the groups we wanted to represent in the Delphi and they initially consisted of five stakeholder groups;

a) Researchers, (health science students, academics, and journal editors)
b) Clinicians (Doctors and allied health professionals, medical students)
c) Community (industry, patients, other students and other groups)
d) Industry (medical devices, commercial research, commercial funders, pharmaceutical companies, health media)
e) Policy makers, health commissioners, and non-commercial funders

Online Delphi studies do not specify the optimal panel size necessary to achieve valid consensus[18]. Delphi panel size is commonly guided by time and resource cost allocation, the availability of willing participants, plus the scope of the research question. The intention is to maximize the number of respondents invited to avoid complications from attrition and to increase the representative nature of the population who participate[18]. This may allow more choices to be made well. If there are insufficient responses from a stakeholder group it can be merged for the second round of the Delphi.

Recruitment

Respondents were identified through the ORCHID[19] database, journals, social media, PubMed, collaborating citizen science, and patient advocacy groups, social media, open forums and email lists as well as through contacts in the Advisory Group. (Points of contact are invited to nominate participants, often referred to as snowball sampling.) In addition, survey participants from the research in chapter 6 were invited to respond along with an updated list of trialists (2017) from PubMed. A minimum of two reminders were sent to non-responders. The Delphi remained open in both rounds until there were no additional responses for four consecutive weeks and then the data were collected for analysis. Consensus was reached in two rounds.

Delphi Software

The Delphi was hosted on Survey Monkey® and questions were piloted for readability and context. This system is similar to that used in the MOMENT[20] study where an online Delphi was incorporated to determine the core outcome set for trials investigating otitis media with effusion in children. Survey Monkey® was programmed to maintain the assigned categories and randomization conditions. To visualize the rounds with randomization, see Figure 25.

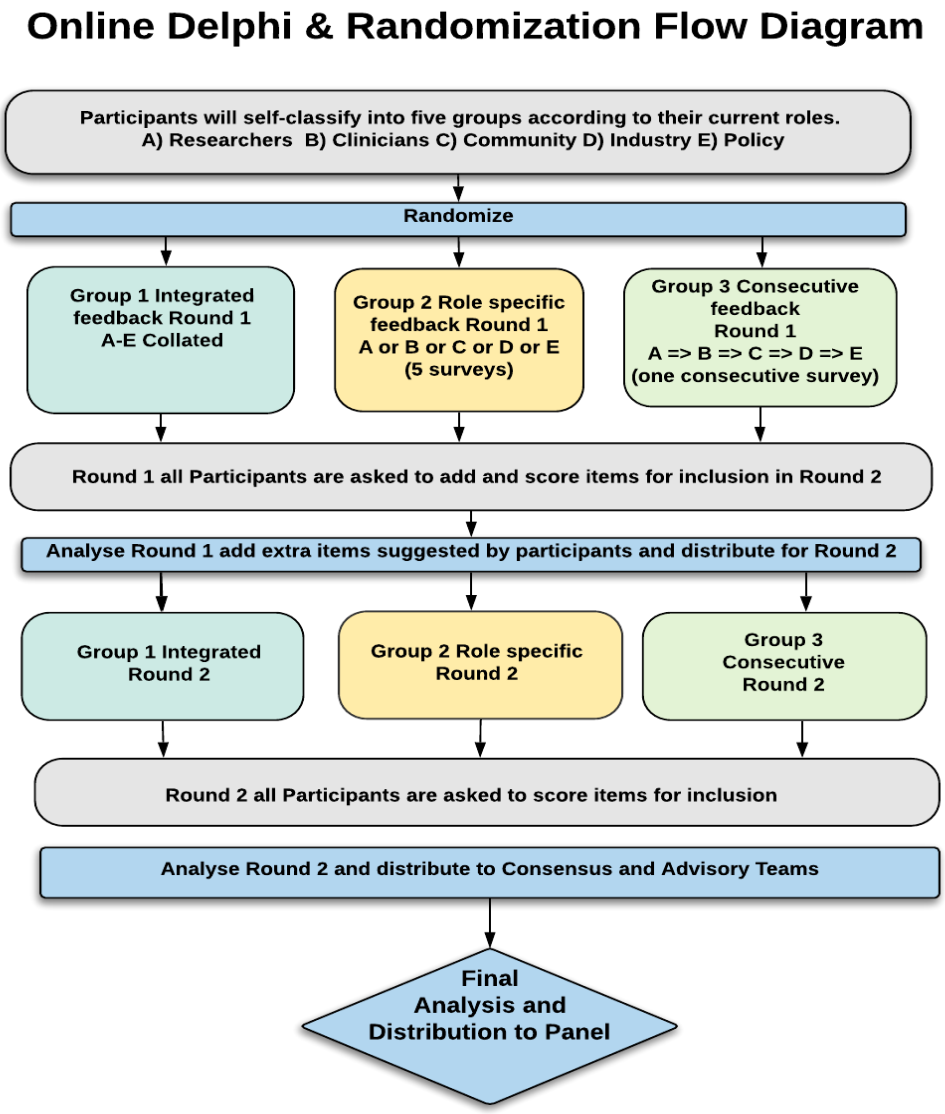


Figure-25 Online Delphi process outline

Round-1

- In round-1, demographic information was collected and stored in a secure database that is used to provide the respondent with a unique identifier, which allows identification of individuals who complete the Delphi.
- In round-1 participants were self-assigned into five stakeholder groups, a) Researchers, b) Clinicians, c) Community d) Industry e) Policy. They remained in the assigned groups to balance the representativeness of the Delphi. In the event that a respondent might self-classify or identify themselves as fitting

more than one category, they were invited to choose and participate in only one of the five categories. Where stakeholder groups were less than 5 members their input was merged into the community group.

- Participants were asked to score 60 items +/- in an online questionnaire developed through examination of the literature, discussion and draft protocol work. This round was exploratory, and participants were invited to add questions they perceived as relevant. They were also invited to clarify each question and offer improvements for the way it is phrased. Participant responses led to the prioritization of items for later inclusion or exclusion.
- There was space for comments on each item. These comments were collated and shared with the advisory team and with respondents who completed round one (Appendices PLOT-D Round 1 Background Discussion .
- A Likert-type scale was used with answers ranging from 1 least important to 5 most important[21]. Items added by respondents were reviewed and qualitative feedback coded by three members of the research team to ensure relevancy. Where there was still uncertainty the advisory group were consulted to reach consensus.
- The priority attributed to ranked items was calculated as a percentage of responses for all categories.
- The addition of Delphi items ceased after Round-1 and any added items were carried forward to Round-2.

Randomization

All participants were randomized into three categories, Integrated feedback, Role specific feedback and Consecutive feedback as described in figure-2. To ensure that rounds were

sent to the correct individuals (i.e. in accordance with their randomization), individuals were assigned to categories by the survey software.

- **Integrated (Group-1):** received one feedback result for each outcome/response revealing the collated (a-e) panel responses.
- **Role specific (Group-2):** received the feedback result for each outcome/response but what they saw was limited to their assigned stakeholder panel (a or b or c or d or e) or if merged a or b or c.
- **Consecutive (Group-3):** received feedback results for each outcome/question revealing the separate responses of all stakeholder panels a+ b+ c+ d+ e)

Additional Rounds

- All three categories (integrated, consecutive, role specific) received an identical list of items in the second round.
- The feedback reflected the category to which participants were randomized.
- This is an evaluative phase where participants scored the items.
- This round identified ranking influence pertaining to the Delphi feedback method.
- A third round was added if needed to reach consensus. This round followed the same process as in round-2.
- Following all rounds, the final responses to items were analyzed. Inclusion consensus was defined as >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale [22].
- Delphi responses were discussed with the Advisory Group. This feedback dictated the structure and content of the consensus meeting.

Analysis plans

During each round in the Delphi study, the items were scored from 1 to 5 by each participant. The proportion of respondents who gave each of these five scores was calculated as a percentage of the total responses. The final responses were analyzed for each of the three intervention groups across the five stakeholder groups. For the SWATs, we explored differences and similarities between the rankings for stakeholder groups within each feedback method.

We did not weight the items or generate propensity scores to adjust for a non-representative sample, because the goal was to involve all stakeholders and let them decide what is relevant through prioritization of the items over each Delhi round. The scoring was reported and analyzed by stakeholder group and again with the stakeholder groups combined. The feedback to participants showed absolute numbers and percentages so that prioritization choices were visible across stakeholder groups, and the perspectives of smaller stakeholder groups could be preserved. The top five disparities and similarities in ranking between stakeholder groups was sought to report common ground and to identify potential barriers for later problem-solving.

Patient and Public Involvement

Thirty members of the public, including patients, students and community members worked with us to develop and user test the Delphi questions and were part of the advisory group, recruiting and dissemination teams. I am grateful to Cochrane Task Exchange, Society For Participatory Medicine, Stanford Medicine X, PCORI, and The BMJ for putting me in touch with these incredible PPI partners. In addition, Julie Sprakel, Lenny

Vasanthan, Michael Mittelman and Urvi Gupta are included as authors, having met the criteria for authorship.

Ethical Considerations

The research is British Psychological Society research-ethics guidelines compliant[23]. Participants were informed of their right to withdraw at any time without penalty and reassured that identifying data would be removed. Data already collected and aggregated will not be removed. Participants who were members of a panel who also collaborated in the publication of the research were at their discretion included as named contributors, however their personal data remained de-identified. The researchers have no competing interests. This study has undergone independent scientific review. The study protocol ethical approval number is CUREC[24] MSD-IDREC-C1-2013-174 and R58550/RE001.

Screening and Clinical Data

Relevant participant eligibility and socio-demographic data were gathered automatically by voluntary public input after informed consent for its collection was given. Demographic and identifiable information was stored securely and used to provide participants with a unique identifier that was tied to completion rates.

Data Security

Data were stored securely online with a password access protected, dynamic IP system. Entry is limited to project-dedicated CUREC listed personnel. Any paper printouts of data were filed securely, and access was limited to principal investigators. Randomization took place following the entry of demographic data and completion of round one.

Incentives

Research results were offered to participants. Respondents received an acknowledgement for completion.

Randomization of Delphi Items

Delphi items were not randomized as the building of a protocol requires sequential thought and the responses are likely to be most reflective of building a protocol when they are left in a consecutive order where respondents can see the protocol in their minds as they rate the priorities. The styles of prioritization were mixed from parallel to vertical and verbal to numbers based to reduce automated answering. Additionally, the items were left open for responses until four consecutive weeks passed without additional responses. Although randomization is commonly used to reduce bias, the cognitive dissonance and structural deficits that would result from the randomization of questions outweighed the benefits.

Adaptive questioning

Adaptive questioning was used to build on existing questions in order to reduce unnecessary steps for participant responses.

Number of Items

The number of items and pages was commensurate with other validated research guidelines as too many questions increase resource costs and adversely influences completion rates. We used a progress bar so participants could see the proportion of questions they had completed.

Completeness check

An automated completeness check was done with java script and which was tested when the project was piloted. All items contained a non-response option such as “not applicable”. One response will be “other” where the respondent can leave comments to share areas where their response falls outside of a listed category. Participants were also able to advance to other questions or submit the Delphi even when a question was left unanswered.

Review answers capacity

Respondents could review and change responses, save results, and complete the Delphi later if they were interrupted or faced technical challenges. Participants were warned that they must click submit to send responses to the database.

IP check

IP checks were not used to identify duplicate entries as each respondent had a unique identifier and was only able to submit the survey once. In addition, identification and storage of IP numbers carries greater risk for a data breach. In the event of technical failure, aborted submissions could be reset to allow respondents to complete the Delphi.

Analysis

Delphi participants were not considered respondents until they completed all rounds. The scoring was reported as a percentage across categories to enable prioritization choices across groups in a way that the roles and the perspectives of smaller stakeholder groups were not lost. The highest consensus items were presented by individual categories and across groups. The greatest disparities and similarities in ranking between stakeholder groups were included to identify common ground and problem solve potential barriers.

Consensus Meeting

The consensus conference following the rounds was modelled after the OMERACT approach[25] where equal representation of all stakeholders including citizen volunteers is the standard. Invited representatives included volunteers from the Delphi panel stakeholder groups as well as advisory board members.

Consensus meeting purpose:

1) To determine minimum items required for a valid and useful participatory online trials protocol and a research reporting guideline.
2) To come to agreement concerning the explanations and recommendations to further define definitions for the protocol items.
3) To agree a practical dissemination strategy (ways to get this information to people who need it) and to define key recommendations.

Consensus meeting timing

The formal PLOT-D consensus meeting will occur online and face to face, following the thesis in collaboration with Medicine X, Stanford University, PAHO and PCORI who are completing a parallel Delphi with researchers, patients and public, clinicians and funders. We have agreed to co-create an Equator reporting guideline on protocol development and reporting for online participatory trials. The internal consensus meetings took place online using conferencing software with the advisory board who discussed Round-1. They were supplied with data in graphs and tables for each question along with participant comments from round -1 along with the advisory boards comments from Round-1. The challenge of how to manage the corrupted data was discussed and we agreed to include only what we could be sure of rather than making even reasonable assumptions based on features that

failed. The consensus was clear for each question and we made no allowances to include any question outside the range in the protocol. We were surprised that declarations of personal competing interests for patients and members of the public did not reach consensus and some members of the advisory board are renewing their efforts to raise public awareness of this concern. In the interests of transparency, we will declare this item did not reach consensus but that we will still include this in the reporting guideline.

