MAXIMISING THE IMPACT OF PATIENT-REPORTED OUTCOME TRIAL RESULTS TO BENEFIT PATIENTS AND SOCIETY

by

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Abstract

There is an increasing need to demonstrate the return on medical research investment through benefit to patients, society and the economy. Patient-reported outcomes (PROs), such as quality of life and symptom data, are increasingly collected in clinical trials and may provide evidence, which can lead to a range of impacts. However it is unclear whether PRO impact is realised in practice. In addition, the different types of impact associated with PRO trial results, their barriers and facilitators, and appropriate impact metrics are not well defined.

The doctoral research constituting this thesis adopted a mixed-methods approach with the aim of: a) synthesising existing methodological frameworks for healthcare research impact; b) determining the range of potential impacts associated with PRO data collected in trials, identifying potential PRO impact metrics and barriers and defining common facilitators to maximise PRO impact and; c) examining real-world evidence of PRO trial data impact and highlight optimal pathways to such impact. A number of studies were undertaken to address the aims.

First, a systematic review of the literature identified 24 existing non-PRO-specific frameworks and over 80 impact metrics, which were then synthesised into a novel impact matrix and a simplified consolidated methodological framework for use by researchers and other stakeholders to help maximise the impact of healthcare research.

Second, informed by this framework, an additional systematic review sought to determine the potential impact of PRO data collected in clinical trials and examined real-world evidence of PRO trial data impact based on Research Excellence Framework (REF). This systemic review suggested that PRO trial data has the potential to inform

clinical practice, clinical guidelines and, health policy; support drug approval, pricing and reimbursement decisions and; inform clinical and shared decision-making and consent for treatment. Furthermore, this second systematic review highlighted perceived methodological problems regarding the design, conduct and analysis and reporting of PRO data from clinical trials; which may hinder the impact of PRO data from clinical findings. Potential facilitators aimed at maximising PRO trial impact were also identified. The review identified 12 (n=69, 17%) REF 2014 impact case studies, which reported impact directly attributable to PRO findings. Including changes to international clinical guidelines and national guidelines, influencing cost-effectiveness analysis and drug approvals.

Finally, in order to gain deeper understanding about the topics identified in the second systematic review, 24 semi-structured qualitative interviews were conducted with international stakeholders. Interviewees suggested PRO trial findings could lead to impact in the five impact categories identified in the aforementioned 'pathways to research impact' methodological framework. However, it was suggested that broader international stakeholder collaboration is required to tackle existing barriers and maximise the realisation of PRO trial impact on patients and society.

In conclusion, this thesis has identified a range of potential impacts from PRO data which may benefit patients and society. However, a number of barriers need to be addressed to fully realise these benefits. This research highlights that the measurement of research impact, and specifically PRO research impact, is an essential exercise to better allocate limited funding, provide accountability and minimise research waste. Nonetheless, determining and implementing impact metrics is a complex task and will

require greater stakeholder collaboration and engagement throughout the research pathway.

Dedication

To my husband, for your encouragement and infinite love

To mum and dad, thanks for your love and support despite the distance

To my brother, thanks for always being there for me

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Contributorship statement

All the chapters within this thesis are product of my own work, assisted by continuous guidance from my supervisors: Prof Melanie Calvert, Dr Derek Kyte, Dr Anita Slade and Dr Christel McMullan.

Dr Thomas Keeley, University of Birmingham Research Fellow and now working for GlaxoSmithKline (GSK), was involved in the concept, design and analysis of Chapter 3. Olalekan Lee Aiyegbusi (PhD candidate, University of Birmingham) was involved in the identification of eligible studies, as second reviewer, and provided feedback on the systematic reviews presented in Chapters 3 and 4.

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List of abbreviations

AIHS	Alberta Innovates & Health Solutions
ASCO	American Society of Clinical Oncology
CAHS	Canadian Academy of Health Sciences
CARE-HF	CArdiac REsynchronisation in Heart Failure
CIHR	Canadian Institutes of Health Research
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT-PRO Extension	CONsolidated Standards Of Reporting Trials
COREQ	Consolidated criteria for reporting qualitative research
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CPROR	Centre for Patient Reported Outcomes Research
CRD	Centre for Reviews and Dissemination
EMA	European Medicines Agency
EPiC	The Evaluation of Patient-Reported Outcome (PRO) Protocol Content and Reporting in UK Cancer Clinical Trials
ER	Emergency room
ESC	European Society of Cardiology
ESTRO	European Society for Radiotherapy & Oncology
FDA	US Food and Drug Administration
HEIs	Higher Education Institutions
HEFCE	Higher Education Funding Council for England
HRQL	Health-related quality of life
IOM	Impact Oriented Monitoring
ISOQOL	The International Society for Quality of Life Research
MHRA	The Medicines and Healthcare products Regulatory Agency
NCRI	The National Cancer Research Institute
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
OMERACT	Outcome Measures in Rheumatology
PCORI	Patient-Centered Outcomes Research Institute

PFDD	Patient-Focused Drug Development
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
PRO-CTCAE	Patient Reported Outcomes – Common Terminology Criteria for Adverse Events
PROMs	Patient-reported outcome measures
PROSPERO	Prospective Registering of Systematic Reviews
PROTEUS	Patient-Reported Outcomes Tools: Engaging Users & Stakeholders
RAE	Research Assessment Exercise
RCT	Randomised Controlled Trial
REF	Research Excellence Framework
RIF	Research Impact Framework
RQF	Research Quality Framework
SIAMPI	Social Impact Assessment Methods
SISAQOL	Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data
SPIRIT-PRO Extension	Standard Protocol Items: Recommendations for Interventional Trials – PRO extension
UK	United Kingdom
PRO Instruments	
CHAQ	Child Health Assessment Questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment - Core Quality of Life Questionnaire
EORTC QLQ-LC13	European Organization for Research and Treatment - Quality of Life Questionnaire - 13-item lung cancer-specific
EQ-5D	European Quality of Life Instrument - 5 Dimension
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessment Questionnaire
MSAF	Myelofibrosis Symptom Assessment Form
SF-36	Short-Form Health Survey 36-item questionnaire
TSS	Total Symptom Score
VAS	Visual Analogue Score

Formatting

This thesis has been formatted according to the University of Birmingham 'Alternative Format Thesis Guidelines', which allows the incorporation of sections that are in a format suitable for submission for publication in a peer-reviewed journal. Full regulations available at:

https://intranet.birmingham.ac.uk/as/studentservices/graduateschool/documents/public/rsa/alternative-format-thesis-guidelines.pdf

Please consider:

- The thesis includes 2 publications. Therefore, the pagination of the publications are not included in the pagination sequence of the thesis submission.
- The incorporation of publication-style chapters in the thesis will inevitably lead to some duplication since each publication-style chapter will have self-contained components that will overlap with parts of the other sections of the thesis.
- Referencing and numbering of tables and figures are self-contained within each chapter.
- The remaining chapters are written in publication format. PLOS Medicine guidelines were followed for consistency for chapters 1-3, 5 and 6. (https://journals.plos.org/plosmedicine/s/submission-guidelines)
- Health and Quality of Life Outcomes guidelines were followed for Chapter 4. (https://hqlo.biomedcentral.com/submission-guidelines/preparing-your-manuscript/review)

Chapter 1: Introduction and background

Introduction to the research

The research within this thesis focuses on the impact of healthcare research and specifically, patient reported outcome (PRO) data collected in clinical trials. The aim of this chapter is to provide a general background and justification for the research; and to outline the aims, objectives and structure of the thesis.

Background

A. Clinical trials

Randomised controlled trials (RCTs) are considered the 'gold standard' tool for determining the efficacy and cost-effectiveness of healthcare interventions [1]. In RCTs, participants are randomly allocated to two or more groups in order to statistically test a clinical intervention. One of the intervention groups is referred as the 'experimental' or 'treatment' group, while the other is known as the 'control' group. The control group can receive a placebo (i.e. dummy drug), usual care, or no intervention [2]. Outcomes are measured at specific time points and the difference in outcomes between the groups is statistically assessed [3].

In clinical trials, the outcomes of interest are often defined as primary and secondary outcomes or endpoints. The primary outcome refers to the main measured variable (e.g. progression free survival or improvement in clinical signs or symptoms such as fatigue) based on the primary hypothesis of the intervention. The primary endpoint should be 'the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial' [4, 5]. The primary endpoint refers to the analysed parameter (e.g. change-from-baseline at 6 weeks in mean fatigue score) [6]. Secondary endpoints assess additional effects of the intervention, side effects or tolerability and may be used to support the primary endpoint [4, 7]. All other types of endpoints are referred as exploratory endpoints.

Exploratory endpoints include outcomes that are unlikely to show an effect but are included to evaluate new hypotheses or clinical important events that are expected to occur too infrequently to show a treatment effect [8]. In order to ensure that any outcomes are identified in line with the proposed hypothesis it requires sufficient power to capture those changes. The number of participants involved in a trial is determined by the power needed to identify a real difference in the primary endpoint [8].

Clinical trials should possess internal and external validity if the results are to inform patient care. Internal validity refers to what extent the treatment effects are attributed to differences in treatment and not confounding (i.e. differences in baseline characteristics between treatment groups that influence treatment and outcome measures) [9]. To achieve optimal trial design and conduct, confounding factors and bias must be reduced to a minimum. Bias is defined as a systematic error or any deviation of the study outcomes from the 'truth' [10]. Careful consideration should be given to randomisation, allocation concealment, blinding and loss to follow up to minimise bias [10]. External validity or generalisability refers to whether the outcomes of the trial can be applied to other setting and patients [9, 11]. While the design and conduct of the study are important to ensure the quality of the clinical trial, it is also important to ensure that outcomes reflect the patient's experiences.

B. Clinical Trials and Patient-Reported Outcomes

One of the important ways of capturing outcomes in clinical trials is through the use of patient reported outcomes (PROs). PRO is an 'umbrella' term, defined by the U.S. Food and Drug Administration (FDA) as *"any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"* [12]. Clinical trials often assess outcomes

such as mortality and morbidity, disease exacerbation or clinical events. Although these clinical outcomes are of great importance, PROs are increasingly collected in clinical trials to provide evidence of the impact of disease or treatment on patient health-related quality of life (HRQL) or symptom severity [13]. HRQL is a multi-dimensional concept that describes or characterises the effect of a disease or treatment on a number of domains that capture a patients' physical functioning, psychological impact and social functioning [13, 14]. Although HRQL is considered a PRO, the terms should not be used interchangeably. The term PRO refers to the source of the report – i.e. the patient; whereas HRQL refers to the concept or content of the report [15]. Between 2007 and 2013, 27% of the clinical trials registered in *ClinicalTrials.gov* collected PRO data [16]. PRO data in clinical trials is collected through self-reported questionnaires known as PRO measures or 'PROMs' [14, 17, 18]. Broadly, PROMs can be classified as disease-specific or generic instruments [14, 19]. The former can be tailored to specific conditions, populations, or certain functions; such as the Oxford Hip Score (OHS) [19, 20]. Generic instruments or 'measures of health status' focus on general aspects of HRQL, irrespective of the disease or condition of the patient [20, 21]. These measures are not designed to assess disease specific effects. Therefore, they might not be suitable to detect small treatment effects [14]. A frequently used generic measure is the 36-Item Short Form Survey (SF-36) [21]. Disease specific measures are often considered to have greater validity and credibility and are more relevant to patients; whereas generic measures allow comparison between different conditions [19].

Trial participants are asked to self-complete PROM questionnaires, which may be available in a number of different formats e.g. paper-based or electronic. These may be completed at different time-points during the study without influence from a third

party e.g. clinician. This type of data can often provide valuable additional information on the impact of side effects from therapeutic interventions on a patient's HRQL. PROs may capture information about benefits or harms that could be overlooked using conventional clinical measures [22]. PROs are used as a way to define and measure endpoints in clinical trials. In addition, they can also provide valuable evidence on the efficacy, effectiveness and tolerability of interventions to drug/device approvals, labelling claims and reimbursement [12, 23, 24].

In clinical trials, health utility PROMs are used to determine patients' preference values on their health status, which are widely used in cost-effectiveness and cost-utility analysis [14, 18, 25]. Single item measures include a single aspect of one PRO instrument. For instance, the item might ask the patients to rate their health on a seven-point scale ranging from very poor to excellent. These measures are less burdensome to collect; however, they are not widely used as their reproducibility, reliability and precision of measurement may be compromised [26]. The European Quality of Life Instrument – 5 Dimensions (EQ-5D) is the most common generic instrument and assesses: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [27]. Utility measures characterise the effects of an intervention into a value between 0 (death) and 1 (perfect health) [25]. There may be situations in which utility falls below 0, meaning that the health status is perceived as worse than death.

The answer given to the five domains of the EQ-5D are transformed to generate a summary score, which indicates the overall utility. Health utility can be combined with survival data to generate quality adjusted life years (QALYs) [28]. QALYs are incorporated in clinical trials to enable comparison among healthcare interventions and inform cost-effectiveness.

Cost-effectiveness analysis expresses value for money in terms of incremental cost-effectiveness ratio (ICER), which is calculated as the difference in costs divided by the difference in QALYs (health utility) gained. In the UK, the use of QALYs is required by the National Institute for Health and Care Excellence (NICE) to inform health technology assessment (HTA) [29]. During the NICE appraisal process, the ICER is compared with a £20,000 to £30,000 threshold per QALY to determine whether the health intervention represents an efficient use of resources [30]. A health intervention is considered 'economically dominant' when total costs are lower compared to standard care and clinical outcomes are improved.

In addition, some cost-effectiveness analyses rely on mapping of disease specific HRQL data to generate health utility values. For instance, Tocilizumab a drug used to treat systemic juvenile idiopathic arthritis was approved by NICE based on the health utilities submitted by the manufacturer and improvements in function, increased quality of life and reduction in joint damage. The health utilities were mapped from the Child Health Assessment Questionnaire (CHAQ) scores, using a mapping formula derived in adults rheumatoid arthritis that mapped Health Assessment Questionnaire [HAQ] results onto EQ-5D utilities [31, 32].

PROs may be assessed as primary, secondary or exploratory endpoints within a trial depending on the study aims and objectives [23]. Although PROs are used to measure disease-specific symptoms and aspects of functioning directly related to a disease or HRQL. For example, PROs consistently serve as primary endpoints in psychiatric disorders, palliative care and in painful conditions, such as migraine and gastrointestinal disorders [12, 23, 33, 34]. However, it is still relatively uncommon to incorporate PROs as primary endpoint. PROs are more often included in trials as secondary or exploratory outcomes to provide patient-centred assessment of

treatment benefits and toxicity [35, 36]. For instance, among the 13,584 oncology trials registered in *ClinicalTrials.gov* between 2007 and 2013*,* only 2,453 (18%) of the trials listed PRO as an outcome measure. Of these 5% and 13% were primary and secondary outcomes, respectively [16].

PROs included as secondary outcomes provide 'added value' data that may contrast with or may support the primary outcome of the study [33, 36]. Such 'value' has the potential for securing labelling claims and in providing supportive information for reimbursement [33, 37-39]. Increasingly PROs are not only used to measure efficacy but also to assess the tolerability and safety of interventions through the assessment of patient reported adverse events/symptoms [40], using tools such as the National Cancer Institute's patient's adverse event monitoring (Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) [41, 42]. In addition, PROs may be incorporated as a secondary endpoint to satisfy health HTA and regulatory requirements around the demonstration of economic value [23, 33].

C. The importance of PROs in clinical trials

PRO trial data can be used to inform patients, clinicians, payers and policy-makers about the impact of a health intervention and its effects, specifically symptoms, functioning and/or HRQL [18, 35, 41, 43]. For instance, PRO data can provide relevant information surrounding how patients with the same condition feel during and after a treatment, which cannot be gained by clinical outcomes alone [36, 44]. In addition, they can help provide information around patient-centred benefits and side effects of a treatment, helping patients to choose the right intervention for them [34-36]. As an example, head and neck cancers are often associated with severe side-effects that can have a profound impact on quality of life [45-47]. Surgery is used as the primary treatment resulting in disfigurement, social withdrawal, anxiety and poor

quality of life [44, 48]. Radiotherapy, also used as primary treatment, administrated alone or in combination with surgery or chemotherapy, can result in oral mucositis amongst patients [44, 49] This is associated with severe side effects such as pain, difficulty swallowing, taste changes, vocal problems and poor quality of life [44]. Therefore, assessment of PRO trial data is essential to inform patients about their treatment options and to provide evidence-based symptom management therapies, supportive care and rehabilitation.

PRO trial data can also be used to inform pharmaceutical labelling claims and drug approval [12]. PRO data may help patients and clinicians understand the risks and benefits of a treatment [50]. For instance, ruxolitinib (Jakafi) was approved by the FDA on the basis of PRO data information that was included in the labelling claim [51]. This oncology drug, used to treat myelofibrosis, was approved based on the reduction in spleen volume and improvement from baseline to week 24 in total symptom score, as measured with the modified Myelofibrosis Symptom Assessment Form version 2.0 (MFSAF v2.0) [51, 52]. The core symptoms of myelofibrosis captured through the MFSAF v2.0 were abdominal discomfort, pain under ribs, night sweats, itching, bone/muscle pain and early satiety (feeling full) [52].

PRO data can also inform and influence healthcare policy and practice. PRO data should be considered in the development of evidence-based guidelines, as it may help identifying unmet needs [53]. In addition, PRO evidence from trials may be used to inform healthcare practice at individual level. For example, shared decision-making regarding treatment for an individual patient [54].

D. PROS in clinical routine practice

Beyond trials, PROs are also increasingly used in routine clinical practice [55, 56]. PRO data can be used to improve healthcare organisation and delivery through the assessment and comparison of providers' performances [55, 57, 58]. Furthermore, PROs can be utilised at an individual patient level, capturing data throughout the care pathway, for instance to better understand the impact of a condition/disease and its treatment on patient HRQL, inform shared decision making and improve healthcare management and outcomes. Routine use of PROMs in clinical care can be used to monitor a patient's progress, and act as an early warning of potential problems, facilitating prompt clinical intervention. Studies have shown that this routine use improves patients' satisfaction with their care and symptom management, and can improve their quality of life and survival rates [59, 60]. Clinicians also reported that they felt the routine use of PROMs improved the consultation, helped reduce their burnout and reduced the burden on them through better work efficiency [61, 62]. Thus PROMs, promoted the provision of better quality of care, shared clinical decision-making, and better utilisation of health resources [58, 63].

E. Research waste and impact

"We need less research, better research, and research done for the right reasons"

Altman, D., 1994

In 2010, US$240 billion were invested in health research worldwide [64]. It was estimated that about 85% of healthcare research investment in 2009 was wasted [64]. The most common causes of this waste stemmed from conducting unnecessary research, the selection of inadequate research questions, 'poor quality' research design and methods, failure to publish research on time, 'poor quality' reporting and

lack of dissemination [64-66]. Making available misleading research is arguably considered as unprofessional, unethical and unacceptable [67].

Although some research waste is inevitable, it is important to improve the efficiency and impact of research to maximise the benefit of funding allocated to healthcare research [65, 68]. Therefore, it is important that the research community provide evidence to inform and justify the funding allocated by sponsors, funders and academic institutions [69]. Assessing healthcare research impact is an essential exercise to ensure that research questions are relevant to policy and practice, and to demonstrate accountability and research benefits [69, 70]. The Higher Education Funding Council for England (HEFCE, 2014), defines research impact as "*an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia"* [71].

In general, methodological frameworks propose to measure research impact through four different approaches: i) academic-orientated frameworks, ii) interaction process between stakeholders and researchers, iii) partnership between researchers and policy-makers and iv) evaluation of the pathways to impact [72]. Measuring research impact is complex, indirect and hard to attribute. However, it is an essential exercise to inform limited resources allocation, maximise research impact and minimise research waste. Short-term benefits of research are easier to attribute whereas long-term benefits are more difficult to capture as they are slow to emerge, hard to measure and sometimes unexpected [69, 73].

Currently, the measurement of healthcare research impact is predominantly undertaken in Canada, Australia and the United Kingdom (UK) [69]. For instance, in the UK, the Research Excellence Framework (REF) has been adopted to assess

academic research impact in the higher education sector. The REF is a review process undertaken by expert panels (senior academics, international members and research users) who evaluate the impact of research reported in those case studies submitted by UK Higher Education Institutions (HEIs) [71]. Examples of other available methodological frameworks include the Payback Framework used to assess health research impact through academic outputs and wider societal benefits [70]; the SIAMPI model (Social Impact Assessment Methods for research and funding instruments through the study of Productive Interactions between science and society) focused on productive interactions, especially exchanges between researchers and stakeholders [74] and the Research Contribution Framework, which uses contribution analysis to explain influence in policy and practice [75]. Nonetheless, there is a lack of consensus around what are the most appropriate frameworks and impact measures by which to monitor the impact of healthcare research, demonstrate benefits of conducting research and accountability [69, 72], especially in studies utilising PROs.

While preventing research waste is important, it is also important that results of healthcare research, such as clinical trials, are available to inform future healthcare research and clinical practice and provide an evidence base to support decision-making and clinical guidelines [65, 76]. A recent study reviewing patterns of publication of clinical trials funded by US National Institutes of Health (NIH) in peer-reviewed journals, demonstrated that between 25% and 50% of the clinical trials were never published [76]. Non-reporting of trial data represents further source of research waste, as results might be duplicated or not implemented into clinical practice [66, 76].

Justification for research

PROs have the potential to lead to a range of impacts including improving health outcomes for patients, if collected and analysed in clinical trials and adequately reported in the literature [77, 78]. PRO trial results, if captured in a scientifically rigorous way, should therefore exert considerable impact on future patient care, informing decision-making in the clinical setting, supporting pharmaceutical labelling claims and influencing healthcare policy [12, 21, 34, 79-81]. However, empirical evidence investigating the range of potential impact associated with PRO data collected in trials, real-world evidence of PRO trial impact, potential PRO impact metrics, common barriers and facilitators to maximising PRO impact and optimal pathways to PRO impact is lacking.

Recent research suggests important PRO protocol-specified hypotheses, data collection methods and statistical plans are often sub-optimal, missing data rates are high and PRO findings are routinely excluded from arising trial publications [35, 81, 82]. There is growing evidence that there is substantial research waste in relation to PROs. The recent EPIC study (evaluation of patient-reported outcome protocol content and reporting in UK cancer clinical trials) demonstrated that relevant PRO protocol items are frequently omitted and non-reporting of PRO findings was widespread. In addition, where PRO data was published, it was often significantly delayed and reporting quality suboptimal [83]. This could lead to inconsistent assessment of important patient-centred outcomes [84], risking biased and unreliable trial results with high levels of missing data [85]. Thus, compromising the impact of PRO trial data on future patient care. This practice may reduce the impact on future patient care; mislead healthcare policy and waste limited healthcare and

research resources [65, 80, 84]. Therefore this study set out to determine the impact of PRO trial results on future patient care and society.