Results

The Research findings completed in previous chapters 2-6 were used to inform the development of items proposed for the Delphi (PLOT-D). The authors and the advisory committee agreed 57 items for Round-1 and piloted them on the online SurveyMonkey platform with 30 user-testers. Of the 571 invitees who entered the SurveyMonkey platform, 415 (73%) completed more than 3 Delphi items beyond the demographics.

Delphi respondent demographics

The 415 Delphi respondents reported their primary roles and years of experience and the country of residence. Delphi participants classified themselves as; Researchers (health science students, academics, and journal editors 59%), Clinicians (doctors and allied health professionals, medical students 35.4%), Community (community members, patients, carers, other students and other groups) 3.6% Industry (medical devices, commercial research, commercial funders, pharmaceutical companies, health media) 1.8% Policy makers, health commissioners and non-commercial funders 0.2%.

The self-reported years of time spent in the current role varied by respondent; 1.3% report 1 year or less, 5.8%, 2-4 years, 27.6% 5-10 years and 65.3% report spending over 10

years in their current role. There were 59 countries of residence represented by 1 or more respondents. Countries with (n=1) respondents were (n=19) although some were classified as “other”. This listing was the third largest category of respondents (n=57) after the USA (n=85) and the UK (n=75). The majority of Delphi respondents originated from 15 countries ranging from 85-12 respondents each, followed by 10 countries ranging from 11-4 respondents each and fifteen countries listing 2-3 respondents. A collage of the countries is represented in Figure 26.



Figure 26 Delphi Countries Collage

Round-1 respondents were identified as participants who answered at least 3 items as prespecified in the methods. Responses were analyzed and the open feedback was coded singularly and then agreed by AP, JS and LV. The feedback comments were used to improve the second round of the Delphi, including the rewording of one question that later reached consensus.

In Round-1, 417 participants were presented with 57 items of which 19 reached consensus, and 13 additional items were suggested by participants and added to Round-2. The 417 participants were invited to Round-2 and the 385 (92%) of people who responded reached consensus again on the original 19 consensus items plus one reworded question and an additional 6 items. The total number of Delphi items that reached consensus was (n=26/50) or 52%.

Meeting Objective One Results

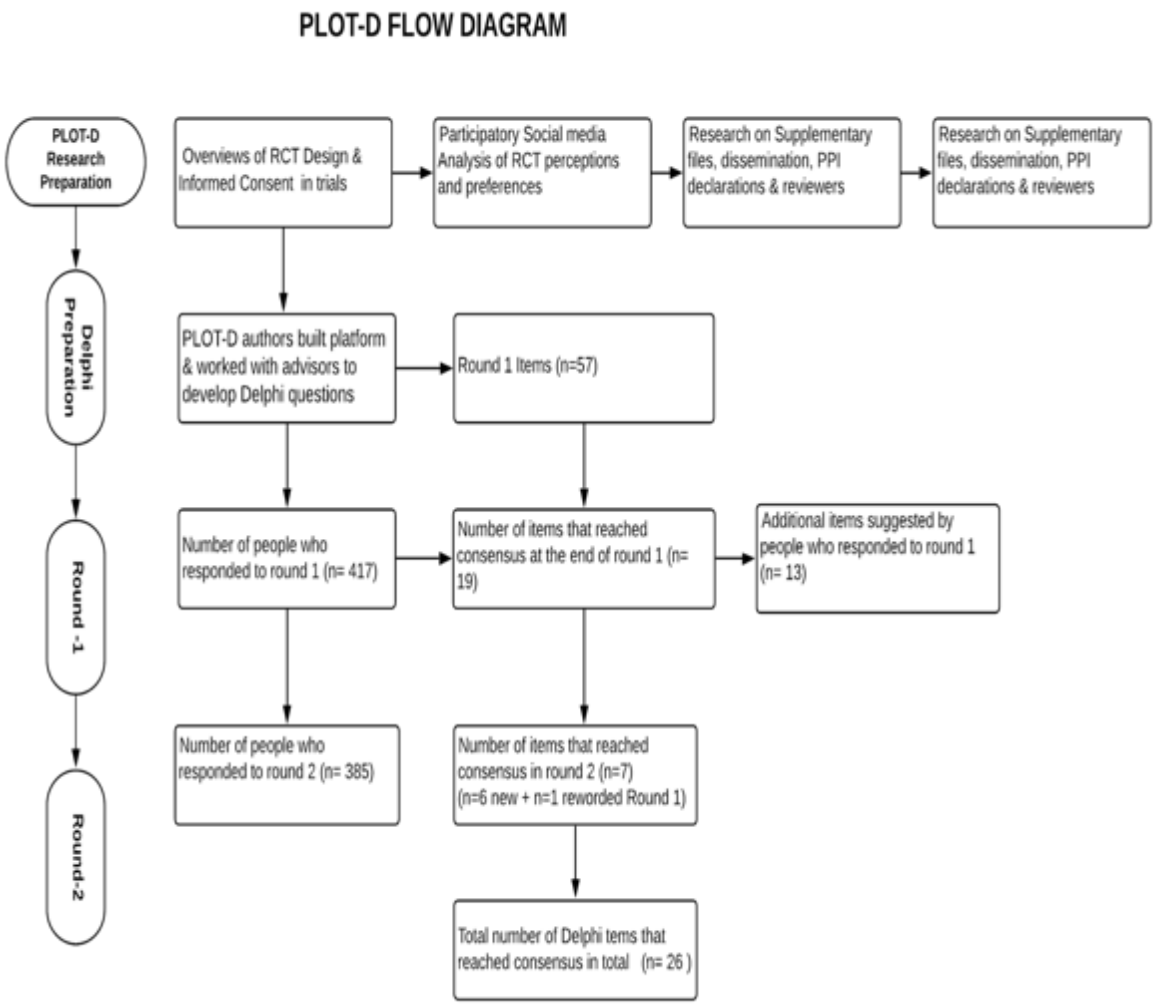


Figure 27 Flow chart used for Delphi research reporting

The first objective was to reach consensus on items ranked by stakeholders as critical for robust trial methods and PPI inclusion. Round-2 Delphi respondents included 385 participants. Of these, 214 viewed integrated feedback where one aggregated score per item was shown from all respondents. 49 saw consecutive feedback where the scores were shown consecutively as items from each group. In the role specific group there were 123 respondents, (46 were researchers, 23 were members of the public and 53 identified as clinicians) each of which saw only the scores from their own role group. Examples of the graphs the participants were shown by grouping are in Figures 28-30.

Round-1 Figure Examples by Presentation Type

Integrative

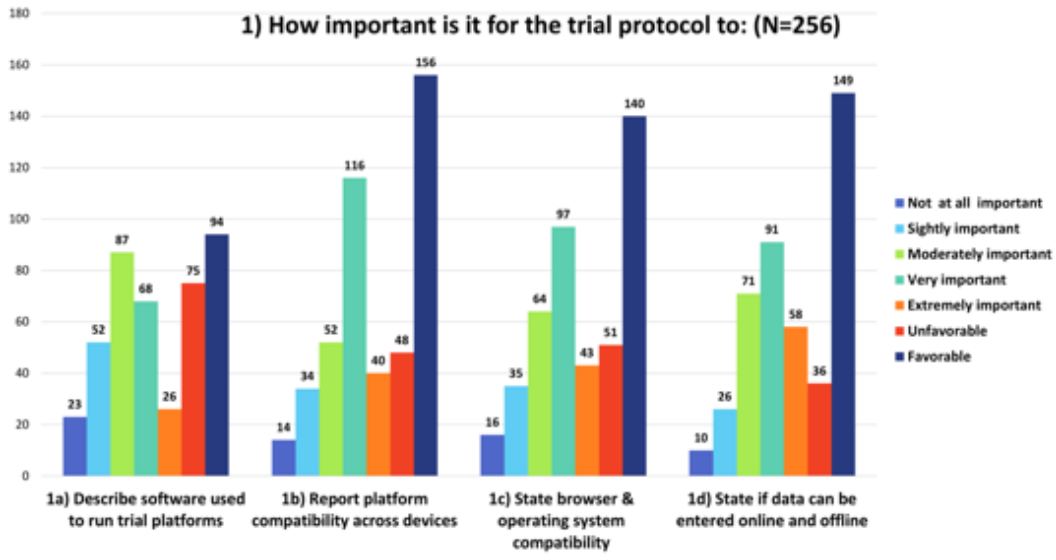


Figure 28 Example of graphs shown to participants in the integrative group

Consecutive

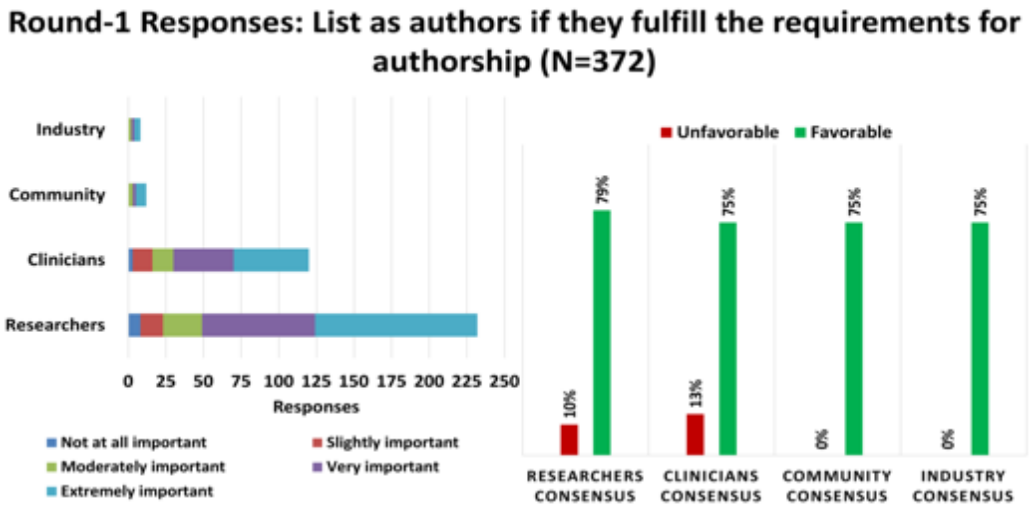


Figure 29 Example of graphs shown to participants in the consecutive group

Role-Specific

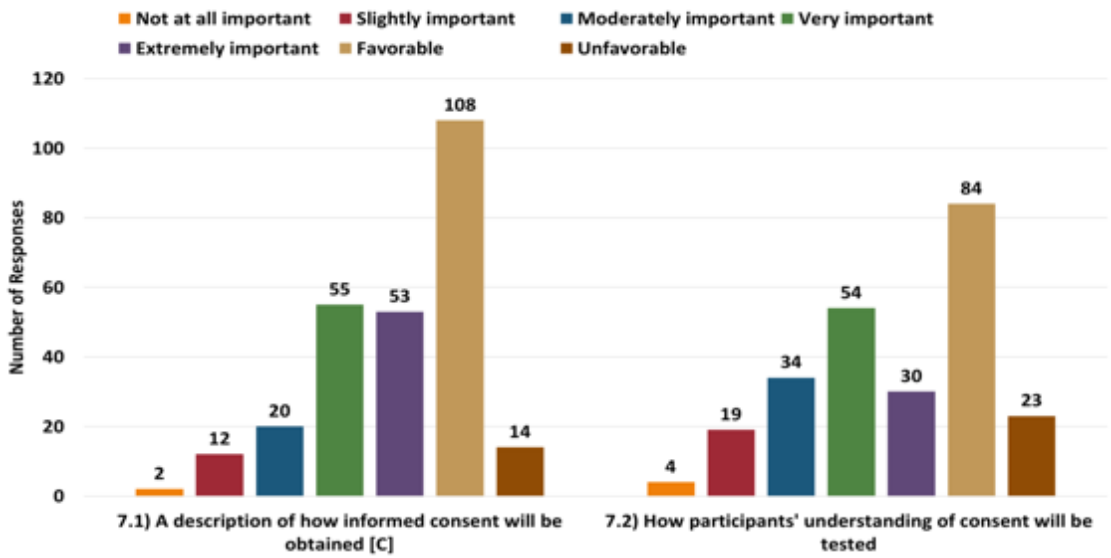


Figure 30 Example of graphs shown to participants in the role specific groups (example only, numbers vary by group size)

After reviewing the graphs for each Round-1 question, respondents then rated the 13 additional items put forward by Round-1 participants in addition to the one reworded question from Round-1. Consensus on all items remained from Round-1 and one

additional Round-1 item reached consensus in Round-2 with 6/13 new items. For Delphi consensus results are ordered from high to low see (Table 26.)

Delphi Results by Question Section

1. **Testing the design of the trial and the delivery of the intervention | Questions 1-3,** 3/18 items reached consensus, 1 in Round-1 (1.8) and 2 in Round-2 reached consensus (3.1, 3.3)
2. **Protocol methods | Questions 4-5,** 13/14 items reached consensus, 11 in Round-1 (4.1-6, 5.1-6) and 2 in Round-2 (4.7, 5.7) 5.7 reached consensus in Round-2 after applying participant feedback to reword the question
3. **Conflicts of interest and informed Consent | Questions 6-8,** 8/12 items reached consensus, 3 in Round-1 (6.1-3) and 5 in Round-2, (7.1, 7.4-6,) while (8.4) reached consensus in Round-2 after discussion with the advisory group given that respondents checked both the multiple options method and more than one of the single options
4. **Acknowledgements and Contributions | Questions 9-11,** 2/10 items reached consensus, 2 in Round-1 (10.2-3) and 0 in Round-2.

Overall respondents were more interested in protocol development and communicating informed consent and conflicts of interest than design testing and intervention delivery. There was little consensus on detailed acknowledgement or contribution declarations other than naming and recognising the contributions of patients and members of the public as contributors or authors. The 57 Delphi items in Tables 22-25 show question items where consensus was invited but not met and items that reached consensus. The items are ordered as they were asked on the Delphi. All questions can be viewed in Chapter 7 PLOT-D Appendices.