Aims

The aim of this thesis was to **a)** synthesise existing methodological frameworks for healthcare research impact; **b)** determine the range of potential impact associated with PRO data collected in trials, identify potential PRO impact metrics and define common barriers and facilitators to maximising PRO impact and; **c)** examine real-world evidence of PRO trial impact and highlight optimal pathways to such impact.

Objectives

A. To identify impact frameworks and metrics aimed at measuring and maximising the impact of healthcare research.
B. To determine the range of potential impact from PRO data from clinical trials.
C. To identify potential PRO impact metrics and determine common barriers and facilitators to maximising PRO impact.
D. To assess Research Excellence Framework (REF) impact case studies to explore real-world evidence of PRO trial impact and highlight optimal pathways to such impact.
E. To explore in-depth international stakeholders' perspectives about the range of potential impacts of PRO clinical trials and impact metrics and; barriers and facilitators to maximise the impact of PRO trial data.

Structure

The thesis presented different studies to address the objectives detailed above:

- Chapter 3, presents a systematic review (published in *PLOS Medicine* in 2017) focused on determining existing, non-PRO-specific, methodological

frameworks and metrics to measure the impact of healthcare research. This addresses objective A.

- Chapter 4 presents an additional systematic review (currently under review in a peer-reviewed journal). This chapter determines the potential impact of PRO data collected in clinical trials and assess real-world evidence of PRO trial data based on REF 2014 case studies. This addresses objectives B, C and D.
- Chapter 5 presents a qualitative study exploring international stakeholders' views on the current impact of PRO data collected in clinical trials. This chapter discusses the principal findings of the research and their implications, highlights strengths and limitations of the research and provides recommendations for future research. This addresses objective E.

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Chapter 2: Methods

Methods

The aim of this chapter is to provide a general overview of the mixed-methods approach used to answer the objectives and aims of this doctoral research. Justification of the choice of methods and alternative methods considered are also discussed. Further detail on the methods used are presented in Chapters 3 and 4 and related appendices. The qualitative methods used in Chapter 5 are described in greater detail in this chapter (albeit some further information on methods is also presented in chapter 5) to provide greater depth and transparency that are not afforded in the word limitations of the manuscript presented in chapter 5.

The aims of the thesis were to **a)** synthesise existing methodological frameworks for healthcare research impact; **b)** determine the range of potential impact associated with PRO data collected in trials, identify potential PRO impact metrics and define common barriers and facilitators to maximising PRO impact and; **c)** examine real-world evidence of PRO trial impact and highlight optimal pathways to such impact.

The thesis incorporated qualitative and quantitative methods (mixed-methods approach) of data collection and analysis to answer the objectives of this doctoral research [1, 2]. The use of the mixed-methods approach provided a more complete understanding of the research question, as this approach allowed the thesis to draw on the strengths of both qualitative and quantitative methods [1, 3]. Table 1 depicts the mixed-methods research process followed.

Table 1. Mixed-methods research process

Knowledge gap	Aims	Methods
Lack of consensus around the most appropriate method to measure healthcare research impact	To identify the most appropriate ways of measuring healthcare research impact by synthesising existing methodological frameworks for healthcare research impact	Systematic review and synthesis of methodological healthcare impact frameworks (Chapter 3)
Lack of evidence on how PRO data impact from clinical trials is utilised	To determine the range of potential impact associated with PRO data collected in trials, identify potential PRO impact metrics and define common barriers and facilitators to maximising PRO impact	Systematic review and synthesis of the potential impact of PRO data from clinical trials and identify barriers and facilitators to maximising PRO impact (Chapter 4)
Limited evidence regarding real-world impact of PRO trial data and optimal pathways to maximise such impact	To examine real-world evidence of PRO trial impact and highlight optimal pathways to such impact	To explore international stakeholders' perspectives surrounding the impact of PRO trial data and barriers and facilitators upon patients and society through qualitative interviews with key stakeholders (Chapter 5)

Systematic reviews

A. Introduction

Systematic reviews are considered to be an efficient method of integrating large numbers of critical pieces of information. This information is aggregated into a manageable and cohesive review in order to answer a specific question and allow rational decision making [4, 5]. Systematic reviews use explicit methods to search,

critically appraise and synthesise relevant literature systematically [4, 6]. Thus, two systematic reviews were undertaken to answer objectives A, B, C and D of the thesis. The first systematic review (Chapter 3) focused on **objective A:** identifying impact frameworks and metrics to measure and maximise the impact of healthcare research. The second systematic review (Chapter 4) focused on **objective B:** determining the range of potential impacts of PRO data collected from clinical trials, **objective C:** identifying potential PRO impact metrics and determining common barriers and facilitators to maximising PRO impact; and **objective D:** assessing Research Excellence Framework (REF) 2014 impact case studies to explore real-world evidence of PRO trial impact and highlight optimal pathways to such impact. Both reviews were conducted and reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement, used by the Cochrane Collaboration [7]. Further details on methods can be found in Chapter 3, page 6 of the publication and Appendix 1.1 and Chapter 4, Appendix 2.1

B. Justification for choice of methods

Systematic reviews are considered the highest level of evidence in research evidence hierarchies [7]. They are used by health providers, researchers and policy makers to evaluate the evidence on effectiveness of healthcare interventions to enable informed decision-making [8-10]. Systematic review are a fundamental scientific technique that seeks to answer a clearly defined research question by following a transparent and reproducible pre-specified methodology [8]. Furthermore, systematic reviews attempt to identify all existing studies that meet the pre-defined eligibility criteria; with the purpose of systematically identifying, appraising and synthesising research evidence, whilst minimising selection bias. If applicable, systematic reviews can present a statistical summary of the findings in a meta-

analysis [6, 8, 11]. However, systematic reviews can be time consuming, costly to carry out and, require considerable effort and resource to ensure they are comprehensive [8, 10].

Systematic reviews often adhere to the Cochrane Collaboration guidelines [6] and the Centre for Reviews and Dissemination (CRD) on how to conduct a review [12]. Additionally, prospective registration of medical research and medical systematic reviews is recommended to avoid duplication, reduce research waste and increase transparency [9, 10, 13]. PROSPERO, the international prospective database register for systematic reviews, has the aim of providing lists of *a priori* registered health and social care protocols of systematic reviews. In order to reduce the risk of duplication and selective reporting, by enabling comparison between the prospectively submitted protocol and the completed review [10, 14].

C. Alternative methods

There are alternative methods that could have been used to synthesise the existing literature. The most common methods are rapid and narrative (non-systematic) literature reviews, which are described below:

Rapid reviews are valuable to synthesise evidence in a short timeframe for informing decision-makers of a specific end-user, usually healthcare and policy makers [15, 16]. Nonetheless, there is no clear consensus around the methodology rapid reviews follow. In general, the methodology is not as rigorous as that followed by full systematic reviews, potentially raising the risk of bias [15, 17]. Common types of bias include: a) selection bias, which refers to the lack of inclusion of relevant literature; b) author bias, which refers to the inclusion of articles that are of interest to the author;

and c) publication bias, which refers to the publication or non-publication of the results, depending on the obtained findings [6, 18].

The literature searches conducted within rapid reviews might be limited to a smaller number of databases, whereas systematic reviews attempt exhaustive literature searches [6, 19]. In many rapid reviews, the research evidence included is not critically appraised and the synthesis of the results does not provide depth of information and recommendations [16]. Consequently, rapid reviews should be carefully interpreted as their limited transparency regarding methodology and reporting raises the risk of certain types of bias (e.g. author, assessment, selection and publication bias), which if eventually present may undermine validity and utility of the findings [15, 16].

Non-systematic narrative literature reviews attempt to summarise evidence about a general research question [20, 21]. This method can be more time efficient and less resource-intensive than a full systematic review. However, the methodology followed is not pre-specified and clearly described. For instance, the search strategy is not pre-specified, a systematic way to conduct the search strategy is not followed and the findings may not be critically appraised and validated [21], rising the risk of bias. Therefore, the findings may not be reproducible, published and may not support evidence-based practice [20, 21].

Directed content analysis

A. Introduction

In Chapter 4, a systematic review was conducted to answer thesis **objective B:** to determine the range of potential impacts of PRO data collected from clinical trials, **objective C:** identify potential PRO impact metrics and determine common barriers

to maximising PRO impact and; **objective D:** assess Research Excellence Framework (REF) 2014 impact case studies to assess real-world evidence of PRO trial data impact and determine facilitators aimed at maximising PRO trial data impact. In order to extend the conceptual 'pathways to research impact' methodological framework developed in Chapter 3, directed content analysis was used.

B. Justification for choice of methods

Directed content analysis aims to validate or extend/refine a conceptual theory, which refers to basing new research on previous knowledge [22-24]. This approach was chosen, as it is considered a transparent and comprehensive method, which may enhance the rigour of data analysis and comparison of the results across the included studies [22, 24]. Directed content analysis uses predetermined codes to label the data. New categories and subcategories are created when the data cannot be coded under the existing structure, which allows capture of all the events that explain a phenomenon (exhaustiveness) [22, 24]. This method was chosen as the predetermined codes used to analyse the included articles and case studies were contained in the aforementioned 'pathways to research impact' methodological framework [25]. One of the main limitations of directed content analysis is the use of prior information available to the researcher, which can result in the introduction of confirmation bias, which might lead to the identification of supportive evidence rather than information that might not support a conceptual theory [22]. To mitigate this, regular meetings with experts on the topic were held to review and examine the categories and subcategories created before and during the coding stage [22].

C. Alternative methods

An alternative method considered was conventional content analysis. Content analysis is appropriate when an existing theory or range of literature is limited [24]. However, this approach does not focus on the refinement of an existing methodological framework. Although conventional content analysis allows the data to be categorised into themes (inductive category development), it does not incorporate the use of predetermined categories [22]. Furthermore, directed content analysis follows a more structured process that results in a more comprehensive and exhaustive data analysis, as detailed in Chapter 4, page 54. Therefore, conventional content analysis would not be useful in answering objectives B and C of the thesis, as this method would not enable direct incorporation and refinement of the 'pathways to research impact' methodological framework.

Systematic Evaluation of Research Excellence Framework Case Studies

In Chapter 4, the Research Excellence Framework (REF) 2014 case studies database was assessed in order to identify real-world evidence of PRO trial impact. The REF 2014 database was chosen as it provided a robust national database for identifying impactful PRO clinical trials, objective C of the thesis.

A. Introduction

The REF is a system for assessing the quality of research in UK HEIs [26]. REF impact case studies, aggregated in the REF 2014 database, are four-page documents divided into: i) summary of the impact, ii) underpinning research, iii) references to the research, iv) details of the impact, and iv) sources to corroborate the impact. Thus, case studies describe the research undertaken and its arising impact, whilst providing supportive evidence [26]. According to the REF, impact is

defined as *"changes and benefits to the economy, society, culture, public policy and services, health, the environment and quality of life beyond academia"* [26].

The case studies were categorised in 36 subject areas (units of assessment, UOA) and are aggregated into four main areas (Main Panel A, B, C and D). The systematic review conducted in Chapter 4 focused on Main Panel A, as it encompasses clinical areas more likely to retrieve information on PRO trial impact. The UOA within Main Panel A were:

	Units of Assessment (UOA)	
Main Panel A	1	Clinical medicine
	2	Public Health, Health Services and Primary Care
	3	Allied Health Professions, Dentistry, Nursing and Pharmacy
	4	Psychology, Psychiatry and Neuroscience
	5	Biological Sciences
	6	Agriculture, Veterinary and Food Science

B. Justification for choice of methods

The REF 2014 database is an indexed text search engine that retrieves impact case studies based on an entered search criteria. The REF 2014 database allows one to run simple, Boolean, directed and wildcard searches. Furthermore, the database provides a collection of tag terms that are applied to each case study and are used to refine results. The tags included were: submitting institution, unit of assessment, summary impact type, research subject area, impact global location, impact UK location and interdisciplinary [27]. For search strategy details see Chapter 4, Appendix 1.

One of the main strengths of the REF 2014 database is that the case studies included represent research judged to be of the highest quality conducted and submitted by the UK HEIs. 6,695 case studies were submitted; however, only 6,637 were authorised for 'publication', since the remaining presented confidential information. In addition, the case studies presented meaningful, far-reaching and properly articulated impact, which was demonstrated through convincing evidence. Moreover, the impact focused on the benefits of research rather than the pathways to impact, allowing the assessment of real-world impact on society from a particular research study [28]. Therefore, the case studies were considered by the authors as the best available information to assess and demonstrate the impact of PRO trial data.

However, one of the main limitations is that not all the PRO clinical trials in which UK HEIs have participated may have been included in the REF 2014 database; hence, some examples could have been missed. This exclusion was a consequence of the assessment criteria implemented by the REF expert panel and the skills of the submitting HEIs to articulate and demonstrate research impact. In addition, the REF case studies were led by UK HEIs which also could have led to the exclusion of key impactful international PRO clinical trials. Lastly, the REF 2014 requested from HEIs to link impact to specific high quality research outputs (e.g. socioeconomic impacts) resulting in the exclusion of impact on industry, public engagement and policy advice, which are expected benefits of research. The REF 2021 will provide the opportunity for HEIs to demonstrate research impact through these areas [29].

C. Alternative methods

An alternative method to the use of the REF 2014 database would have been to conduct a systematic review of all the existing PRO clinical trials. The advantage of

adopting this approach would have been a bigger and more representative sample of included studies, which would have included more than UK-based research. However, it would not have been possible to review the impact of all PRO clinical trials within the timeframe of the PhD as there are a huge number of such trials, 26,337 (27%) of the registered trials in *ClinicalTrials.gov* database [30]; and trial publications/reports do not routinely include information on impact, making it very difficult to evaluate. We therefore decided to use the REF 2014 sample, as it was more manageable to review during the PhD process, but would still provide a representative sample of UK PRO clinical trials research and include information on purported impact, objective D of the thesis.

Reviewing documents such as clinical guidelines and FDA or EMA drug approvals was also considered as an additional method; however, this could have limited the identification of certain types of impact to changes in clinical guidelines and PRO labelling claims approvals, rather than looking at the broader range of impacts associated with PRO trial data.

The use of qualitative methods exclusively was considered in determining the potential and real-world impact of PRO data collected from clinical trials (objectives B, C and D). However, they were deemed unsuitable as qualitative methods aim at developing concepts to better understand and interpret social phenomena in natural settings [31, 32]. This was not appropriate for these objectives, as it was necessary to conduct a systematic review prior to the use of qualitative techniques to better understand the range of impacts of PRO clinical trials. Qualitative research was used sequentially to complement areas not amenable to the conducted systematic reviews and case studies review.

Qualitative methods

This section outlines the methods used to answer **objective E** of the thesis: to explore in-depth international stakeholders' perspectives about the range of potential impacts of PRO clinical trials and impact measurement metrics, and barriers and facilitators to maximise the impact of PRO trial data. The methods were as follows: A) ethical approval, B) sampling and recruitment procedure, C) data collection, and D) data analysis.

The results of the systematic review 'The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis' (Chapter 4) suggested that PRO trial findings had the potential to inform clinical practice, clinical guidelines and health policy; support drug approval, pricing and reimbursement decisions and; inform clinical decision-making, shared decision-making and consent for treatment.

However, the systematic review did not provide detailed information on the different types of impact identified and only a few impact metrics were presented to measure such impact. The barriers and facilitators for maximising PRO trial data impact were only superficially identified ('thin' data) [32]. In order to have a better understanding of the potential facilitators and barriers which would maximise PRO trial data impact, qualitative methods were considered to generate 'rich' data (deeply nuanced description, interpretation and meaning of data or events [33]). Therefore, one-to-one semi-structured interviews were identified as an appropriate data collection method to explore the perspectives of international stakeholders involved in the use or review of PRO trial data (Chapter 5).

A. Ethical approval

The research followed the University Code of Practice for Research and Data Protection and Handling Guidelines [34]. Ethical approval was granted by The University of Birmingham Research Ethics Committee in December 2016 (ERN_16-0806) for the qualitative work (Chapter 5).

a) Consent

A ‘participant information sheet’ was sent to the participants before the interview. The participant information sheet provided a brief and clear summary about the qualitative study such as; the objectives of the research, participant’s responsibilities and potential risks. Additionally, it allowed the participants to decide whether the study was of interest and whether they wished to discuss it further.

At the beginning of the interview, participants were asked if they read and understood the information sheet. Furthermore, participants were offered the opportunity to ask questions about the study to ensure they were fully informed about the study prior to providing formal consent for the use of their anonymised data. Verbal consent was taken and recorded if the interview was conducted over the phone, whilst written consent was taken during face-to-face interviews. Participants were informed they had the right to stop the interview at any time with the option of destroying the interview recording and removing it from the analysis if they so wished, up to 10 days after the interview.

b) Participant withdrawal

Participants were able to withdraw without giving a reason up to 10 working days after the interview. This period was considered to be enough for the participants to decide whether they still want to be part of the study and for the research team to

prepare the collected data for analysis. After this point, data were integrated into the analysis and it was therefore not possible to disaggregate the information. Participants were informed of this before the interview had taken place in the participant information sheet and reiterated before confirming verbal consent at the beginning of the telephone interview.

c) Confidentiality

Semi-structured interviews were digitally recorded. Recordings were removed from the recording device as soon as they were uploaded to the secure, password-protected encrypted University server, which is backed up automatically. Once anonymised transcripts were produced, the recordings were destroyed and deleted from the server. Transcripts were produced from the interviews by a transcription company and stored in the same way as the interview recordings. Transcripts, with identifiable information removed, were stored on the University server.

In order to ensure confidentiality of the data, a unique participant ID code was assigned to the participants. The telephone or email addresses provided by participants were only used to arrange the interviews, or to provide study results/publications if requested by the participant. A list of the ID codes and the participant key information were kept in separate password-protected files on the encrypted University of Birmingham central server. No participant was referred to directly in the subsequent reports/publications. Only anonymised quotes were used within study reports/publications. Data will be stored for a period of 10 years. The Custodian of the data is the University of Birmingham. After this period, the data stored will be deleted and destroyed.

B. Study design

a) Introduction

A generic qualitative approach was used for this part of the study. A generic qualitative approach combines several methods or approaches and claims no theoretical assumptions, as compared to other qualitative approaches such as grounded theory, ethnography, or phenomenology [35-37].

In some occasions, a single established methodology is insufficient or inappropriate to answer a research question. Therefore, drawing on the strengths of established methodologies by blending tools and methods provides a better way to understand a phenomenon [35, 36]. However, 'method slurring' can lead to lack of congruence. Researchers must make clear their assumptions and make sure the methods selected are aligning with their assumptions [35, 36]. Although the flexibility of generic studies is subject to criticism, generic qualitative approaches may identify new methodological approaches to support new research areas, new theoretical perspectives or identify new ways of evaluating previous research [36].

b) Justification for choice of methods

A generic descriptive approach was deemed as the most suitable approach as it helped provide a straightforward and rich description of the perspectives of the interviewees while epitomising the qualitative characteristics of the study [35, 37]. In the same way, a generic approach was chosen as no theoretical assumptions were made. Nonetheless, this approach has been criticised for being non theory-based, which can lead to incongruences in the research design [35-37]. To mitigate this, it was clearly stated in this chapter and in the qualitative study (Chapter 5) how the sampling method (purposeful sampling), data collection (semi-structured interviews)

and analysis methods (reflexive thematic analysis) chosen were informed by the research question and the generic approach.

In contrast, the absence of theory to analyse the data can be considered as strength, as the analysis stays close to the participants' perceptions. However, the analysis will depend on the perceptions and inclinations of the researcher. To mitigate this, the researcher's position was clearly stated and a multidisciplinary team including methodologists, clinical and non-clinical experts were involved in the interpretation and analysis of the data [35-38].

C. Sampling and recruitment procedure

a) Introduction

Expert and snowballing purposive sampling methods were used in combination to answer objective D of the thesis (Chapter 5). Expert sampling, a strategy of purposive sampling, aims at identifying key informants who are especially knowledgeable about a topic and can inform it through their knowledge, experience, and expertise [39]. Snowballing, friendship pyramiding or chain sampling is also one of the sampling methods within purposive sampling [40]. Snowballing involves recruiting participants through other participants [32]. Snowballing creates a chain of interviews based on the researcher asking each participant for suggestions about people who have a similar or different perspective about the information being sought, allowing to interview hard-to-reach groups [40, 41]. The "snowball" gathers pace as referrals multiply at each stage.

The researcher continually monitors the recruitment process, which it is sustained until saturation is reached [40]. Saturation is defined as 'data adequacy', the point when the data collected does not provide additional information pertinent to the

developing analytic coding framework (i.e. when nothing new is being added) [42, 43]. The purpose of data saturation is ensuring data replication or redundancy, resulting in a comprehensive and complete theoretical model [42]. Data saturation stresses the importance of 'rich' data collection and analysis rather than the quantity or the number of times an aspect of the phenomenon is discussed by the participants [42].

b) Justification for choice of methods

The selection of expert sampling gave the opportunity to gain valuable insight of the core problems and potential solutions from key informants. In addition, some members of the research team (MC/DK/AS) already had established collaborative relationship with a range of international stakeholders and links with leading academic and industry trialists, journal editors, clinicians, funders and policy-makers and regulators, which facilitated the access to these PRO expert groups.

Initially, the stakeholders known to the research team were approached and some of them were interviewed; however, 17 participants decided not to take part in the study for different reasons. Therefore, those participants who were interviewed were asked if they knew other people who would be interested in being interviewed. Snowball sampling was undertaken as it allowed recruitment of a further representative and diverse sample size in a short period of time, whilst not incurring cost. Nonetheless, snowballing sampling can introduce selection bias as the sample might include an over representation of a subgroup of participants with similar characteristics. To avoid over representation of participants, careful consideration was given to the number of participants selected per stakeholder group. In addition, a sampling frame was used and purposively sampled to gain a maximum variation sample. A limitation of the recruitment process was that the international stakeholders known to the team

may already be PRO advocates, which could have limited the opportunity to explore different perspectives about the importance and impact of PRO data. However, it was felt that if they were already considering ways to maximise impact and as such were best placed to help the research team understand and explore these impacts in future research.

c) Alternative methods

Convenience sampling was considered as an alternative approach to recruit participants for the qualitative project. Convenience sampling is the most common sampling strategy in qualitative research [40]. It is characterised for selecting a sample based on how accessible and convenient it is to the researcher [40]. The recruitment method is through the selection of a number of participants who respond to an advertisement, making this strategy cost efficient and time saving [32, 40]. This method was deemed unsuitable as the research team already had contact with relevant international stakeholders, who could further refer additional eligible participants. In addition, convenience sample is neither purposeful nor strategic, which can lead to incomplete data as the accessible and convenient participants are likely not to be the most informative sources [44].