Table 22 Delphi Questions 1-3

Testing the design of the trial and the delivery of the intervention | Questions 1-3	R1%	R2%
1.0) How important is it for the trial protocol to include statements that:		
1.1 Describe the software used to run the trial platform	N	
1.2 Report platform compatibility across devices (Tablet, Phone, Computer, Other)	N	
1.3 State browser and operating system compatibility (Windows, MAC, Safari, Firefox etc)	N	
1.4 Specify how data can be entered in the trial protocol? (done online and/or offline and/or using a mobile device).	N	
1.5 Consider participant fatigue and report the details as a linked supporting document [NEW]		N
1.6 Include an IT query link for receiving help [NEW]		N
1.7 Accommodate the use of watches and wearable sensors (if applicable)[NEW]		N
1.8 Report how incomplete information will be managed and whether information completed will be lost or saved [NEW]		76.1
2.0) How important is to report:		
2.1) How passwords are generated	N	
2.2) How passwords are recovered	N	
2.3) Whether the device allows "remembering" of the login and password	N	
2.4) Alternative secure login options like, text confirmation to a mobile phone, or email confirmation to a personal computer [NEW]	N	
2.5) A plan for user testing of passwords restrictions to manage tensions between attrition and security [NEW]		N
3.0) How important are each of the following areas for understanding or replicating research:		
3.1) Describing the intervention fully to facilitate replication and reduce bias? [Consensus reached]	95.93	
3.2) Presenting source code/screenshots/flowcharts of the algorithms or working examples for the intervention (only as applicable)	N	
3.3) Describe methods and the expected frequency of communication concerning the intervention (e.g. SMS, face to face, interactive voice response, video, electronic conferencing, forum, email)? [Consensus reached]	78.43	
3.4) Describe ways users provide intervention feedback e.g. Opinions about content or user interface, usability, access, connectivity	N	
3.5) Inclusion of a data sharing plan [NEW]		N

N = No consensus

Table 23 Delphi questions 4-5

Protocol methods | Questions 4-5	R1%	R2%
4.0) How important is it to:		
4.1) Test trial platform functionality (e.g. enrolment, data entry, password recovery, error reporting, security, step transitions etc) [consensus reached]	91.25	
4.2) Test the usability of the intervention from the participants' perspective [consensus reached]	95.82	
4.3) Test the participants understanding of the intervention [consensus reached]	93.50	
4.4) Track the time required per visit to learn the allocated tasks [consensus reached]	81.59	
4.5) Track the time required per visit to respond to the tasks [consensus reached]	79.10	
4.6) Troubleshoot potential areas where participants might drop out [consensus reached]	90.42	
4.7) Add a predefined analysis plan and test this with a pilot [NEW]		74.27
5.0) How important is it to include definitions in plain language and supply links to explanations of these declarations to aid participants' understanding of each of the following:		
5.1) Data security procedures [consensus reached]	87.90	
5.2) Confidentiality statements [consensus reached]	90.06	
5.3) Declarations about the extent to which you can make the raw data available to others [consensus reached]	80.77	
5.4) Plans to share the research with others including patients and members of the public [consensus reached]	82.77	
5.5)Including a Patient and Public Involvement (PPI) plan (as applicable) with guidance on how to write it	N	
5.6) Declarations of the access and rights participants have to their own research data [consensus reached]	81.11	
5.7) Include survey or questionnaire methods within the protocol (if they are used)*		73.18

N = No consensus

5.7 This item reached consensus after Delphi participants suggest we reword to qualify if they are used within the study*

Table 24 Delphi Questions 6-8

Conflicts of interest and informed Consent | Questions 6-8	R1%	R2%
6.0 How important is it for members of the research team to declare financial or personal competing interests:		
6.1 Researchers' to declare financial competing interests [consensus reached]	93.44	
6.2 Patients' and members of the public to declare financial competing interests [consensus reached]	71.13	
6.3 Researchers' personal competing interests? [consensus reached]	86.05	
6.4 Patients' and members of the public to declare personal competing interests?	N	
7.0 How important is it for researchers to include the following information in the trial protocol?		
7.1) A description of how informed consent will be obtained e.g. (handwritten, digital, audio, video, biometrics, facial recognition, proxy consent by a parent or guardian).		86.3
7.2) How participants' understanding of consent will be tested (e.g. multiple choice, true/false questions, open responses, checkbox)	N	
7.3) In interventions where understanding could deteriorate, how important is it to re-consent the participants [NEW]		N
7.4) Plan for pre-consent for research in areas like acute or critical care where consent may not be possible [NEW]		76.15
7.5) Consent to allow participant to share personal data with their clinician [NEW]		72.03
7.6) Plan that includes BRAN by explaining Benefits, Risks, Alternatives, do Nothing [NEW]		71.29
8.0) If you were a trial participant, how would you prefer to access the informed consent materials		
8.1) Download the informed consent materials in a portable format e.g. as a PDF	N	
8.2) Read informed consent materials online	N	
8.3) Receive informed consent materials by email	N	
8.4) All or a combination of the other choices*	70.0	

N = No consensus

8.4**In both rounds informed consent had people checking multiple answers which led to consensus but just less than consensus for checking a combination of the other choices*

Table 25 Delphi Questions 9-11

Acknowledgements and Contributions | Questions 9-11	R1%	R2%
9.0) How important it is to include these statements about volunteer research partner involvement in documents and publications about the trial:		
9.1) The areas of the research process where volunteer research partners made contributions	N	
9.2) The ways the volunteer research partners contribution added value to the research and the research team	N	
9.3) How important is it to state in the protocol and later report in a paper how the partners will be recruited and trained? [NEW]		N
9.4) How important is it to include in the protocol what volunteers receives in exchange for their work [NEW]		N
10.0) How important is it to acknowledge the contributions of volunteer research partners e.g. members of the public, advocacy organizations, carers, or patients:		
10.1) In the methods section within the body of the report	N	
10.2) In the contributorship or acknowledgement section (if available) [consensus reached]	79.41	
10.3) As authors if they fulfil the requirements for authorship [consensus reached]	84.07	
11.0 How important is it have a plan for thanking and naming volunteers (unless they request to be anonymous):		
11.1) Thank patient organizations or advocacy groups by name	N	
11.2) Thank research partners by name (with their permission)	N	
11.3) Thank the individual partners by name (with their permission) and the patient/advocacy organization(s) to which they belong (as applicable)?	N	
11.4) Thank but not name volunteers and partners who choose to remain anonymous?	N	
11.5) Thank individual research partners and volunteers by name (with their permission) in a supplementary file or in a linked online document when there are too many volunteers to name in the manuscript?	N	

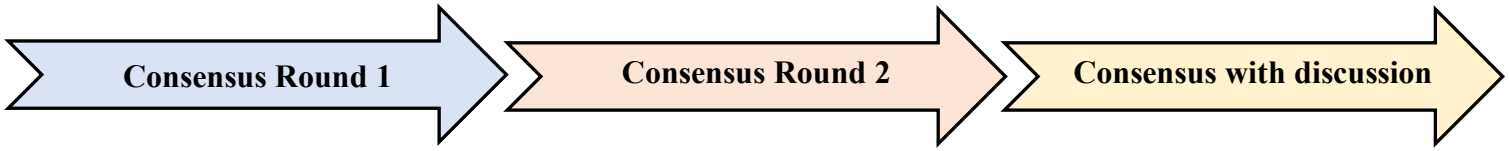


Table 26 Consensus for Delphi items

Delphi items that reached consensus across categories from highest to lowest	%
3.1) Describe the intervention fully to facilitate replication and reduce bias	95.93
4.2) Test the usability of the intervention from the participants' perspective	95.82
4.3) Test the participants understanding of the intervention	93.5
6.1 Researchers' to declare financial competing interests	93.44
4.1) Test trial platform functionality (e.g. enrolment, data entry, password recovery, error reporting, security, step transitions etc)	91.25
4.6) Troubleshoot potential areas where participants might drop out	90.42
5.2) Plain language for confidentiality statements	90.06
5.1) Plain language for security procedures	87.9
7.1) A description of how informed consent will be obtained e.g. (handwritten, digital, audio, video, biometrics, facial recognition, proxy consent by a parent or guardian).	86.3
6.3 Researchers' personal competing interests? [consensus reached]	86.05
10.3) As authors if they fulfil the requirements for authorship [consensus reached]	84.07
5.4) Plans to share the research with others including patients and members of the public	82.77
4.4) Track the time required per visit to learn the allocated tasks [consensus reached]	81.59
5.6) Declarations of the access and rights participants have to their own research data	81.11
5.3) Declarations about the extent to which you can make the raw data available to others	80.77
10.2) In the contributorship or acknowledgement section (if available)	79.41
4.5) Track the time required per visit to respond to the tasks	79.1

Delphi items that reached consensus across categories from highest to lowest	%
7.4) Plan for pre-consent for research in areas like acute or critical care where consent may not be possible [NEW]	76.15
1.8 Report how incomplete information will be managed and whether information completed will be lost or saved [NEW]	76.1
4.7) Add a predefined analysis plan and test this with a pilot [NEW]	74.27
5.7) Include survey or questionnaire methods within the protocol (if they are used)*	73.18
7.5) Consent to allow participant to share personal data with their clinician [NEW]	72.03
7.6) Plan that includes BRAN by explaining Benefits, Risks, Alternatives, do Nothing [NEW]	71.29
6.2 Patients' and members of the public to declare financial competing interests	71.13
8.4) All or a combination of the other choices**	70

*5.7 This item reached consensus after Delphi participants suggested we reword to qualify to use the item only if a questionnaire or surveys are used within the study**

8.4 *In both rounds the informed consent item had individual respondents checking multiple answers which led to consensus.***

Objective 2 Results

The second objective was to identify the top disparities and similarities in ranking between stakeholder groups to identify common ground as well as potential barriers for later problem solving. We assessed the five items where consensus was reached by some groups but not all and the differences at consensus. We looked only at items that met consensus individually or collectively.

Table 27 Delphi similarities and disparities

The top five disparities and similarities in ranking between stakeholder roles and groups			
Similarities	**Group High**	**Group Low**	**Differences**
4.2) Test the usability of the intervention from the participants' perspective	Consecutive	Integrated	3.04%
3.1) Describing the intervention fully to facilitate replication and reduce bias?	Researchers	Integrated	4.45%
4.3) Test the participants understanding of the intervention	Consecutive	Integrated	7.74%
7.6) Plan that Includes BRAN by explaining Benefits, Risks, Alternatives, do Nothing [NEW]	Researchers	Consecutive	7.96%
5.4) Share research with patients/public	Consecutive	Patients	9.42%
Disparities	**Group High**	**Group Low**	**Differences**
10.3) As authors if they fulfil the requirements for authorship	Consecutive	Public	23.03%
7.4) Pre-consent for research for acute/critical care where consent may not be possible [NEW]	Clinicians	Public	24.34%
7.5) Consent to allow participant to share personal data with their clinician [NEW]	Researchers	Public	24.64%
5.7) Include survey or questionnaire methods used within the protocol	Consecutive	Researchers	30.32%
10.2) In the contributorship or acknowledgement section (if available)	Clinicians	Public	30.33%

The items with the most similarity tended to explain risk, information sharing, study process and bias. They included; 4.2) the testing of intervention usability from the participants' perspective; 3.1) Describing the intervention fully to facilitate replication and

reduce bias; 4.3) Testing participant understanding of an intervention, and finally to use 7.6) BRAN to explain the Benefits, Risks, Alternatives, do Nothing [NEW] of interventions and sharing research with the public 5.4). The differences were negligible and varied between 3.04% to 9.42%. The integrated group tended to score slightly lower on this outcome. These areas with the greatest disparity seemed to be trust and acknowledgement based. We asked how volunteers ought to be recognised 10.3) as authors if they fulfil the requirements for authorship; 7.4) If pre-consent for research for acute/critical care where consent may not be possible; 5.7) to include survey or questionnaire methods used within the protocol and finally where patients or volunteers need to be recognised, 10.2) In the contributorship or acknowledgement section (if available) For this area differences ranged 23.03% to 30.33%. Table 27 shows the differences by groups involved.

Items that scored highly by groups but not highly enough to reach Delphi consensus are shown in Table 28 . These items revolved around contributions, recognition and training.

Table 28 Consensus in groups but not main Delphi

The Items that reached consensus individually for groups or stakeholder panels but not in the Delphi		
Questions	**Groups in Favour**	**Delphi**
2.1) How passwords are generated	Role Specific | Public | (76.9%)	51.44
3.4) Describe ways users provide intervention feedback e.g. opinions about content or user interface, usability, access, connectivity (Public	Role Specific | Public & (75%) & Integrated (76.28%)	68.63
9.2) The ways the volunteer research partners contribution added value to the research and the research team	Clinicians | role specific (72.72%)	68.65
9.3) How important is it to state in the protocol and later report in a paper how the partners will be recruited and trained? [NEW]	Role Specific | Public (70%) & Clinicians (77.27%)	69.84
9.4) Include in the protocol what volunteers receive in exchange for their work [NEW]	Consecutive & Role Specific | Clinicians (77.27)	67.12

Objective 3 Results

To explore how ranking is influenced by the method of feedback provided in the Delphi The current findings indicate that in the top-rated priorities there are only small differences. Question 6.1 was a top item for researchers, clinicians and the public however differences were the greatest here and ranged from 0-8%. In table 29 where general consensus was not reached, knowing how passwords were generated was only important enough to the public to reach consensus. It may be important to find out why.