D. Data collection

a) Introduction

Semi-structured interviews were chosen to support an in-depth exploration of the participants' views and experiences. This type of interview consists of asking participants open-ended questions to explore a topic, from which the researcher or participants may slightly diverge in order to explore an idea in more detail [45]. The interview schedule was informed by the systematic review conducted in Chapter 4, which was subsequently refined by two pilot interviews and discussion with the

research team (CM/DK/AS/MC). In addition, the interview schedule developed iteratively as data collection progressed in parallel to initial analysis.

b) Justification for choice of methods

Semi-structured interviews were deemed suitable to explore the views and perceptions of stakeholders, as they enable further discussion and clarification of answers. One of the main strengths of qualitative semi-structured interviews is that they allow the participants to raise issues that the researcher did not anticipate, even if the interview schedule was informed by previous literature, and therefore collect 'rich' and detailed data about the participants' experiences [32]. On the other hand, semi-structured interviews can be time consuming and costly for researchers to organise, conduct and transcribe. Semi-structured interviews lack anonymity as they tend to be conducted face-to-face, which could be a barrier for potential participants and affect the recruitment process and the make-up of the sample [32]. To mitigate these limitations, participants were informed before accepting the interview invitation of the approximate length of the interview (approximately 45 minutes) and they were asked to choose the most convenient time and location to carry out the interview.

c) Alternative methods

An alternative method considered to collect data from participant was the use of focus groups, which are useful for exploring how different participants' beliefs, concerns, experiences and opinions are around a particular topic [31]. In addition, the data are generated as the participants interact between themselves, which is the data in and of itself. Enabling the researcher to gain a larger amount of data in a shorter period, compared to semi-structured interviews [46]. Nonetheless, focus groups can be difficult to organise and the data could be influenced by a dominant participant (skewed data). This method would have been ideal to make comparison

between stakeholder groups; however, this was not possible given the nature of the study sample. It would not have been possible to arrange a focus group as it would have be difficult to find a suitable time and place because of the different time zones, locations and busy schedules of the participants. Although remote focus groups were an option, it was felt that, for practical and technological reasons, it might be too much of a burden for the participants.

E. Data analysis

a) Introduction

Reflexive or organic thematic analysis aims to analyse, identify and report patterns (themes) of meaning across a dataset in relation to a research question [32, 47]. Reflexive thematic analysis offers flexibility around theoretical orientation and data collection, which allows the researcher to be actively engaged in the data analysis. The flexibility of this approach allows the code to constantly evolve by renaming, changing and collapsing codes [47]. Furthermore, reflexive thematic analysis offers a more accessible form of analysis, specifically for those who are new to qualitative research [32, 47, 48]. According to Braun and Clarke (2006), the six stages to conduct reflexive thematic analysis include:

Stage	Description
I. Familiarisation with data	Familiarisation with data set (interview transcripts) by 'repeated reading' of the data and searching for meaning and patterns.
II. Generating initial codes	Production of initial codes from the data. Codes identify a characteristic of the data and refer to the most basic element of the data set that can be assessed in a meaningful way. Coding can be done manually or through a software programme (QSR NVivo).
III. Searching for themes	Organisation of the different codes into potential themes and consideration of how different codes may combine to

		form an overarching theme (sub-theme).
IV.	Reviewing themes	Review and refinement of the themes developed at two different levels. Level one, review the coded data extracts from a coherent pattern. Level two, consider the validity of the individual themes in relation to the data set and consider whether the themes reflect the meaning of the data in full.
V.	Defining and naming themes	Identification of the bottom line of each theme and determine what aspects of the data each theme captures.
VI.	Writing themes	Refers to the final analysis of the themes and write up of the thematic analysis.

b) Justification for choice of methods

Reflexive thematic analysis was chosen as it aligns with the principles set by the qualitative generic approach. This form of qualitative data analysis does not require exhaustive and technical knowledge compared to other approaches, making thematic analysis an uncomplicated and easy approach for new qualitative researchers [48]. Moreover, the 'flexible' element of reflexive thematic analysis allowed the team to use a hybrid deductive-inductive approach based on the aforementioned methodological framework 'pathways to research impact' (Chapter 3) [25] to identify types of impact, impact measurement metrics, and barriers and facilitators to impact. See Chapter 5 pages 88-89 for more detail around deductive and inductive coding.

In order to explore the perspectives of the international PRO stakeholders (objective E) it was necessary to conduct an in-depth analysis through a flexible method that allowed the conceptualisation of the data to evolve and develop constantly. Thus, reflexive thematic analysis was chosen as it allowed the researcher to actively

engage and interpret the data, leading to an in-depth analysis of the PRO international stakeholders perspectives.

c) Alternative methods

Two alternative approaches of thematic analysis were considered to analyse the dataset. These were coding reliability and codebook thematic analysis and are described below:

Coding reliability approach is characterised for conceptualising themes through a pre-conceptualised codebook. The themes drive the coding process and are also the output of the coding process. Therefore, this type of thematic analysis is known as a 'partially' qualitative approach to thematic analysis [47]. The underlying logic of the approach is positivist, which focuses on the importance of reliable and replicable coding (e.g. coding reliability measures) [49]. Therefore, coding reliability would have not allowed a deep engagement of the researcher into the data as coding reliability is a rigid approach, which would not have led to a rich analysis of the dataset.

Codebook thematic analysis is characterised for determining the themes in advance of full analysis, and themes are conceptualised as domain summaries. Furthermore, the themes can evolve and be developed through the coding process [47]. This type of thematic analysis sits between coding reliability and reflexive thematic approach, as it follows a structured approach from coding reliability, except from the coding reliability measures, and the flexible approach of reflexive thematic analysis. Codebook thematic analysis includes framework analysis [50] and template analysis [51]. However, determining themes in advances does not allow depth of engagement of the research, which could lead to a thin analysis of the dataset.

In summary, this chapter presented a general overview of the methods chosen to answer the five objectives of this doctoral research. The following chapters will provide a detailed description on how each method was used.

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Chapter 3: Assessing the impact of healthcare research: A systematic review of methodological frameworks

Assessing the impact of healthcare research

Measuring the impact of healthcare research is an essential exercise to allocate limited resources, demonstrate accountability and minimise research waste [1-3]. As described in Chapter 1, there is a lack of consensus around the most effective methodological framework and impact metrics to measure the impact of research. Therefore, the aims of this chapter were: i) identify existing methodological frameworks used to measure healthcare research impact and ii) summarise common themes and metrics to measure such impact. This chapter addresses thesis **objective A:** to identify impact frameworks and metrics aimed at measuring and maximising the impact of healthcare research. This chapter has been published in PLOS Medicine [4] (published August 9, 2017; 28,461 views, Altmetric 300 and 15 citations to date) and is presented below in the journal format.

Publication 1:

Cruz Rivera S, Kyte DG, Aiyegbusi OL, Keeley TJ, Calvert MJ. Assessing the impact of healthcare research: A systematic review of methodological frameworks. PLoS Medicine. 2017;14(8):e1002370. (doi.org/10.1371/journal.pmed.1002370)

The work has been further disseminated as outlined in Table 1.

Table 1. Dissemination of publication

Year	Conference	Location	Type of presentation
2017	38th Annual Meeting of the Society for Clinical Trials Being Held Jointly With The 4th International Clinical Trials Methodology Conference (ICTMC)	Liverpool, UK	Poster
2018	Festival of Graduate Research	Birmingham, UK	Poster
2018	Michael K. O'Rouke Best PhD Publication for the College of Medical and Dental Sciences, University of Birmingham	Birmingham, UK	NA
2018	A two-day course hosted by Professor Calvert and the Centre for Patient Reported Outcomes Research (CPROR)	Birmingham, UK	Oral

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RESEARCH ARTICLE

Assessing the impact of healthcare research: A systematic review of methodological frameworks

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: MJC has received consultancy fees from Astellas and Ferring pharma

Abstract

Background

Increasingly, researchers need to demonstrate the impact of their research to their sponsors, funders, and fellow academics. However, the most appropriate way of measuring the impact of healthcare research is subject to debate. We aimed to identify the existing methodological frameworks used to measure healthcare research impact and to summarise the common themes and metrics in an impact matrix.

Methods and findings

Two independent investigators systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica Database (EMBASE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL+), the Health Management Information Consortium, and the Journal of Research Evaluation from inception until May 2017 for publications that presented a methodological framework for research impact. We then summarised the common concepts and themes across methodological frameworks and identified the metrics used to evaluate differing forms of impact. Twenty-four unique methodological frameworks were identified, addressing 5 broad categories of impact: (1) 'primary research-related impact', (2) 'influence on policy making', (3) 'health and health systems impact', (4) 'health-related and societal impact', and (5) 'broader economic impact'. These categories were subdivided into 16 common impact subgroups. Authors of the included publications proposed 80 different metrics aimed at measuring impact in these areas. The main limitation of the study was the potential exclusion of relevant articles, as a consequence of the poor indexing of the databases searched.

Conclusions

The measurement of research impact is an essential exercise to help direct the allocation of limited research resources, to maximise research benefit, and to help minimise research waste. This review provides a collective summary of existing methodological frameworks for

and travel fees from the European Society of Cardiology outside the submitted work. TJK is in full-time paid employment for PAREXEL International.

Abbreviations: AIHS, Alberta Innovates—Health Solutions; CAHS, Canadian Academy of Health Sciences; CIHR, Canadian Institutes of Health Research; CINAHL+, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; ERA, Excellence in Research for Australia; HEFCE, Higher Education Funding Council for England; HMIC, Health Management Information Consortium; HTA, Health Technology Assessment; IOM, Impact Oriented Monitoring; MDG, Millennium Development Goal; NHS, National Health Service; MEDLINE, Medical Literature Analysis and Retrieval System Online; PHC RIS, Primary Health Care Research & Information Service; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROM, patient-reported outcome measures; QALY, quality-adjusted life year; R&D, research and development; RAE, Research Assessment Exercise; REF, Research Excellence Framework; RIF, Research Impact Framework; RQF, Research Quality Framework; SDG, Sustainable Development Goal; SIAMPI, Social Impact Assessment Methods for research and funding instruments through the study of Productive Interactions between science and society.

research impact, which funders may use to inform the measurement of research impact and researchers may use to inform study design decisions aimed at maximising the short-, medium-, and long-term impact of their research.

Author summary

Why was this study done?

- There is a growing interest in demonstrating the impact of research in order to minimise research waste, allocate resources efficiently, and maximise the benefit of research. However, there is no consensus on which is the most appropriate tool to measure the impact of research.
- To our knowledge, this review is the first to synthesise existing methodological frameworks for healthcare research impact, and the associated impact metrics by which various authors have proposed impact should be measured, into a unified matrix.

What did the researchers do and find?

- We conducted a systematic review identifying 24 existing methodological research impact frameworks.
- We scrutinised the sample, identifying and summarising 5 proposed impact categories, 16 impact subcategories, and over 80 metrics into an impact matrix and methodological framework.

What do these findings mean?

- This simplified consolidated methodological framework will help researchers to understand how a research study may give rise to differing forms of impact, as well as in what ways and at which time points these potential impacts might be measured.
- Incorporating these insights into the design of a study could enhance impact, optimizing the use of research resources.

Introduction

In 2010, approximately US$240 billion was invested in healthcare research worldwide [1]. Such research is utilised by policy makers, healthcare providers, and clinicians to make important evidence-based decisions aimed at maximising patient benefit, whilst ensuring that limited healthcare resources are used as efficiently as possible to facilitate effective and sustainable service delivery. It is therefore essential that this research is of high quality and that it is impactful—i.e., it delivers demonstrable benefits to society and the wider economy whilst minimising research waste [1,2]. Research impact can be defined as 'any identifiable 'benefit to, or

positive influence on the economy, society, public policy or services, health, the environment, quality of life or academia' (p. 26) [3].