Table 29 Stakeholder priorities

Top 9 items prioritised by Researchers, Clinicians and the Public				
Role	**Consensus Item Questions**	**By role**	**Overall**	**+/-**
Researcher	4.2) Test the usability of the intervention from the participants' perspective	97.72%	95.82%	1.80%
Researcher	4.1) Test trial platform functionality (e.g. enrolment, data entry, password recovery, error reporting, security, step transitions etc)	95.46%	91.25%	4.21%
Researcher	6.1) Researchers' to declare financial competing interests	93.33%	93.44%	.11%
Public	4.6) Troubleshoot potential areas where participants might drop out	94.12%	90.42%	3.70%
Public	6.1) Researchers' to declare financial competing interests	85.00%	93.44%	8.00%
Public	3.1) Describing the intervention fully to facilitate replication and reduce bias?	95.00%	95.30%	.30%
Clinician	3.1) Describing the intervention fully to facilitate replication and reduce bias?	97. 78%	97.78%	0%
Clinician	6.1) Researchers' to declare financial competing interests	97.78%	93.44%	4.34%
Clinician	5.2) Plain language for confidentiality statements	95.46%	90.06	5.40%

We then looked at items that reached overall consensus by all groups and the scores of each. The scores did not vary significantly by how the information was presented whether

by working with all stakeholder feedback aggregated together, within one's own group only, or with the knowledge of what responses each group provides (Figure 31)

The Delphi malfunctioned for the function of randomizing panels of integrated and consecutive feedback after an update and before the Delphi participants had completed the Delphi. This left some participants randomised and some not. We were forced to use the smaller sample of the role specific panel only as it was the one that was left uncorrupted.

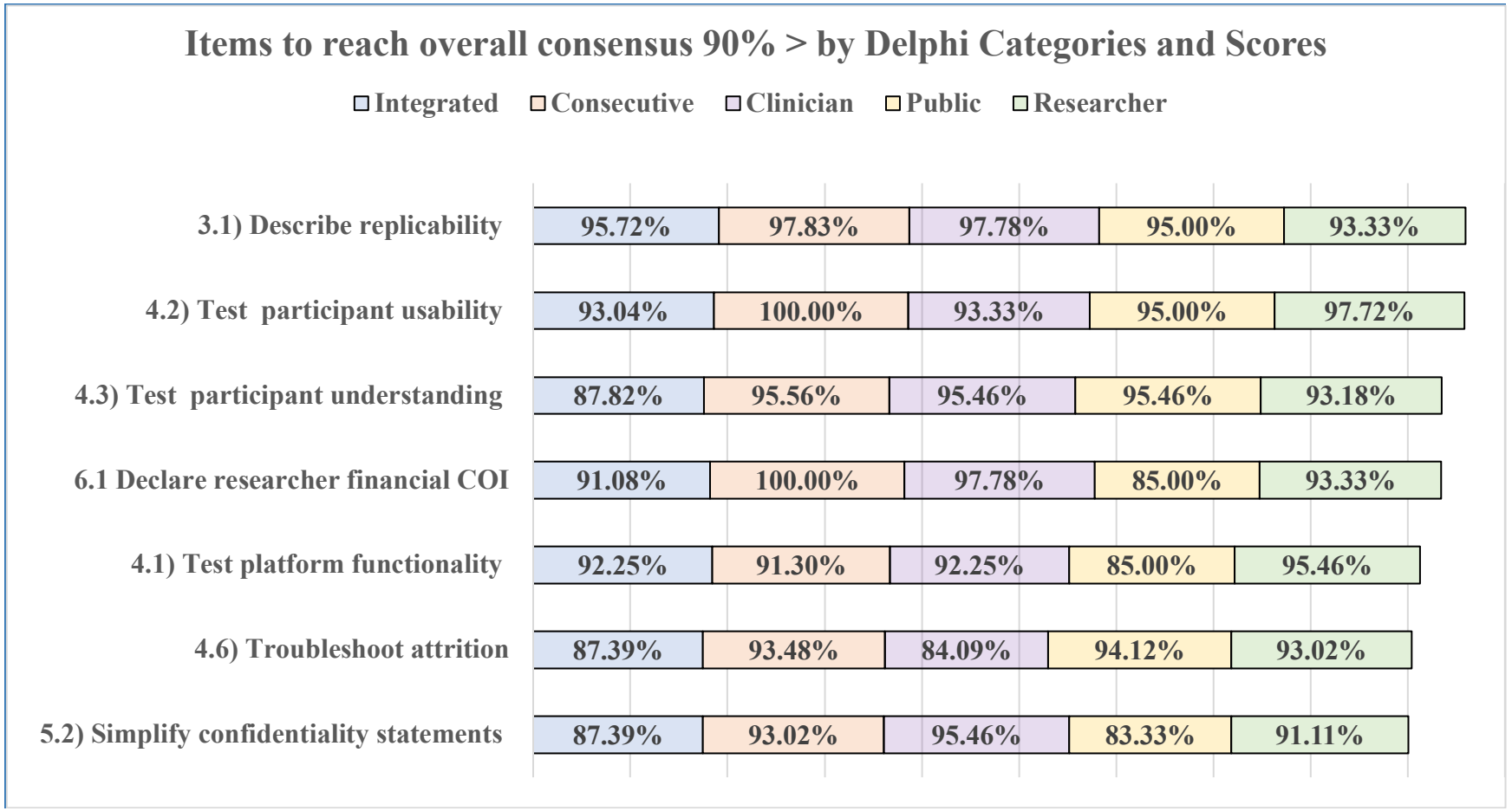


Figure 31 Overall consensus by category

Discussion

The aim of PLOT-D was to develop robust and practical methods for building participatory online trial protocols. The first objective was to reach consensus on items ranked by stakeholders as critical for robust trial methods for online trials and PPI inclusion. The Delphi came to consensus on (n=26/50) or 52% of the outcomes suggested by the advisory board and the Delphi respondents in two rounds. The advisory board only needed to confer on two items and both came to a consensus in Round-2. The comments given by the respondents were helpful not only for the Delphi but in understanding the differences in research process and ethics around the world. Respondents agree that standardization through a protocol and trial reporting guideline for participatory online trials would be helpful.

Our second objective was to identify the top disparities and similarities in ranking between stakeholder groups and this was encouraging as consensus was high and the disparities were apparent in a limited number of items, however the high discrepancies need to be teased out with discussion and replicated. For the third objective we explored how ranking is influenced by the method of feedback provided in the Delphi by conducting two nested trials within the Delphi. These are like feasibility pilots that might be repeated in other populations. The findings indicate information presentation did not substantially influence consensus although the group where feedback was presented consecutively did come to lower consensus by 1-3% across items. When we sampled a 1/3 of patients, clinicians and researchers their consensus did not differ from that of the main study.

The responses to items in the Delphi were similar to those of the volunteers who piloted the platform. We invited all stakeholder groups to be involved with the pilot to co-produce question items in anticipation of meeting the needs of respondents. The open comments from Round-1 were constructive and helpful. Respondents indicated why they did not respond to some items by sharing that protocols, ethics, registration and word count might all determine what they report in papers or write up in the protocol. It appears that gaps between stakeholder groups were less about power struggles and more about practical concerns, methods, training needs, resource constraints, misunderstanding of terms and inexperience with co-production.

Limitations of the Delphi and Challenges encountered

The stakeholder groups varied in size and in the proportion of those who did not provide complete data, making some of the stakeholder-intervention groups too small for a meaningful analysis. In addition, the survey software updated mid-Delphi and corrupted the grouping feature which randomized all participants into groups. For example, the integrated and consecutive panels also contained role groupings which were corrupted. The role specific grouping was already separated into the roles so this remained intact. All data had to be analyzed and cross checked from server backups and the decision was made by our advisory panel was that it would be preferable to use the smaller group size rather than try to piece together the roles of the participants in the integrated or consecutive feedback groups. The reason for this was that we were concerned that if this was done with the underlying errors it could change the numbers and therefore the results. The smallest groups were collapsed and a computer randomized sample was collected to match the smallest stakeholder group and these data were presented for comparison within the main analysis.

The purpose of this preliminary and exploratory work is to develop improved methods for building a protocol for a participatory randomized controlled trial. We first built a database and conducted a descriptive analysis, "C*reating a database of internet-based clinical trials to support a public-led research programme: A descriptive analysis"* [19], then I completed a systematic overview of systematic reviews, "*Patient and Public Involvement in Clinical Trials Design: An Overview of Systematic Reviews*" and followed this with an analysis of "*Self-Management Open Online Trials in Health*". We encountered a lack of standardization, guidance and significant research reporting gaps where it may be useful to be useful to build, suggest, and test best methods. Occasionally, when working on research we find others are doing similar and complementary work and that more can accomplished by joining forces than by working alone. The history and the future of PLOT-D research follows this example. I refer to the process of development for the CONSORT[26]research reporting guidelines where two groups Asilomar and SORT published and developed on similar mandates[27].

> "*At the suggestion of Drummond Rennie, Deputy Editor of JAMA, representatives from both groups met in 1996, in Chicago, USA. The remit of this group was to merge the best of the SORT and Asilomar proposals into a single, coherent evidence-based recommendation. The meeting resulted in the Consolidated Standards of Reporting Trials (CONSORT) Statement, which was first published in 1996"* [27].

Joining strengths and combining forces and abilities has resulted in long lasting collaboration with meetings in 1999, 2001, 2007 and CONSORT revisions in 2001 and 2010. [27]. This seems a reasonable approach and the way forward in a field with emergent technology and where methods will need to bridge gaps between in person communication and online internet platforms. The PLOT-D consensus meeting will occur online and face to face, following the thesis in collaboration with Medicine X, Stanford University, PAHO and PCORI who are completing a parallel Delphi with researchers, patients and public,

clinicians and funders. We have agreed to co-create an Equator reporting guideline on protocol development and reporting for online participatory trials.

Contributions

AP led the research and managed the team, designed the analysis, coding scheme and data extraction forms with feedback from all authors, EPPI Reviewer staff, CerQual and from volunteers. Julie Sprakel, Urvi Gupta, Michael Mittelman and Lenny Vasanthan, Sara Schroter, Jack Dowie and Mette Kaltoft acted as an advisory board and JS and AP coded Round-1 responses, all authors agreed the protocol.

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Chapter Eight | Thesis Conclusion

There is a significant emphasis in the Patient and Public Involvement literature about unbalanced power differentials, deceptions and unheard voices, these are indeed a reality. There are also those who see co-production as separate and "advanced" Public and Patient Involvement rather than a continuum of collaboration based on the research questions, skills of the team and allocated resources. These distinctions were not the focus of this thesis. Figure 32 illustrates how building a bridge to better methods in online trials might work as defined through the findings for the seven objectives of the thesis. It is practical rather than philosophical to provide support for getting started.

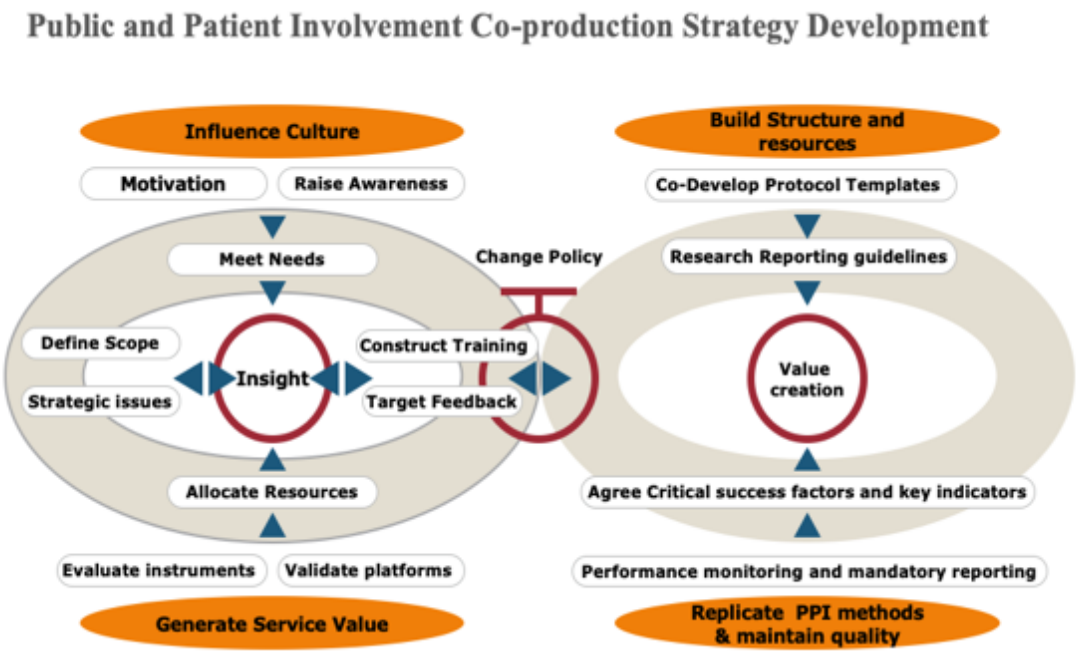


Figure 32 PPI from practice to policy change

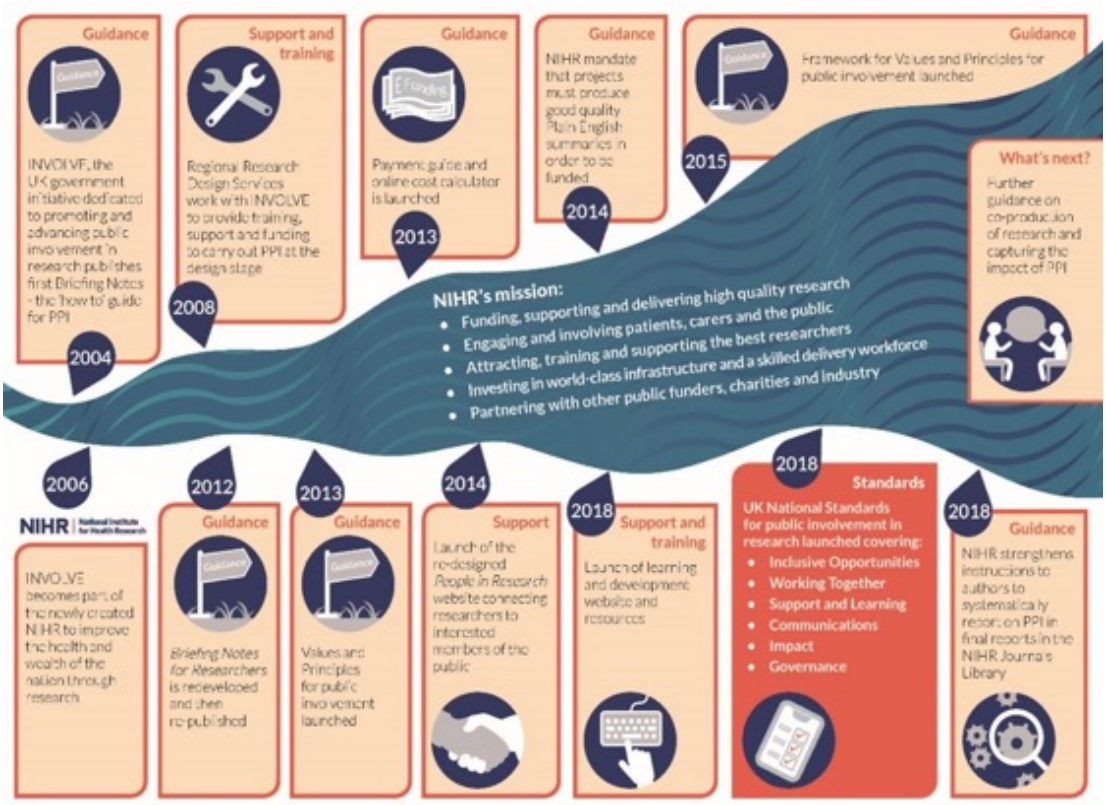
In the early days of this thesis, I faced practical challenges such as registering volunteers as authors who did not have "institutions" or advanced degrees, formidable open access fees without institutional support and frameworks that simply did not work no matter how diligently they were applied. As a research team, we faced privacy breaches, technology

failures, personal hardships, jaded participants, and those who offered benefits they failed to deliver. It is for people like us who want to practice good methods but lack exemplars that this content was developed. There are those who want to grow better research, methods and relationships and for this population, co-developing research reporting and protocol guidelines will help bridge gaps, improve research replicability and provide a community, where we can learn from each other.

Meeting the Mission Through a Fresh Pair of Eyes

Occasionally we meet those who unknown to us are already working on the changes we have invested in. This was the case with the NIHR and the co-production initiative, a plan 15 years in the making as is portrayed in (Figure 33) This infographic was created at my request by Joanna McManus (NIHR) and used here by permission.

Figure 33 NIHR: moving towards co-production



The NIHR employs PPI partners at all levels of governance and review and provides training through online web resources, face to face workshops, 1:1 methodology guidance, fair compensation guides for PPI and even a jargon dictionary. [2] [3] *NIHR mandate states all studies they fund to be available as Open Access.* [4]

A Tale of Two Trials

In conclusion and as exemplars for this thesis, I share two examples. First, meet REMOTE[5], the first FDA phase 4 investigative new drug trial to be approved for an online trial. The intervention was to evaluate tolterodine extended release (ER) 4 mg for overactive bladder. The trial was a replication of a clinic-based physician-led trial for the same intervention, everything was done online except for the laboratory testing that patients did in their own communities[5]. The media portions were excellent, the incentives were generous, and the methodology met FDA standards.[6]

Participants were recruited from nine states in the USA. The landing page was viewed by 20,901 people with 17,950 watching the information video. Of these, 7,230 individuals expressed an interest in participating, and 5157 confirmed their interest via email. Only 1519 met initial eligibility requirements, but only 770 (51%) passed the identity verification step[5]. This left the enrolment at 456 (59%) who signed informed consent. After a medical history review, 237 (52%) remained. After consent, 119 (50%) individuals passed the laboratory tests and were invited to keep a 3-day bladder diary. The trial was terminated early due to low numbers randomized. Only 18 participants were randomized to treatment[5].

When Trials Fail

The multi-step recruitment, screening and identity verification processes frustrated participants, and they dropped out, but there is no formal record of their perceptions available[57] (personal correspondence). A pilot was not done as the intervention was patterned after two earlier successful online trials of another intervention.[8] The synergy of how minor events can make or break a trial was not considered. For example, attrition occurred with each additional step participants were required to take. It makes sense to

investigate how repeated demands, however minor, influence completion rates. The authors report the patients may have needed support to manage the complexity of enrolment, but no one asked the participants or drop outs what should constitute this support and how it should be delivered. In retrospect, it is a lesson to pilot all protocols, solicit targeted participant feedback and recognize that powerful technology will not replace good trials management. It also demonstrates that the behaviours of one population can differ from a similar community under different conditions such as an online platform.[6]

Research done differently

An internet-based trial for a similar condition netted a very different outcome. This group investigated pelvic floor muscle training for urinary stress incontinence[9]. The study compared two treatment interventions for stress urinary incontinence with no face-to-face contact: one was Internet-based, and one was conducted by postal mail. These researchers conducted a systematic review, tested their platform before the trial, used qualitative research pre- and post-trial and adapted the research going forward to their findings.[10,11] From 250 participants who were randomized and enrolled, only 12% were lost to follow-up. Participants were promoted in levels according to their improvement. There was consistent, prompt follow-up, where the research was completed and reviewed before the study. This trial excelled in building researcher to participant access within the trial and contact was not exclusively needs or crisis-based.[6]

Life Lessons

I use these examples as learning tools and not to assign blame. I sought out the investigators of the first trial and the pharmaceutical executive who sponsored them. They were generous with their insights and open about the shortcomings.

Many years ago, as part of the Red Cross disaster team for Hurricane Andrew[12], we were instructed to mark and report the dead and mark properties with an X that were beyond reconstruction. It seemed so little, and I learned from this that the most challenging emotion was not fear, anger, or sadness, it was helplessness. We were admonished not to look back as other teams would follow to meet the needs we were not equipped for. We were encouraged to focus on the living without respect to their current state or behaviours as that is what we were trained for. I learned through this thesis that research is the same because as each one of us adds what we can and lends support to those around us, the change will come.

Reporting PPI and Co-Production

While the PPI co-production evidence base has expanded over the past decade, the reporting of co-production in research papers is inconsistent and partial, with minimal information about the context and process of public involvement,[13] Inconsistent or absent reporting contributes to an evidence base where the collective understanding of what works, for whom, why, and in what context is fragmented.[14] Omitting descriptions of PPI activity can misrepresent study intentions. Reporting of PPI can help others to optimize precious resources devoted to involving patients, and the public.

The *BMJ* makes reporting PPI a requirement for all the research articles it publishes and provides guidance and examples of PPI.[15] Other journals have followed suit including *Lancet Psychiatry*, *CMAJ*, *Research Involvement and Engagement*, and several other journals published by BMJ Publishing Group.[16] For comprehensive reporting and planning of PPI, the GRIPP-2 long and short form research reporting guidelines are available.[13]

Conclusions

We are on the brink of an essential change in research. We are moving from a model of researcher-driven action to co-production, with the patient, public and clinician partners actively identifying the need for research and actively involved in the production of knowledge and its implementation.[17] The time is ripe for effective advocacy, and reporting of PPI in research that grows beyond logging patient experience to the real power shift of co-created research and social policy aimed to refine clinical practice and deliver community benefit.[18] Researchers and patients will continue to learn how to negotiate effective partnerships and identify shared interests.[19] Victor Fuchs noted as early as 1968 that measuring productivity in the service economy, was challenging because consumers and providers of services "*always work together to create value*". [20] It is time to create value by embracing different types of contributions and impacts as we aim for service improvement through effective co-production partnerships and implementation.

Take home point: Constructing the future by building a bridge between methods, research reporting and co-production is one way to enable a platform where difficult research questions can be answered, reported, expanded and shared.

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10 Sjöström M, Umefjord G, Stenlund H, *et al.* Internet-based treatment of stress urinary incontinence: 1- and 2-year results of a randomized controlled trial with a focus on pelvic floor muscle training. *BJU International* 2015;**116**:955–64.

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Word Counts by Chapter

Table 30 Word count excluding bibliography, declarations, tables and figures

Thesis Volume One (42,918/70468) 251 pages	*42,918*
Thesis Declarations	*1231*
Chapter One | Thesis Introduction	*3094*
Chapter Two | Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews	*6737*
Chapter Three | Mind the Gap in Clinical Trials: A Participatory Action Analysis with Citizen Collaborators	*5246*
Chapter Four | SMOOTH: Self-Management Open Online Trials in Health | An Analysis of Existing Online Trials	*4370 & 3291*
Chapter Five | Reporting and Publishing Gaps, Growth, and Methods in Patient and Public Involvement	*5659*
Chapter Six | Informed Consent in Randomized Controlled Trials: An Overview of Systematic Reviews	*6553*
Chapter Seven | Protocol Lab for Online Trials Delphi (PLOT-D)	*5399*
Chapter Eight | Thesis Conclusion	*1338*
Appendices section excluding bibliographies	*7600*
Abstracts, Bibliographies, Tables, Figures	*26559*

Appendices Table

Table 31 Appendices Table and locations

Chapter	Supplementary files
Thesis Introduction	Ethics 2014-2022 page 242-244,
Chapter Two | Patient and Public Involvement in the Design of Clinical Trials: An Overview of Systematic Reviews	PROSPERO 2018 CRD42018085076 SWAR 9,10 Repository Literature search terms, Excluded studies Page 245
Chapter Three | Mind the Gap in Clinical Trials: A Participatory Action Analysis with Citizen Collaborators	Protocol Registration: Research Registry # UIN: 670 http://www.researchregistry.com
Chapter Four | SMOOTH: Self-Management Open Online Trials in Health | An Analysis of Existing Online Trials	Protocol, study registrations, ORCHID Search terms, Excluded studies, partial data extraction, Page 247
Chapter Five | Reporting and Publishing Gaps, Growth, and Methods in Patient and Public Involvement	NCT03021863, NCT03021863 and supplementary materials are available in the published articles
Chapter Six | Informed Consent in Randomized Controlled Trials: An Overview of Systematic Reviews	PROSPERO 2018 CRD42018085076 Literature search terms, Excluded studies Page 247-252
Chapter Seven | Protocol Lab for Online Trials Delphi (PLOT-D)	NCT03498690 and NCT03498690 and the SWAT Repository 71,73, 75. Advisory board notes and comments on Delphi Round-1 for Round-2 Page 252-262

Any data not included such as data extraction online templates can be made available on reasonable request by contacting Dr Amy Price | dr.amyprice@gmail.com

SWAT repository
https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

SWAR repository
https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWARStore/

Delphi Survey Link
https://www.surveymonkey.com/r/Preview/?sm=k_2F_2FhCjGaF_2F5Jeg9gslAyvjAwSuDRU2BZhdteEfD66JVADJ35CwKJrfv4EJZidENq

CUREC Ethics

Amy Price
5 MontaguCrescent Edmonton
N18 2HA

10th August 2018

Dear Amy,

Research Ethics Approval - CUREC 1

Study title: Protocol Labs for Open Trials

The above application has been considered on behalf of the Medical Sciences Interdivisional Research Ethics Committee (IDREC) in accordance with the procedures laid down by the University for Ethical Approval of all research involving human participants.

I am pleased to inform you that, on the basis of the information provided to the IDREC, the proposed research has been judged as meeting appropriate ethical standards, and approval has been granted for a period of **5 years**, commencing on **30th September 2018**. The reference number for this study is **R58550/RE001**.

This is **subject to:**

your following the BPS guidelines for online research
it is your responsibility to comply with the requirements for administering any tests or questionnaires and, if in doubt, to contact the publisher of those tests or questionnaires.
if new research staff are engaged, the PI is responsible for ensuring they are suitably qualified by training and/or experience.

I would like to remind you that your study may be selected for review by the MS IDREC during an annual audit.

Amendments

Should there be any subsequent changes to the study, you should submit details to the MS IDREC for consideration and approval. Details of changes must be listed on an amendment form. If your study received University Sponsorship through CTRG, then the amendment will first need to be submitted to CTRG for approval of continued Sponsorship.

Please do not hesitate to contact me if you have any queries. Yours Sincerely

Dr. Helen Barnby-Porritt
Research Ethics Manager, Medical Sciences

H. Barnby-Porritt

CONFIDENTIAL

Ref: MSD-IDREC-C2-2014-045

Dr Amy Price
5 Montagu Crescent
Edmonton
London
N18 2HA

18th December 2014

Dear Dr Price

Application to IDREC

I am writing to let you know that your application for ethical approval has been approved on the basis of the information which you have provided, for a period of 24 months.

It is your responsibility to comply with the requirements for administering any tests or questionnaires and if in doubt to contact the publisher of those tests or questionnaires.