There are many purported benefits associated with the measurement of research impact, including the ability to (1) assess the quality of the research and its subsequent benefits to society; (2) inform and influence optimal policy and funding allocation; (3) demonstrate accountability, the value of research in terms of efficiency and effectiveness to the government, stakeholders, and society; and (4) maximise impact through better understanding the concept and pathways to impact [4–7].

Measuring and monitoring the impact of healthcare research has become increasingly common in the United Kingdom [5], Australia [5], and Canada [8], as governments, organisations, and higher education institutions seek a framework to allocate funds to projects that are more likely to bring the most benefit to society and the economy [5]. For example, in the UK, the 2014 Research Excellence Framework (REF) has recently been used to assess the quality and impact of research in higher education institutions, through the assessment of impact cases studies and selected qualitative impact metrics [9]. This is the first initiative to allocate research funding based on the economic, societal, and cultural impact of research, although it should be noted that research impact only drives a proportion of this allocation (approximately 20%) [9].

In the UK REF, the measurement of research impact is seen as increasingly important. However, the impact element of the REF has been criticised in some quarters [10,11]. Critics deride the fact that REF impact is determined in a relatively simplistic way, utilising researcher-generated case studies, which commonly attempt to link a particular research outcome to an associated policy or health improvement despite the fact that the wider literature highlights great diversity in the way research impact may be demonstrated [12,13]. This led to the current debate about the optimal method of measuring impact in the future REF [10,14]. The Stern review suggested that research impact should not only focus on socioeconomic impact but should also include impact on government policy, public engagement, academic impacts outside the field, and teaching to showcase interdisciplinary collaborative impact [10,11]. The Higher Education Funding Council for England (HEFCE) has recently set out the proposals for the REF 2021 exercise, confirming that the measurement of such impact will continue to form an important part of the process [15].

With increasing pressure for healthcare research to lead to demonstrable health, economic, and societal impact, there is a need for researchers to understand existing methodological impact frameworks and the means by which impact may be quantified (i.e., impact metrics; see Box 1, 'Definitions') to better inform research activities and funding decisions. From a

Box 1. Definitions

- **Research impact:** 'any identifiable benefit to, or positive influence on, the economy, society, public policy or services, health, the environment, quality of life, or academia' (p. 26) [3].
- **Methodological framework:** 'a body of methods, rules and postulates employed by a particular procedure or set of procedures (i.e., framework characteristics and development)' [18].
- **Pathway:** 'a way of achieving a specified result; a course of action' [19].
- **Quantitative metrics:** 'a system or standard of [quantitative] measurement' [20].
- **Narrative metrics:** 'a spoken or written account of connected events; a story' [21].

researcher's perspective, understanding the optimal pathways to impact can help inform study design aimed at maximising the impact of the project. At the same time, funders need to understand which aspects of impact they should focus on when allocating awards so they can make the most of their investment and bring the greatest benefit to patients and society [2,4,5,16,17].

Whilst previous researchers have summarised existing methodological frameworks and impact case studies [4,22–27], they have not summarised the metrics for use by researchers, funders, and policy makers. The aim of this review was therefore to (1) identify the methodological frameworks used to measure healthcare research impact using systematic methods, (2) summarise common impact themes and metrics in an impact matrix, and (3) provide a simplified consolidated resource for use by funders, researchers, and policy makers.

Methods

Search strategy and selection criteria

Initially, a search strategy was developed to identify the available literature regarding the different methods to measure research impact. The following keywords: 'Impact', 'Framework', and 'Research', and their synonyms, were used during the search of the Medical Literature Analysis and Retrieval System Online (MEDLINE; Ovid) database, the Excerpta Medica Database (EMBASE), the Health Management Information Consortium (HMIC) database, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL+) database (inception to May 2017; see S1 Appendix for the full search strategy). Additionally, the nonindexed Journal of Research Evaluation was hand searched during the same timeframe using the keyword 'Impact'. Other relevant articles were identified through 3 Internet search engines (Google, Google Scholar, and Google Images) using the keywords 'Impact', 'Framework', and 'Research', with the first 50 results screened. Google Images was searched because different methodological frameworks are summarised in a single image and can easily be identified through this search engine. Finally, additional publications were sought through communication with experts.

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see S1 PRISMA Checklist), 2 independent investigators systematically screened for publications describing, evaluating, or utilising a methodological research impact framework within the context of healthcare research [28]. Papers were eligible if they included full or partial methodological frameworks or pathways to research impact; both primary research and systematic reviews fitting these criteria were included. We included any methodological framework identified (original or modified versions) at the point of first occurrence. In addition, methodological frameworks were included if they were applicable to the healthcare discipline with no need of modification within their structure. We defined 'methodological framework' as 'a body of methods, rules and postulates employed by a particular procedure or set of procedures (i.e., framework characteristics and development)' [18], whereas we defined 'pathway' as 'a way of achieving a specified result; a course of action' [19]. Studies were excluded if they presented an existing (unmodified) methodological framework previously available elsewhere, did not explicitly describe a methodological framework but rather focused on a single metric (e.g., bibliometric analysis), focused on the impact or effectiveness of interventions rather than that of the research, or presented case study data only. There were no language restrictions.

Data screening

Records were downloaded into Endnote (version X7.3.1), and duplicates were removed. Two independent investigators (SCR and OLA) conducted all screening following a pilot aimed at

refining the process. The records were screened by title and abstract before full-text articles of potentially eligible publications were retrieved for evaluation. A full-text screening identified the publications included for data extraction. Discrepancies were resolved through discussion, with the involvement of a third reviewer (MJC, DGK, and TJK) when necessary.

Data extraction and analysis

Data extraction occurred after the final selection of included articles. SCR and OLA independently extracted details of impact methodological frameworks, the country of origin, and the year of publication, as well as the source, the framework description, and the methodology used to develop the framework. Information regarding the methodology used to develop each methodological framework was also extracted from framework webpages where available. Investigators also extracted details regarding each framework's impact categories and subgroups, along with their proposed time to impact ('short-term', 'mid-term', or 'long-term') and the details of any metrics that had been proposed to measure impact, which are depicted in an impact matrix. The structure of the matrix was informed by the work of M. Buxton and S. Hanney [2], P. Buykx et al. [5], S. Kuruvila et al. [29], and A. Weiss [30], with the intention of mapping metrics presented in previous methodological frameworks in a concise way. A consensus meeting with MJC, DGK, and TJK was held to solve disagreements and finalise the data extraction process.

Results

Included studies

Our original search strategy identified 359 citations from MEDLINE (Ovid), EMBASE, CINAHL+, HMIC, and the Journal of Research Evaluation, and 101 citations were returned using other sources (Google, Google Images, Google Scholar, and expert communication) (see Fig 1) [28]. In total, we retrieved 54 full-text articles for review. At this stage, 39 articles were excluded, as they did not propose new or modified methodological frameworks. An additional 15 articles were included following the backward and forward citation method. A total of 31 relevant articles were included in the final analysis, of which 24 were articles presenting unique frameworks and the remaining 7 were systematic reviews [4,22–27]. The search strategy was rerun on 15 May 2017. A further 19 publications were screened, and 2 were taken forward to full-text screening but were ineligible for inclusion.

Methodological framework characteristics

The characteristics of the 24 included methodological frameworks are summarised in Table 1, 'Methodological framework characteristics'. Fourteen publications proposed academic-orientated frameworks, which focused on measuring academic, societal, economic, and cultural impact using narrative and quantitative metrics [2,3,5,8,29,31–39]. Five publications focused on assessing the impact of research by focusing on the interaction process between stakeholders and researchers ('productive interactions'), which is a requirement to achieve research impact. This approach tries to address the issue of attributing research impact to metrics [7,40–43]. Two frameworks focused on the importance of partnerships between researchers and policy makers, as a core element to accomplish research impact [44,45]. An additional 2 frameworks focused on evaluating the pathways to impact, i.e., linking processes between research and impact [30,46]. One framework assessed the ability of health technology to influence efficiency of healthcare systems [47]. Eight frameworks were developed in the UK [2,3,29,37,39,42,43,45], 6 in Canada [8,33,34,44,46,47], 4 in Australia [5,31,35,38], 3 in the

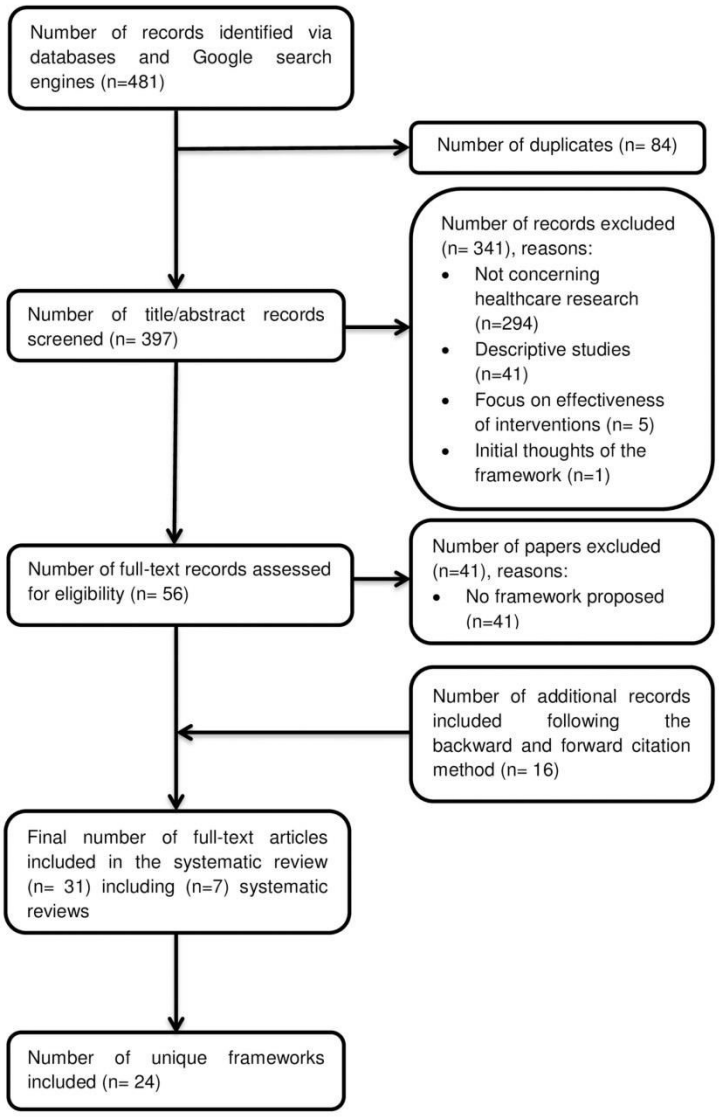

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

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Netherlands [7,40,41], and 2 in the United States [30,36], with 1 model developed with input from various countries [32].

Table 1. Methodological framework characteristics.