In addition this approval is conditional upon our receipt of the hard copy of your CUREC 2 form signed by your head of department which we will acknowledge on receipt (Please note that should this not appear or the head of department is unwilling to sign then this approval would not be valid);

Principal Researchers:	Dr Amy Price
Department:	Primary Health Care Services
Project title:	Drinking Water to Prevent or Reduce Weight Gain – An Online Randomized Controlled Trial with Adult Participants
Start date:	April 2015
IDREC approval:	5th April 2015
IDREC Number:	MSD-IDREC-C2-2014-045

Amendments

If your research requires you to change techniques or procedures then you should first go through your research and check whether this changes the ethical issues. If these remain the same then the committee will require notification of the changes to lodge with the project. If there are significant alterations then the committee will require a succinct letter explaining these.

Please do not hesitate to contact me if you have any queries about this matter.

Yours sincerely

Gill Halstead
Research Ethics Co-ordinator, Medical Sciences

Chapter 2 Appendices

Appendix-2:1

Table 32Overview search terms for MedLine

#	SEARCH TERMS Patient and Public Involvement in the Design of Clinical Trials
1	1 (research adj2 (involv* or participat* or engag* or collaborat* or cooperat* or co-operat*)).ti,ab.
2	consumer participation/ or patient participation/
3	((public or patient? or citizen? or survivor? or volunteer? or consumer? or user? or stakeholder?) adj3 (involv* or participat* or engag* or collaborat* or cooperat* or co-operat*)).ti,ab.
4	(expert adj (patient? or user? or consumer?)).ti,ab.
5	((public or patient? or citizen? or survivor? or volunteer? or consumer? or user? or stakeholder?) adj (panel? or group?)).ti,ab.
6	(advisory adj (panel? or group?)).ti,ab.
7	2 or 3 or 4 or 5 or 6
8	exp Biomedical Research/
9	Research Personnel/
10	Research Subjects/
11	exp Clinical Trials as Topic/
12	Research Design/
13	((health or healthcare or clinical or biomedical or medical or gene or genetic or genomic or social care) adj research*).ti.
14	(trial? or study).ti.
15	researcher?.ti.
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	7 and 16
18	1 or 17
19	medline.ti,ab.
20	(systematic and review).ti,ab.
21	meta-analysis.pt.
22	(meta-synthesis or metasynthesis or meta-ethnography or metaethnography or meta-study or meta study).ti,ab.
23	(evidence synthesis or realist synthesis or realist review).ti,ab.
24	19 or 20 or 21 or 22 or 23
25	18 and 24
26	(overview and systematic).ti.
27	meta-review.ti.
28	"review of reviews".ti.
29	"review of systematic reviews".ti.
30	umbrella.ti. and (review or systematic).mp.
31	(policy and brief and evidence).ti.
32	26 or 27 or 28 or 29 or 30 or 31
33	18 and 32

Appendix-2:2

Table 33 Excluded Studies PPI in design chapter 2

Patient and Public Involvement in the Design of Clinical Trials		
Author	**Citation**	**Reason**
Evans 2103	Evans D, Coad J, Cottrell K, *et al.* Public involvement in research: assessing impact through a realist evaluation. *Health Services and Delivery Research* 2014;7:1–128.	Not PPI
Sarrami-Foroushani 2014	Sarrami-Foroushani P, Travaglia J, Debono D, *et al.* Key concepts in consumer and community engagement: a scoping meta-review. *BMC Health Services Research* 2014;14:250.	Not PPI
Sarrami-Foroushani 2104	Sarrami-Foroushani P, Travaglia J, Debono D, *et al.* Implementing strategies in consumer and community engagement in health care: results of a large-scale, scoping meta-review. *BMC Health Services Research* 2014;14:402.	Not PPI
Simpson 2002	Simpson EL, House A. Involving users in the delivery and evaluation of mental health services: systematic review. BMJ. 2002 Nov 30;325(7375):1265–1265.	Not PPI
Tempfer 2011.	Tempfer CB, Nowak P. Consumer participation and organizational development in health care: A systematic review. *Wiener Klinische Wochenschrift* 2011;123:408–14.	Not PPI
Ward 2012	Ward J, de Motte C, Bailey D. Service user involvement in the evaluation of psycho-social intervention for self-harm: a systematic literature review. *Journal of Research in Nursing* 2013;18:114–30.	Not PPI
Higginson 2013.	Higginson IJ, Evans CJ, Grande G, *et al.* Evaluating complex interventions in End of Life Care: the MORECare Statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. *BMC Medicine* 2013;11:111.	Not systematic review
Jagosh 2012	Jagosh M, Macaulay A, Pluye P, *et al.* Uncovering the Benefits of Participatory Research: Implications of a Realist Review for Health Research and Practice. *Milbank Quarterly* 2012;90:311–46.	Not systematic review
Jamshidi 2014	Jamshidi E, Morasae EK, Shahandeh K, *et al.* Ethical Considerations of Community-based Participatory Research: Contextual Underpinnings for Developing Countries. *International Journal of Preventive Medicine* 2014;5:1328–36.	Not systematic review
Oliver 2008	Oliver SR, Rees RW, Clarke-Jones L, *et al.* A multidimensional conceptual framework for analyzing public involvement in health services research. *Health Expectations* 2008;11:72–84.	Not systematic review
Staniszewska 2011	Staniszewska S, Brett J, Mockford C, *et al.* The GRIPP checklist: Strengthening the quality of patient and public involvement reporting in research. *International Journal of Technology Assessment in Health Care* 2011;27:391–9.	Not systematic review
Wilson 2015	Wilson, P. et al., 2015. ReseArch with Patient and Public invOlvement: a RealisT evaluation – the RAPPORT study. Health Services and Delivery Research, 3(38), p.1-176. Available at: http://www.journalslibrary.nihr.ac.uk/hsdr/volume-3/issue-38.	Not systematic review

Chapter 4 Appendices

Registration and protocol

Research Registry# 1986 http://www.researchregistry.com/browse-the-registry.html#home/registrationdetails/5856b9bd759db5ec4609d880/.

Protocol: Price A, Burls AJ, Vasanthan, et al. Self-management open online trials in health [SMOOTH] an analysis of existing online trials [Protocol]. *PeerJ* Published Online First: 2017. https://doi.org/10.7287/peerj.preprints.2671v1. https://peerj.com/preprints/2671/.

Supplementary data

Appendix 1 ORCHID Search Strategy

Appendix 2 Glossary and additional graphs

Appendix 3 Included and excluded studies plus additional data

Chapter 6 Appendices

Table 34 Search terms for overview of informed consent

	Search Terms for Informed Consent Overview
#	Search Terms
1	communications media/
2	exp educational technology/
3	exp audiovisual aids/
4	video recording/
5	exp videoconferencing/
6	video games/
7	(video* or dvd* or film* or cd-rom* or audiovisual* or audio-visual* or multimedia or multi-media).tw.
8	information systems/
9	online systems/
10	exp computers/
11	exp computers/
12	hypermedia/
13	user computer interface/
14	computer assisted instruction/
15	computer assisted instruction/
16	(computer* and (sound or audio* or graphic* or imag* or game* or gaming)).tw.
17	computeri#ed.tw.
18	(interactive or animation*).tw.
19	internet/

	Search Terms for Informed Consent Overview
#	Search Terms
20	(internet or web or website* or webcast*).tw.
21	(computer adj (assisted or aided or based or mediated or generated)).tw.
22	medical informatics/
23	decision support techniques/
24	decision-making computer assisted/
25	((decision* or decid*) adj4 (tool* or technolog* or technique* or system* or program*)).tw.
26	Patient Education as Topic/
27	(leaflet? or brochure? or handout? or hand-out? or booklet? or (information adj2 (sheet? or tool* or material?))).ti,ab.
28	(patient information or patient education).ti,ab.
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	exp Informed Consent/
31	consent*.tw.
32	(informed adj2 (decision? or choice*)).tw.
33	Therapeutic Misconception/
34	exp Disclosure/
35	disclos*.tw.
36	((improv* or increas* or enhanc* or patient) adj3 (understanding or comprehension or knowledge)).tw.
37	30 or 31 or 32 or 33 or 34 or 35 or 36
38	clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs.
39	29 and 37 and 38
40	Cochrane database of systematic reviews.jn.
41	search:.tw.
42	meta-analysis.pt.
43	MEDLINE.tw.
44	systematic review.tw.
45	40 or 41 or 42 or 43 or 44
46	39 and 45
47	meta-analysis.pt.
48	MEDLINE.tw.
49	systematic review.tw.
50	47 or 48 or 49
51	39 and 50
52	29 and 37 and 50

Table 35 Table of Excluded studies Over for informed consent

Table of Excluded Studies		
#	Citation	Exclusion
1.	Abdoler E, Wendler D. Using data to improve surrogate consent for clinical research with incapacitated adults. *Journal of Empirical Research on Human Research Ethics* 2012;**7**:37–50.	Surrogate Consent
2.	Armstrong S, Langlois A, Laparidou D, *et al.* Assessment of consent models as an ethical consideration in the conduct of prehospital ambulance randomised controlled clinical trials: a systematic review. *BMC Medical Research Methodology* 2017;**17**:142.	Consent models only
3.	Ayuso C, Millán JM, Mancheño M, *et al.* Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. *European Journal of Human Genetics* 2013;**21**:1054–9.	Not about RCTs
4.	Badin M, Brown H, Burns KEA, *et al.* Use of alternative consent models in randomized trials of acute care research: A systematic review. *American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS* 2014;**189**:4468.	Surrogate Consent
5.	Bernardes MJ, Nunes R. Consentimento dos doentes para a publicação de casos clínicos: Revisão da literatura. *Arquivos de Medicina* 2013;**27**:58–64.	Not about RCTS
6.	Brunoni AR, Tadini L, Fregni F. Changes in Clinical Trials Methodology Over Time: A Systematic Review of Six Decades of Research in Psychopharmacology. *PLoS ONE* 2010;**5**:e9479.	Not about informed consent
7.	Chan TW, Mackey S, Hegney DG. Patients' experiences on donation of their residual biological samples and the impact of these experiences on the type of consent given for the future research use of the tissue: a systematic review. *International Journal of Evidence-Based Healthcare* 2012;**10**:9–26. d	Not about RCTs
8.	da Silva MEM, Coeli CM, Ventura M, *et al.* Informed consent for record linkage: a systematic review. *Journal of Medical Ethics* 2012;**38**:639–42.	Not about RCTS
9.	DiazOrdaz K, Slowther A-M, Potter R, *et al.* Consent processes in cluster-randomised trials in residential facilities for older adults: a systematic review of reporting practices and proposed guidelines. *BMJ Open* 2013;**3**:e003057.	Cluster RCT not individual consent
10.	Eisenhauer ER, Tait AR, Rieh SY, *et al.* Participants' Understanding of Informed Consent for Biobanking: A Systematic Review. *Clinical Nursing Research* 2017:105477381772269.	Not about RCTs
11.	Elaine M, Agüero M, Montenegro Suris A, *et al.* El Consentimiento Informado En the Informed Consent in International Clinical Trials Including Developing. *Cuadernos de bioetica* 2008;**19**:67–79.	One database

Table of Excluded Studies		
#	Citation	Exclusion
12.	Ellis PM. Attitudes toward and participation in randomized clinical trials in oncology: A review of the literature. *Annals of Oncology* 2000;**11**:939–45.	Not about informed consent
13.	Eltorki M, Uleryk E, Freedman SB. Waiver of informed consent in pediatric resuscitation research: a systematic review. *Academic Emergency Medicine* 2013;**20**:822–34.	Surrogate Consent
14.	Feldman WB, Kim AS, Josephson SA, *et al.* Effect of waivers of consent on recruitment in acute stroke trials. *Neurology* 2016;**86**:1543–51.	Surrogate Consent
15.	Frank B, Gupta S, McGlynn DJ. Psychotropic medications and informed consent: a review. *Annals of Clinical Psychiatry* 2008;**20**:87–95.	Not about RCTs
16.	Fritz R, Bauer JG, Spackman SS, *et al.* Confidence in outcome estimates from systematic reviews used in informed consent. *The Journal of Evidencebased Dental Practice* 2016;**16**:220–7.	Not about informed consent
17.	Garrison NA, Sathe NA, Antommaria AHM, *et al.* A systematic literature review of individuals' perspectives on broad consent and data sharing in the United States. *Genetics in Medicine* 2016;**18**:663–71.	Not about RCTs
18.	Gillies K, Entwistle V, Treweek SP, *et al.* Evaluation of interventions for informed consent for randomised controlled trials (ELICIT): protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials [Electronic Resource]* 2015;**16**:484.	Protocol
19.	Khan A, Capps BJ, Sum MY, *et al.* Informed consent for human genetic and genomic studies: a systematic review. *Clinical Genetics* 2014;**86**:199–206.	Not about RCTs
20.	Kho ME, Duffett M, Willison DJ, *et al.* Written informed consent and selection bias in observational studies using medical records: systematic review. *BMJ* 2009;**338**:b866.	Not about RCTs
21.	Kirk S. Methodological and ethical issues in conducting qualitative research with children and young people: A literature review. *International Journal of Nursing Studies* 2007;**44**:1250–60.	Surrogate consent
22.	Kuthning M, Hundt F. Aspekte schutzbedürftiger patienten sowie der einwilligung nach aufklärung in klinischen prüfungen. *GMS German Medical Science* 2013;**11**:1–12.	Surrogate consent
23.	Le Breton A, Hervé C, Pirnay P. Informations et consentement au cours de soins dentaires associés à la recherche biomédicale. *Santé Publique* 2013;**25**:803.	One database
24.	Linde K, Dincer F. How Informed Is Consent in Sham-Controlled Trials of Acupuncture? *The Journal of Alternative and Complementary Medicine* 2004;**10**:379–85.	One database
25.	Liu C, Cox Ronald B. J, Washburn IJ, *et al.* The Effects of Requiring Parental Consent for Research on Adolescents'	Surrogate consent