Framework	Original source for modified framework	Framework description	Impact categories	Methodology followed to develop the framework			
				Literature review	Stakeholder involvement	Methods to incorporate stakeholder views	Pilot phase
Buxton and Hanney **Payback Framework [2]** UK, 1996	• The classic/ purist/knowledge-driven model • The problem-solving/ engineering model • The political model • The enlightenmen/ percolation/ limestone model • The interactive/ social interaction model [48–54]	Framework used to assess health research impact through academic outputs and wider societal benefits	• Knowledge benefits • Benefits to future research and research use • Political and administrative benefits • Health sector benefits • Broader economic benefits	Yes, but no systematic approach reported	None reported	None reported	A case study approach was undertaken to determine the effectiveness of the model and exemplify the impact categories
Canadian Institutes of Health Research (CIHR) [9] Canada, 2005	• Payback Framework [2]	Framework designed to gauge the impact of health research and the benefits of investing in health research	• Knowledge production • Research targeting and capacity • Informing policy • Health and health sector benefits • Economic impacts	Yes, but no systematic approach reported	Meetings, presentations, and panel discussions with the Canadian government, academics, health research stakeholders, and international funding agencies	Not specified	No information reported in the main paper or on the webpage
Canadian Academy of Health Sciences (CAHS) [33] Canada, 2009	• Payback Framework [2] • CIHR framework [9]	Framework focused on evaluating how research activity influences decision making in order to improve health, the economy, and social benefits	• Advancing knowledge • Building capacity • Informing decision making • Health • Broad socioeconomic impact	Yes, but no systematic approach reported	Semistructured interviews were conducted to collect stakeholder, sponsor, and external expert feedback	Conceptual cluster analysis was used to analyse the data collected, which helped to capture the perspective of different stakeholders involved in the health system	Six papers were commissioned to test the applicability of the framework. After modifications, the project was sent to external review and changes were made until its approval
K. Graham et al. **Alberta Innovates—Health Solutions (AIHS) impact framework [34]** Canada, 2012	• Payback Framework [2] CAHS model [33]	A framework to measure, assess, and illustrate the relationship between research investment and impact. The ultimate goal is to contribute to the most societal benefit among the people	• Advancing knowledge • Building capacity • Informing decision making • Health • Broad socioeconomic impact • Organisational performance	No systematic approach reported	None reported	None reported	The CAHS model was assessed for applicability and feasibility through retrospective and prospective studies and other tools to map pathways to impact. The findings of the assessment provided feedback to improve the AIHS model
G. Cohen et al. [35] Australia, 2014	• Payback Framework [2] • AIHS framework [34]	To evaluate the policy and practicebenefits of research outputs, which take place later and beyond the research setting	• Scholarly outputs • Translational outputs • Policy or practice impacts • Long-term population outcomes	No systematic approach reported	Two online surveys and semistructured interviews were conducted among the primary chief investigators of the research grants included	Not specified	Case studies were summarised and presented to an experience panel, which scored the relevant impact categories of this framework
S. Kuruvilla et al. **Research Impact Framework (RIF) [29]** UK, 2006	• Payback Framework [2]	Conceptual framework to describe the possible impacts of health research outcomes	• Research-related impacts • Policy impacts • Service impacts: health and intersectorial • Societal impacts	No systematic approach reported	Semistructured interviews with principal investigators of selected projects	Thematic analysis was adopted to analyse the data. The categories of the framework were used as themes	The RIF was validated through consistency with available health research literature and empirical analysis of research projects
L. Kalucy et al. **Primary Health Care Research & Information Service (PHC RIS) [31,55]** Australia, 2007	• Payback Framework [2]	Methodology designed to assess primary healthcare research. Strong collaboration, personal relationships and the participation of practitioners, health care managers, and policy makers in the definition of the research questions and in the research process were identified as the strongest pathways to impact	• Knowledge production • Research targeting, capacity, building, and absorption • Informing policy and product development • Health and health sector benefits • Broader economic benefits • Research transfer	No systematic approach reported	Part 1: Telephone interviews were conducted among the 4 chief investigators of the included projects funded by the National Health and Medical Research Council	Data provided by the interviewees were analysed following the Payback Framework and thematic analysis approach	Parts 2–17: chief investigators completed an online questionnaire to refine the methodology to measure research impact

(*Continued*)

Table 1. (*Continued*)

Framework	Original source for modified framework	Framework description	Impact categories	Methodology followed to develop the framework			
				Literature review	Stakeholder involvement	Methods to incorporate stakeholder views	Pilot phase
J. Guinea et al. **Impact Oriented Monitoring (IOM) [32]** Various countries, 2015	• Payback Framework [2]	Methodology used to identify and assess the impacts of health projects through a set of predefined categories	• Advancing knowledge • Capacity building and research targeting • Informing decision making, practice, and policy • Population health and health sector benefits • Dissemination and knowledge transfer	No systematic approach reported	A project coordinators' survey was conducted to determine and collect all the possible public health research benefits. An end users' survey was conducted to determine the usefulness and practicality of the results of the coordinators' survey to measure research impact. Additionally, a scoring matrix was developed to assess project impacts	Not specified	A small sample of research projects was used to test some of the methods incorporated to measure research impact
J. Lavis et al. **Exchange model [44]** Canada, 2003	-	Assessment tool to measure decision-making impact of health research. Impact measures are categorised according to the level of impact to be measured and the mechanism of research uptake: producer-push, user-pull, and exchange measures	• Producer-push process • User-pull process • Exchange process	No systematic approach reported	None reported	None reported	Two examples were used to demonstrate how the assessment tool can be used
L. Meagher et al. [43] UK, 2008	• Linkage and exchange model [56]	Methodology for assessing research impact of policy and practice	• Primary knowledge producers • Knowledge users, beneficiaries, brokers, and intermediaries • Impacts or research (outcomes) • Research impact processes • Lessons learned and recommendations • Methods for identifying and assessing nonacademic research impact	Yes, but no systematic approach reported	Award holders of the UK's Economic and Social Research Council (ESRC) within the psychology field, heads of departments, ESRC-funded principal researchers, and research users were recruited to conduct a questionnaire and survey; 2 focus group interviews, semistructured interviews, media-related searches, and case studies to determine the level of engagement with research users, impact and processes, activities, and roles leading to impact	Not specified	None
P. Buykx et al. **The Health Services Research Impact Framework [5]** Australia, 2012	• PHC RIS [31] • RIF [29] • Exchange Model [44]	Framework for recording and monitoring the impact of health research. This framework consolidates the most relevant elements of the PHS RIS, RIF, and exchange model	• Knowledge generation and communication • Capacity building, training, and leadership • Informing policy • Improving health and health systems impact • Social and economic benefit impact	No systematic approach reported	None reported	None	Not available in the main paper
Higher Education Funding Council for England (HEFCE) **Research Assessment Exercise (RAE) [39]** UK, 2005	-	The aim of the RAE is to assess the quality of research conducted by academic institutions in the UK, in order to inform funding decisions by higher education funding bodies.	• RAE1: Staff information • RAE2: Research output • RAE3: Research scholarships • RAE4: Attractiveness for external funding • RAE5: Further information on groups of research	None reported	Focus groups, workshops, and meetings with HEFCE institutions, funding body officers, external experts, and stakeholder groups	Not specified	None

(*Continued*)

Table 1. (*Continued*)

Framework	Original source for modified framework	Framework description	Impact categories	Methodology followed to develop the framework			
				Literature review	Stakeholder involvement	Methods to incorporate stakeholder views	Pilot phase
C. Donovan **Australian Research Quality Framework (RQF) [38] Substituted in 2015 by the Excellence in Research for Australia (ERA) framework** Australia, 2008	–	A 5-point rating scale to evaluate research excellence and societal returns of publicly funded research. This framework highlights the importance of end-users' interactions to enhance the use of research	The impact rating scale: • Research has produced an outstanding social, economic, environmental, or cultural benefit. • Research has produced a significant social, economic, environmental, or cultural benefit. • Research has produced new policies, products, attitudes, behaviours, or outlooks in the end-user communities. • Research has engaged with the end-user community to address a social, economic, environmental, or cultural issue. • Research has had limited or no identifiable social, economic, environmental, or cultural outcome.	None reported	The technical working group on research impact (senior university managers, representatives from business and industry, experts in impact evaluation, and members of the development advisory group) and the Australian higher education sector participated during different phases of the development of the framework. The Australian higher education sector was consulted. The technical working group was in charge of further development of the framework characteristics	Not specified	None
HEFCE **Research Excellence Framework (REF 2014) [3]** UK, 2011	• RQF [38,39]	Framework for assessing the quality of research of UK higher education institutions	• REF1: Staff details • REF2: Research outputs • REF3: impact template and case studies • REF4: Environmental data • REF5: Environmental template	Scoping study, no systematic approach reported	An initial consultation on the REF was conducted among HEFCE institutions and other stakeholders to determine the potential of introducing bibliometric indicators in the REF. A second consultation was conducted based on the results of the first initiative, which included proposals on how to assess the impact of research	Not specified	A pilot exercise was conducted to test and develop bibliometric indicators to measure research quality. A second pilot was conducted to test the proposals to assess research impact
R. Jacob and M. McGregor **Health Technology Assessment (HTA) Organisation Assessment Framework [47]** Canada, 2007	–	The impact of health technology assessment is measured by the ability to influence the efficiency of the healthcare system	Levels of importance according to the type of policy involved: • Level 1: General statements of ministerial policy • Level 2: Planning guidelines for health services organisation • Level 3: Practice norms prescribed by the professional corporation • Level 4: Ministry rules concerning coverage of health services • Level 5: Hospital rules concerning utilisation of services • Level 6: Ministry decisions on the organisation of specific health services • Level 7: Ministry decisions concerning the allocation of resources	No, a case study approach was undertaken to determine the impact of health technology assessment on policy decision	Interviews and questionnaires were conducted with stakeholders affiliated with the Canadian Ministry of Health; those who were involved in defining policy were contacted to corroborate the supporting documentation collected	Not specified	None

(*Continued*)

Table 1. (*Continued*)

Framework	Original source for modified framework	Framework description	Impact categories	Methodology followed to develop the framework			Pilot phase
				Literature review	Stakeholder involvement	Methods to incorporate stakeholder views	
R. Landry et al. **Research Utilisation Ladder [46]** Canada, 2001	• Knott and Wildavsky Model [57]	Assessment of the pathway in which research progresses towards its utilisation by decision makers and practitioners	• Transmission • Cognition • Reference • Effort • Influence • Application	Yes, but no systematic approach reported	A mail survey and telephone calls were used to identify potential participants. Once the participants were recruited, a questionnaire focused on utilisation knowledge was distributed. The stakeholders involved were faculty members of different Canadian universities	Not specified	A modified version of the Knott and Wildavsky model was used to measure knowledge utilization from the data collected. A quantitative approach was adopted to analyse the data of the model
C. Sarli et al. **The Becker Medical Library Model for Assessment of Research Impact** [38] US, 2010	• W. K. Kellogg Foundation Model [58]	Methodology beyond citation counts, to assess research impact as a result of research output. This model allows the interaction between researchers and institutions to document and quantify the impact of research	• Research output • Knowledge transfer • Clinical implementations • Community benefit	Yes, but no systematic approach reported	Authors consulted expert opinion, researchers, clinicians, and librarians to identify indicators to measure research impact	Not specified	The evidence available to measure the impact of the Ocular Hypertension Treatment Study was analysed using the preliminary framework. The outcomes refined the framework leading to a tool to assess research impact
V. C. Brueton et al. [37] UK, 2014	• The Becker Model [36]	Framework used to better report and assess impact of methodological research	• Advancement of knowledge • Implementation	No systematic approach reported	Two semistructured interviews and email queries to the methodologists for the included projects were used to examine other indicators and analyse evidence of research implementation	Not specified	None
Royal Netherlands Academy of Arts and Sciences **The social impact of applied research** [41] The Netherlands, 2002	–	Measuring the societal impact of applied research, as an incentive for researchers to improve their performance within this field	• Science and certified knowledge • Education and training • Innovation and professionalism • Public policy • Collaboration and visibility	Yes, but not systematic approach reported	None	None	None
A. Weiss **Logic Model for Medical Research** [39] US, 2007	• United Way Model [59]	Measurement outcomes (awareness, implementation, and patient benefit) provide the basis to assess the quality of the investment in research	• Initial outcome: awareness • Intermediate outcome: implementation • Long-term outcome: patient benefit	No systematic approach reported	None	None	Qualitative methods and a case study were conducted to assess the impact of the model developed
J. Canavan et al. [45] UK, 2009	• Models of research impact: A cross sector review of literature and practice [60]	This approach proposes 6 recommendations that can increase the likelihood of an effective and practical measurement of research impact policy	Recommendations: • Commissioner-researcher partnerships • Embedded researcher model • Planning for impact from the outset • Adopting facilitative research methodological strategies • Following good practice towards research impact • Connecting research measurement to performance management	Yes, but no systematic approach reported	None	None	A case study was developed to exemplify the framework proposed