Table of Excluded Studies		
#	Citation	Exclusion
	Risk Behaviors: A Meta-analysis. *Journal of Adolescent Health* 2017;**61**:45–52.	
26.	Mandava A, Pace C, Campbell B, *et al.* The quality of informed consent: Mapping the landscape. A review of empirical data from developed countries. *Journal of Medical Ethics: Journal of the Institute of Medical Ethics* 2012;**38**:356–65.	One database
27.	Megone C, Wilman E, Oliver S, *et al.* The ethical issues regarding consent to clinical trials with pre-term or sick neonates: a systematic review (framework synthesis) of the analytical (theoretical/philosophical) research. *Trials* 2016;**17**:443.	Surrogate consent
28.	Millan-Gonzalez R. [Informed Consent and the Approval by Ethics Committees of Studies Involving the Use of Atypical Antipsychotics in the Management of Delirium]. *Revista Colombiana de Psiquiatria* 2012;**41**:150–64.	One database
29.	Mystakidou K, Panagiotou I, Katsaragakis S, *et al.* Ethical and practical challenges in implementing informed consent in HIV/AIDS clinical trials in developing or resource-limited countries. *SAHARA-J: Journal of Social Aspects of HIV/AIDS* 2009;**6**:46–57.	One database
30.	Nichol G, Huszti E, Rokosh J, *et al.* Impact of informed consent requirements on cardiac arrest research in the United States: exception from consent or from research? *Resuscitation* 2004;**62**:3–23.	Surrogate consent
31.	Olson CM, Jobe KA. Reporting approval by research ethics committees and subjects' consent in human resuscitation research. *Resuscitation* 1996;**31**:255–63.	Surrogate consent
32.	Palmer BW, Savla GN. The association of specific neuropsychological deficits with capacity to consent to research or treatment. *Journal of the International Neuropsychological Society* 2007;**13**:1047–59.	Surrogate consent
33.	Palmer BW, Harmell AL, Dunn LB, *et al.* Multimedia Aided Consent for Alzheimer's Disease Research. *Clinical Gerontologist* 2017;**41**:1–13.	Not systematic review
34.	Rebers S, Aaronson NK, van Leeuwen FE, *et al.* Exceptions to the rule of informed consent for research with an intervention. *BMC Medical Ethics Vol 17 2016, ArtID 9* 2016;**17**:1–11.	Surrogate consent
35.	Rithalia A, McDaid C, Suekarran S, *et al.* A systematic review of presumed consent systems for deceased organ donation. *Health Technology Assessment* 2009;**13**:iii, ix-95.	Surrogate consent
36.	Ross S, Grant A, Counsell C, *et al.* Barriers to Participation in Randomised Controlled Trials. *Journal of Clinical Epidemiology* 1999;**52**:1143–56.	Not about informed consent

Table of Excluded Studies		
#	Citation	Exclusion
37.	Singhal N, Bhola P. Ethical practices in community-based research in non-suicidal self-injury: A systematic review. *Asian Journal of Psychiatry* 2017;**30**:127–34.	Not about RCTs
38.	Smith DC, Boel-Studt S, Cleel ,, *et al.* Parental consent in adolescent substance abuse treatment outcome studies. *Journal of Substance Abuse Treatment* 2009;**37**:298–306.	Surrogate consent
39.	Taljaard M, Mcrae AD, Weijer C, *et al.* Inadequate reporting of research ethics review and informed consent in cluster randomised trials: review of random sample of published trials. *BMJ* 2011;**342**:d2496.	Cluster RCT not individual consent
40.	Tamariz L, Palacio A, Robert M, *et al.* Improving the Informed Consent Process for Research Subjects with Low Literacy: A Systematic Review. *Journal of General Internal Medicine* 2013;**28**:121–6.	One database
41.	Trung LQ, Morra ME, Truong ND, *et al.* A systematic review finds underreporting of ethics approval, informed consent, and incentives in clinical trials. *Journal of Clinical Epidemiology* 2017;**91**:80–6.	Not about RCTs

Chapter 7 PLOT-D Appendices

PLOT-D Round 1 Background Discussion

Thank you for your participation in Round-1. This Delphi is going well with several hundred participants, and we have learned from you. Your comments were most helpful to clarify concepts and add important items, you also gave great feedback on why some items were of decreased importance for you.

An Online Delphi is a structured communication tool developed through multiple rounds of questions presented online for evaluation to participants. The online Delphi in combination with consensus meetings is presently used in achieving consensus in the construction of core outcome sets. As of 2014, 75% of COMET core outcome set consensus research projects successfully used this method[1]. Delphi research is increasingly used to develop core outcome sets across diagnosis, intervention, effectiveness, and public and patient involvement and methodology research[11,12].

The Delphi method has been used to build reporting guidelines for PPI research[3], to establish guideline recommendations for inclusion of patient-reported outcomes in clinical trial protocols (the spirit-pro extension)[4] and has been modified for use in developing clinical practice guidelines for traumatic brain injury[5] Researchers are using Delphi methods to develop community involvement in healthcare policy and research, clinical practice guidelines and patient information materials[10] A Delphi can serve as an interactive consensus tool, a forecast of emerging opinions, as an assessment for gaps in research,[6] and as a shared decision–making method[2].

The respondents usually answer questionnaires in a minimum of two rounds and this is the second round. This communication will share with you the consensus to date and may serve to guide your

response. The figures included with the questions will show you how other respondents answered. Questions added because of respondent feedback will say NEW and we invite you to answer these.

General Comments

Comment: "*It would be helpful to remind us, on each webpage, if we are answering these questions for a protocol of the study or for the actual conduct of the study - it is easy to get mixed up when reading these specific questions "*

"*My problem here is the "holiday suitcase problem": you can make a case for adding an extra sweater, or pair of trousers, or shoes, and it is hard to argue against that. but then you won't be able to close the suitcase and go on holiday. the current vogue is to add more and more information to consent forms. it is not entirely clear how this helps patients: indeed, there are studies (look them up!) that show the more information you put in a consent form, the less patients understand"*

Response: We hope people can look at the questions and visualize how to include the elements of conducting the study by representing them in the protocol. For those who consider the information could go in another document or that some organisations will have standard procedures please consider that a link to other documents is perfectly acceptable and counts as including the materials in the protocol.

Comment: Many people shared "*It was the first time I was asked to consider one or more of these questions and I am not so confident about my level of expertise"*

Response: This Delphi is meant to find consensus that meets the needs of those who are writing a protocol for the first time so a variety of levels of expertise is what we were hoping for. We agree that knowing how experienced we are in answering the questions would add to the study so we have added a level of experience option to each set of questions.

Thank you so much for participating in the Delphi. Your answers may change or stay the same.

For any questions, concerns or communications please contact Amy Price
amy.price@kellogg.ox.ac.uk

Specific Question Sets

Question 17

Q17. How important is it for the trial protocol to include statements?

- **Describing the software used to run the trial platform?**
- **Reporting platform compatibility across devices (Tablet, Phone, Computer, Other)?**
- **Stating browser and operating system compatibility (Windows, MAC, Safari, Firefox etc.)?**
- **Stating if data can be entered both online and offline?**

Table 36 Q17

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
9.59%	40	20.14%	84	124	29.73%	32.85%	137	27.34%	114	10.07%	42	156	37.41%	417
4.09%	17	14.18%	59	76	18.17%	24.04%	100	41.35%	172	16.35%	68	240	58.70%	416
5.29%	22	14.42%	60	82	19.71%	24.04%	100	37.74%	157	18.51%	77	234	56.25%	416
3.12%	13	11.51%	48	61	14.63%	27.10%	113	38.13%	159	20.14%	84	243	58.27%	417

. This item does not yet have the consensus for inclusion as defined by the protocol >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale. The last column shows number who responded from the 571 participants.

Comment: So long as available. the 'nuts and bolts' don't need to be upfront
Action added: How important is it to consider participant fatigue and add the details in a linked supporting document. (To all questions)

Comment: If the platform is fully accessible to all devices/platforms, then stating compatibility is less important than if the platform is only fully functional on some platforms.
Action added: Rephrase question to reflect reporting the platform/browser compatibility is important if it is limited.

Comment: Add" Do you deem useful any IT query open by clicking on a link for receiving help in understanding?"
Action added: include a link to the IT and Research team for IT queries

Comment: Are you designing in ways that will facilitate use of watches and wearable sensors?
Action added: Add to question

Comment: It is important to ask if incomplete information can be saved or if it will be lost if not complete
Action added: Add to this question and to this Delphi

Comment: What IS important is where the data is being collected and stored (re: USA's Patriot Act, etc.)
Action added: How important is it to state in the protocol if where data is collected and stored complies with data protection standards

Comment: Please add an unsure for those who have not faced these problems themselves and are considering for the first time.
Action added: added unsure option

Comment: If it is key to participation it could be an eligibility criterion and then would need to be described as such
Action added: How important is it to describe in the "eligibility criteria" in the study protocol if it is a key to participation
Tensions Include in protocol or share link in protocol vs proprietary data and too much information

Question 18

Q18. For login and password functions please rate how important it is to report:

- **How passwords are generated**

- **How passwords are recovered**
- **Whether the device allows "remembering" of the login and password**
- **Comments or suggestions? Add items or rephrase the question for clarity.**

Table 37 Q18

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
16.35%	68	22.84%	95	39.19%	163	25.24%	105	22.36%	93	13.22%	55	148	35.58%	416
7.21%	30	13.70%	57	20.91%	87	23.56%	98	31.49%	131	24.04%	100	231	55.53%	416
6.27%	26	16.39%	68	22.66%	181	26.27%	109	33.25%	138	17.83%	74	343	51.08%	415

This item does not yet have the consensus for inclusion as defined by the protocol >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale. The last column shows number of those who responded from 571 participants.

Comment: Frame in usability sense as remembering passwords improves usability dramatically
May or may not be important in context of trial protocol (for example, not particularly important if trial consists of a single online session)
This section is not clear. What do you mean login and passwords? For whom? The researchers? The participants? The assessors?

Action added: Add context and rephrase

Comment: Better security methods are available, such as sending a text confirmation of logging in to the person's mobile phone, or an email confirmation to the person's computer. Passwords should only be used for people who actively state a preference for them over other security methods.
Password security is becoming increasingly important.
Passwords with too many restrictions are not adequate, changing the password every 4 weeks is not adequate. Then I give up answering because it's too much effort.
Action added: Add usability question
Tensions: Data security vs attrition due to login complexity

Question 19

Q19. How important is it for researchers to pre-test the following areas with volunteers before running the trial?

- **The functionality of the trial platform (e.g. Enrolment, data entry, password recovery, error reporting, security, step transitions etc.)**
- **The usability of the intervention from the participants' perspective**
- **The participants understanding of the intervention**
- **The time required per visit to learn the allocated tasks**
- **The time required per visit to respond to the tasks**
- **To troubleshoot potential areas where participants might drop out**
- **I want to include another type of testing or leave a comment about testing or rephrase the question (please specify).**

Table 38 Q19

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
1.26%	5	3.27%	13	4.53%	18	8.79%	35	38.94%	155	47.74%	190	345	86.68%	398
0.50%	2	2.01%	8	2.51%	10	9.52%	38	38.35%	153	49.62%	198	351	87.97%	399
0.25%	1	1.76%	7	2.01%	8	11.31%	45	32.91%	131	53.77%	214	345	86.68%	398

Appendix Table

0.50%	2	2.51%	10	3.01 %	10	17.09%	68	48.99 %	195	30.90%	123	318	79.79 %	398
0.00%	0	1.26%	5	1.26 %	5	17.34%	69	49.50 %	197	31.91%	127	324	81.41 %	398
0.00%	0	2.27%	9	2.27 %	9	13.10%	52	40.81 %	162	43.83%	174	336	84.64 %	397

This item has the consensus for inclusion of all items as defined by the protocol >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated. The last column shows number of those who responded from 571 participants.

Comment: Which clinical benefits participants could receive from their participation.
Action added: Yes

Comment: Test if participants understand correctly what is asked and how they should answer in order to test the process and also check the consistency for testing of implementation fidelity
Action added: Added to the question

Comment: For proper planning until the final product, the analysis results, pre-testing by simulating data and testing data analysis and evaluation is quite important. I have seen it too many times that much time went into preparation and conduct only to find out that analysis of such data were difficult to impossible since better data could have been collected to answer the question of interest. Similarly, **an analysis plan presented up front** can help understanding the (non-) adequacy of the planned study.
Action added: How important is it to add a predefined analysis plan and test this with pilot

Comment: It should be noted that the purpose of some trials may be to study usability or understanding.
Action added: added qualifier

Comment: How comfortable is the intervention for the patient, both psychologically and physically? Risks, level of pain if applicable, parking, location, settings, if overnight stay is required, level of monetary compensation, reaching of targeted population, is a "protected" population involved, etc. Testing randomization, adherence, retention, costs (e.g. advertising) are all relevant to the feasibility of scale-up. Outcome measure should similarly be pre-tested for feasibility, acceptability, and validity before they are used. Test lay language of the protocol
Action added: added qualifiers and options to question

Comment: It is important to inform possible chances to have adverse effects of interventions and to give them other possibilities to not dropout (intention to treat)
Action added: Include option for intention to treat (explain this term)
Tensions: Full disclosure vs Too much information to be comprehended

Question 20

Q20. How important are each of the following areas for understanding or replicating the research?

- **Describing the intervention fully to facilitate replication?**
- **Presenting the source code/screenshots/ flowcharts of the algorithms or working examples for the intervention (only as applicable)?**
- **Describing the methods and expected frequency of communication concerning the intervention (e.g. SMS, face to face, interactive voice response, video, electronic conferencing, forum, email)?**
- **Describing how users can give feedback about the intervention. User feedback could include user opinions about content or user interface, their perceptions about usability, access, connectivity?**
- **Comments or suggestions about the software (please specify) You can also add or rephrase a question to make it clearer.**

Table 39 Q20

Not at all important		Slightly important		Combined		Moderately important		Very important		Extremely important		Combined		Total
0.51%	2	0.76%	3	1.27 %	5	8.10%	32	34.68 %	137	55.95%	221	90.33 %	358	395
1.77%	7	7.59%	30	9.36 %	37	25.06%	99	42.78 %	169	22.78%	90	65.56 %	259	395
0.51%	2	2.28%	9	2.79 %	11	18.48%	73	45.57 %	180	33.16%	131	78.73 %	311	395
1.26%	5	3.54%	14	4.80 %	19	27.53%	109	44.70 %	177	22.98%	91	67.68 %	268	396

This item has partial consensus for inclusion as defined by the protocol [items 1&3] >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale. The last column shows number of those who responded from 571 participants.

Comment: Providing raw data of participants (anonymous) in appendix, similar to one that authors would request for individual participant data. At least, have an online access to store all raw data, so potential researchers can make an application to access the online data. Qualify options here as access may be controlled by privacy laws, funders, data source such as national registries or insurance data. Describing the intervention, source code, etc. is NOT "just" about facilitating replication, it is also about assessing for risk of bias, confounding, and other errors to determine whether the outcome is valid and/or reliable.
Action added: Option now included and qualified

Comment: Mention the "approximate frequency" of communication concerning the information
Action added: How important is it to mention the "approximate frequency" of communication concerning the information to participants

Comment: User feedback could include user opinions about content or user interface, their perceptions about usability, access, connectivity and if it is used to assess the intervention, if later to be used in clinical practice participants could pre-assess the standard of care and approaches. I think the above should not just be done for the intervention, but also be done for standard of care so patients can compare approaches.
Action added: Clarified entry and added standard of care and plan for advising respondents of how the feedback was used.

Comment: Whether it would be important to provide working examples/source code depends on the nature of the intervention. If an intervention is so highly dependent on specifics to permit replication, it raises the question of whether the findings are sufficiently robust as to represent an actual phenomenon as opposed to spurious results.
Action added: Qualified and added comment for consideration
Tensions: Open Data vs harms of Data Abuse

Question 21

Q21. How important is it to include definitions in plain language and supply links to explanations of these declarations to aid participants' understanding of each of the following?

- **Data security procedures**
- **Confidentiality statements**
- **Declarations about the extent to which you can make the raw data available to others**
- **Plans to share the research with others including patients and members of the public**
- **How to write a Patient and Public Involvement (PPI) plan**
- **Declarations of the access and rights participants have to their own research data**

- **Survey or questionnaire methods with the expected declarations**
- **Comments or suggestions? Here you can add items, or rephrase the question for clarity**

Table 40 Q21

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
0.74%	3	5.43%	22	6.17%	25	16.54%	67	37.04%	150	40.25%	163	77.29%	313	405
0.00%	0	3.46%	14	3.46%	14	10.86%	44	34.57%	140	51.11%	207	85.68%	347	405
0.74%	3	6.45%	26	7.19%	29	19.85%	80	38.71%	156	34.24%	138	72.96%	294	403
0.50%	2	5.45%	22	5.95%	24	20.05%	81	39.60%	160	34.41%	139	74.01%	299	404
6.48%	26	14.71%	59	21.19	85	31.92%	128	29.18%	117	17.71%	71	46.89%	188	401
1.24%	5	5.71%	23	6.95	28	12.90%	52	40.20%	162	39.95%	161	80.15%	323	403
4.05%	16	10.89%	43	14.94%	59	24.81%	98	36.46%	144	23.80%	94	60.26%	238	395

This item has partial consensus for inclusion as defined by the protocol [items 1-4&6] >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale

Comment: Plain language is defined as communication that is clear, concise, well organized and follows best practices appropriate to the subject or field and the intended audience. The entire protocol should be in plain language. Always. These are not mutually exclusive explanations. It is important that participants understand what will happen to their data, who will have access during and after the study, and how their personal details will be protected/secured so that they have the chance to decline to participate if they feel uncomfortable about any of these aspects.
Action added: Added this as a question and rephrased existing questions

Comment: I think that I and my doctor should have access to any data of potential interest to us unless there are very strong reasons why not. AND I do not want my medical providers to have access and want assurance they will not have it.
Action added: Added this as a question

Comment: The final question needs rephrasing to clarify what exactly is meant by ' with the expected declarations'
Action added: Eliminated question as it is spurious
Tensions: Plain language vs complete information e.g. dumbing down

Question 22

Q22. How important is it for members of the research team to declare financial or personal competing interests?
Researchers' to declare financial competing interests?
Patients' and members of the public's financial competing interests?
Researchers' personal competing interests?
Patients' and members of the public's personal competing interests?

Table 41 Q22

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
0.48%	2	1.20%	5	1.68%	7	5.74%	24	24.88%	104	67.70%	283	92.58%	387	418
4.33%	18	7.21%	30	11.54%	48	17.31%	72	29.33%	122	41.83%	174	71.16%	296	416
2.39%	10	3.11%	13	5.50%	23	11.48%	48	31.58%	132	51.44%	215	83.02%	347	418
6.24%	26	7.91%	33	14.55%	59	22.30%	93	30.70%	128	32.85%	137	63.55%	265	417

This item has partial consensus for inclusion as defined by the protocol [items 1-3] >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale

Question 23

Q23. How important is it for researchers to include the following information in the trial protocol?
A description of how informed consent will be obtained e.g. (handwritten, digital, audio, video, biometrics, facial recognition, proxy consent by a parent or guardian).
How participants' understanding of this consent will be tested (e.g. questionnaire with multiple choice, true/false questions, open responses, checkbox)?

Table 42 Q23

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
0.95%	4	4.05%	17	5.00%	21	11.19%	47	35.00%	147	48.81%	205	83.81%	352	420
2.63%	11	11.72%	49	14.35%	60	23.44%	98	35.89%	150	26.32%	110	62.21%	260	418

Comments or suggestions? Here you can add items or rephrase the question for clarity.

This item has partial consensus for inclusion as defined by the protocol [items 1] >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale

: Not legal or ethical unless understanding is checked, and consent explicitly obtained
Is reconsent important? I think so!
Action added: Include question of reconsent for multiple interventions over time and for consent review updating in a long study

Comment: (no suggestion at this juncture — just a compliment. It is extremely rare in my experience to ask for user feedback this early. It's great you are doing so as I have often wished for it elsewhere.
I recommend including both how the participants' understanding of the consent will be facilitated and confirmed. (Many may find the idea of testing dysphoric.)
Action added: How important is it to include both how the participants understanding of consent will be facilitated and how it will be confirmed

Comment: Several of you shared multiple ways of gathering informed consent comprehension including open responses, online interview, multiple choice questions, reporting back information, participant web conference meetings to ask questions
Action added: How important is it gather consent comprehension through:

- including open responses
- online interview, multiple choice questions
- reporting back information
- slide presentation with quiz
- Consider having an animated video explaining/providing information on informed consent. Most people understand better when multiple methods are utilized
- Virtual personalized discussion e.g. by web conference, Whats App. or Google hangouts or Zoom with all participants and the PI and senior investigators or trial staff

Tensions: Resource costs and focus vs completeness of informed consent

Question 24

Q24. If you were a trial participant, how would you prefer to access the informed consent materials? I would prefer to be able to (you may tick more than one option for this question):

Answer Choices
download the informed consent materials in a portable format e.g. as a PDF
read informed consent materials online
receive informed consent materials by email
Comments or suggestions? Here you can add items or rephrase the question for clarity.

Table 43 Q24

Responses	
57.38%	237
52.54%	217
50.36%	208

All options met threshold and will be included but further options will be added

Comments: There should be an option to download the same (as pdf) which allows the subject to read it and **come back again in the website/ link to participate.**

Depending on participant characteristics, I would choose the medium for informed consent. I would, however, ask preference from participants.

I think it is important to **highlight the main Points** regarding informed consents Such documents often impossible to read and understand if many pages - avoid that.

Cloud based data storage and retrieval systems

If read online I would like them in mobile/iPad friendly format.

Online to allow definitions for words as a link.

This would have limited application in my area of research (acute care) where often we are in a time critical / life threatening situation. Consider pre-consent of medical consent for research

The information should be downloadable and be in a form that can be shared with other experts. Ensure it is accessible format, e.g. large print Option to have it sent as paper to home
Action added: The above options will be added for participants to rate 1-5 with one being not at all important to 5 being extremely important
Tensions: Resource costs and focus vs completeness of informed consent

Question 25

Q25. Please indicate how important it is to include these statements about volunteer research partner involvement in documents and publications about the trial:
The areas of the research process where volunteer research partners made contributions
The ways the volunteer research partners contribution added value to the research and the research team
Comments or suggestions? Here you can add items or rephrase the question for clarity.

Table 44 Q25

Not at all important	Slightly important	<Combined	Moderately important	Very important	Extremely important	Combined>	Total

Appendix Table

2.68%	10	8.58%	32	11.26 %		28.15%	105	40.21 %	150	20.38%	76	60.59 %	25 5	373
3.74%	14	8.29%	31	12.03 %		28.34%	106	40.64 %	152	18.98%	71	59.62 %	25 8	374

This item does not yet have the consensus for inclusion as defined by the protocol >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale. It met the lower bounds but not higher bounds indicating many are undecided , The last column shows number who responded from the 571 participants

Comments: Several want to see stated how volunteers were recruited
Action added: Add question how important is it to state in the protocol and reported in a paper how partners will be recruited and how they are trained
Comments: What forms of research is this important too, should specify clinical
Action added: Specify in clinical, prevention, health
Comment Add what the voluntary research partner receives in exchange, e g co authorship, acknowledgment in publication etc.
Action added: How important is it to include in the protocol what the volunteer receives in exchange for their work
Tension: Include in main document vs supplementary materials, measure value vs inclusivity

Question 26

Q26. How important is it to acknowledge the contributions of volunteer research partners such as members of the public, advocacy organizations, carers, or patients?
In the methods section within the body of the report
In the contributor ship or acknowledgement section (if available)
As authors if they fulfil the requirements for authorship
Comments or suggestions? Here you can add items or rephrase the question for clarity.

Table 45 Q26

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Tot al
9.89%	37	11.23%	42	21.12 %	7 9	25.40%	95	33.96 %	12 7	19.52%	73	53.48 %	20 0	374
2.68%	10	4.29%	16	6.97%	2 6	19.03%	71	39.68 %	14 8	34.32%	128	74.00 %	27 6	373
3.20%	12	7.47%	28	10.67 %	4 0	12.00%	45	31.73 %	11 9	45.60%	171	77.33 %	29 0	375

This item has partial consensus for inclusion as defined by the protocol [items 2,3] >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale and this is shown by the pink shading

Comments: Advocacy organizations are not persons, name representative rather than organization. clarify what is an author with examples
Action added Clarified
Tension Confidentiality and role clarity issues vs credit for work done

Question 27

Q27. How important is it to do the following?
Thank patient organizations or advocacy groups by name?
Thank research volunteers by name (with their permission)?
Thank the individual volunteers by name (with their permission) and the patient/advocacy organization(s) to which they belong (as applicable)?
Thank but not name volunteers who choose to remain anonymous?
Thank and name research volunteers in the supplementary materials or the research website?
Comments or suggestions? Here you can add items or rephrase the question for clarity.

Appendix Table

Table 46 Q 27

Not at all important		Slightly important		<Combined		Moderately important		Very important		Extremely important		Combined>		Total
4.83%	18	7.51%	28	12.34%	46	23.06%	86	38.61%	144	26.01%	97	64.92%	241	373
11.80%	44	16.89%	63	28.69%	107	23.59%	88	30.56%	114	17.16%	64	47.72%	178	373
14.86%	55	15.68%	58	30.54%	113	25.41%	94	28.11%	104	15.95%	59	44.06%	163	370
6.43%	24	10.72%	40	17.15%	64	20.64%	77	36.73%	137	25.47%	95	65.20%	232	373
12.13%	45	15.63%	58	27.76%	103	26.95%	100	29.38%	109	15.90%	59	45.28%	209	371

This item does not yet have the consensus for inclusion as defined by the protocol >70% of responses rating the items at 4 or greater and not more than 15% of responses rating any item <2 on the graduated scale. The last column shows number who responded from the 571 participants

Comment: Perhaps there could be a separate field in the bibliographic record for this information. Authors in the author field, volunteers in the volunteer field. That way we can acknowledge their contribution to the work in a real way, and not as a "thank you".
Action added: Not possible as this is dependent on the journal software not authors or investigators.

Comment: Need to differentiate between volunteer research partners and participants as there are concerns with naming participants.
Action added: Explain this more clearly as participants may be thanked however partners would be more likely to fulfil authorship or contributor status. To clarify: Participants are thanked in a variety of ways but not named. Partners are named and acknowledged unless they request to be anonymous.
Tensions: Privacy concerns re anonymity vs privacy and details of task vs word count

We will send you a preliminary summary of the results and an email once the research is accepted for publication, if you have selected this option in the Delphi. For any questions, concerns or communications please contact Amy Price amy.price@kellogg.ox.ac.uk