(*Continued*)

Table 1. (*Continued*)

Framework	Original source for modified framework	Framework description	Impact categories	Methodology followed to develop the framework			
				Literature review	Stakeholder involvement	Methods to incorporate stakeholder views	Pilot phase
J. Spaapen and L. van Drooge **Social Impact Assessment Methods for research and funding instruments through the study of Productive Interactions between science and society (SIAMPI) [40]** The Netherlands, 2011	–	Learning tool to better understand how research interactions lead to social impact. This approach focuses on productive interactions, especially exchanges between researchers and stakeholders	Types of productive interactions: • Direct interactions • Indirect interactions • Financial interactions	Yes, but no systematic approach reported	The European commission, research organisations, science policy makers, research councils, academies, and other bodies involved in research were involved in meetings and discussions	A case study approach was used to test the framework. The feedback of the case study representatives was used to refine the framework [61]	Not specified
M. O. Kok and A. Schuit **Contribution Mapping [7]** The Netherlands, 2012	–	An approach to monitor and evaluate contributions to determine how the utilisation of research can contribute to better action for health. The method focuses on processes, actors, and efforts to enhance contributions and enable alignment of efforts.	Research related contributions categories: • Changes in abilities and actions of involved and linked actors • Contributed knowledge products • Contributions through linked utilisation • Indications of utilisation at a distance	Yes, but no systematic approach reported	Investigators of the projects were included. Potential key users and other potential informants were interviewed to draft the model and understand contributions. Stakeholders were consulted to refine the model	Preliminary results were shared with stakeholders for feedback and validation. Once discrepancies were solved, results were shared with stakeholders	Not specified
S. Morton **Research Contribution Framework [42]** UK, 2015	–	Assessment of research impact using contribution analysis to explain the influence in policy and practice	• Final outcome • Policy or practice change • Capacity, knowledge and skill • Awareness, reaction • Engagement, participation • Activities and outputs • Inputs	No systematic approach reported	Semistructured interviews were conducted among project partners that took part in the process of the research (i.e., conferences and workshops) and research users (i.e., practitioners)	A thematic analysis approach was used to analyse the data collected and refine the framework. The themes that emerged were tested against other sources	A case study was used to illustrate how the Research Contribution Framework can assess impact

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Methodological framework development

The included methodological frameworks varied in their development process, but there were some common approaches employed. Most included a literature review [2,5,7,8,31,33,36,37, 40–46], although none of them used a recognised systematic method. Most also consulted with various stakeholders [3,8,29,31,33,35–38,43,44,46,47] but used differing methods to incorporate their views, including quantitative surveys [32,35,43,46], face-to-face interviews [7,29,33, 35,37,42,43], telephone interviews [31,46], consultation [3,7,36], and focus groups [39,43]. A range of stakeholder groups were approached across the sample, including principal investigators [7,29,43], research end users [7,42,43], academics [3,8,39,40,43,46], award holders [43], experts [33,38,39], sponsors [33,39], project coordinators [32,42], and chief investigators [31,35]. However, some authors failed to identify the stakeholders involved in the development of their frameworks [2,5,34,41,45], making it difficult to assess their appropriateness. In addition, only 4 of the included papers reported using formal analytic methods to interpret stakeholder responses. These included the Canadian Academy of Health Sciences framework, which used conceptual cluster analysis [33]. The Research Contribution [42], Research Impact [29], and Primary Health Care & Information Service [31] used a thematic analysis approach. Finally, some authors went on to pilot their framework, which shaped refinements on the methodological frameworks until approval. Methods used to pilot the frameworks included a case study approach [2,3,30,32,33,36,40,42,44,45], contrasting results against available literature [29], the use of stakeholders' feedback [7], and assessment tools [35,46].

Major impact categories

1. Primary research-related impact. A number of methodological frameworks advocated the evaluation of 'research-related impact'. This encompassed content related to the generation of new knowledge, knowledge dissemination, capacity building, training, leadership, and the development of research networks. These outcomes were considered the direct or primary impacts of a research project, as these are often the first evidenced returns [30,62].

A number of subgroups were identified within this category, with frameworks supporting the collection of impact data across the following constructs: 'research and innovation outcomes'; 'dissemination and knowledge transfer'; 'capacity building, training, and leadership'; and 'academic collaborations, research networks, and data sharing'.

1.1. Research and innovation outcomes. Twenty of the 24 frameworks advocated the evaluation of 'research and innovation outcomes' [2,3,5,7,8,29–39,41,43,44,46]. This subgroup included the following metrics: number of publications; number of peer-reviewed articles (including journal impact factor); citation rates; requests for reprints, number of reviews, and meta-analysis; and new or changes in existing products (interventions or technology), patents, and research. Additionally, some frameworks also sought to gather information regarding 'methods/methodological contributions'. These advocated the collection of systematic reviews and appraisals in order to identify gaps in knowledge and determine whether the knowledge generated had been assessed before being put into practice [29].

1.2. Dissemination and knowledge transfer. Nineteen of the 24 frameworks advocated the assessment of 'dissemination and knowledge transfer' [2,3,5,7,29–32,34–43,46]. This comprised collection of the following information: number of conferences, seminars, workshops, and presentations; teaching output (i.e., number of lectures given to disseminate the research findings); number of reads for published articles; article download rate and number of journal webpage visits; and citations rates in nonjournal media such as newspapers and mass and social media (i.e., Twitter and blogs). Furthermore, this impact subgroup considered the measurement of research uptake and translatability and the adoption of research findings in

technological and clinical applications and by different fields. These can be measured through patents, clinical trials, and partnerships between industry and business, government and non-governmental organisations, and university research units and researchers [29].

1.3. Capacity building, training, and leadership. Fourteen of 24 frameworks suggested the evaluation of 'capacity building, training, and leadership' [2,3,5,8,29,31–35,39–41,43]. This involved collecting information regarding the number of doctoral and postdoctoral studentships (including those generated as a result of the research findings and those appointed to conduct the research), as well as the number of researchers and research-related staff involved in the research projects. In addition, authors advocated the collection of 'leadership' metrics, including the number of research projects managed and coordinated and the membership of boards and funding bodies, journal editorial boards, and advisory committees [29]. Additional metrics in this category included public recognition (number of fellowships and awards for significant research achievements), academic career advancement, and subsequent grants received. Lastly, the impact metric 'research system management' comprised the collection of information that can lead to preserving the health of the population, such as modifying research priorities, resource allocation strategies, and linking health research to other disciplines to maximise benefits [29].

1.4. Academic collaborations, research networks, and data sharing. Lastly, 10 of the 24 frameworks advocated the collection of impact data regarding 'academic collaborations (internal and external collaborations to complete a research project), research networks, and data sharing' [2,3,5,7,29,34,37,39,41,43].

2. Influence on policy making. Methodological frameworks addressing this major impact category focused on measurable improvements within a given knowledge base and on interactions between academics and policy makers, which may influence policy-making development and implementation. The returns generated in this impact category are generally considered as intermediate or midterm (1 to 3 years). These represent an important interim stage in the process towards the final expected impacts, such as quantifiable health improvements and economic benefits, without which policy change may not occur [30,62]. The following impact subgroups were identified within this category: 'type and nature of policy impact', 'level of policy making', and 'policy networks'.

2.1. Type and nature of policy impact. The most common impact subgroup, mentioned in 18 of the 24 frameworks, was 'type and nature of policy impact' [2,7,29–38,41–43,45–47]. Methodological frameworks addressing this subgroup stressed the importance of collecting information regarding the influence of research on policy (i.e., changes in practice or terminology). For instance, a project looking at trafficked adolescents and women (2003) influenced the WHO guidelines (2003) on ethics regarding this particular group [17,21,63].

2.2. Level of policy impact. Thirteen of 24 frameworks addressed aspects surrounding the need to record the 'level of policy impact' (international, national, or local) and the organisations within a level that were influenced (local policy makers, clinical commissioning groups, and health and wellbeing trusts) [2,5,8,29,31,34,38,41,43–47]. Authors considered it important to measure the 'level of policy impact' to provide evidence of collaboration, coordination, and efficiency within health organisations and between researchers and health organisations [29,31].

2.3. Policy networks. Five methodological frameworks highlighted the need to collect information regarding collaborative research with industry and staff movement between academia and industry [5,7,29,41,43]. A policy network emphasises the relationship between policy communities, researchers, and policy makers. This relationship can influence and lead to incremental changes in policy processes [62].

3. Health and health systems impact. A number of methodological frameworks advocated the measurement of impacts on health and healthcare systems across the following impact subgroups: 'quality of care and service delivering', 'evidence-based practice', 'improved information and health information management', 'cost containment and effectiveness', 'resource allocation', and 'health workforce'.

3.1. Quality of care and service delivery. Twelve of the 24 frameworks highlighted the importance of evaluating 'quality of care and service delivery' [2,5,8,29–31,33–36,41,47]. There were a number of suggested metrics that could be potentially used for this purpose, including health outcomes such as quality-adjusted life years (QALYs), patient-reported outcome measures (PROMs), patient satisfaction and experience surveys, and qualitative data on waiting times and service accessibility.

3.2. Evidence-based practice. 'Evidence-based practice', mentioned in 5 of the 24 frameworks, refers to making changes in clinical diagnosis, clinical practice, treatment decisions, or decision making based on research evidence [5,8,29,31,33]. The suggested metrics to demonstrate evidence-based practice were adoption of health technologies and research outcomes to improve the healthcare systems and inform policies and guidelines [29].

3.3. Improved information and health information management. This impact subcategory, mentioned in 5 of the 24 frameworks, refers to the influence of research on the provision of health services and management of the health system to prevent additional costs [5,29,33, 34,38]. Methodological frameworks advocated the collection of health system financial, nonfinancial (i.e., transport and sociopolitical implications), and insurance information in order to determine constraints within a health system.

3.4. Cost containment and cost-effectiveness. Six of the 24 frameworks advocated the subcategory 'cost containment and cost-effectiveness' [2,5,8,17,33,36]. 'Cost containment' comprised the collection of information regarding how research has influenced the provision and management of health services and its implication in healthcare resource allocation and use [29]. 'Cost-effectiveness' refers to information concerning economic evaluations to assess improvements in effectiveness and health outcomes—for instance, the cost-effectiveness (cost and health outcome benefits) assessment of introducing a new health technology to replace an older one [29,31,64].

3.5. Resource allocation. 'Resource allocation', mentioned in 6frameworks, can be measured through 2 impact metrics: new funding attributed to the intervention in question and equity while allocating resources, such as improved allocation of resources at an area level; better targeting, accessibility, and utilisation; and coverage of health services [2,5,29,31,45,47]. The allocation of resources and targeting can be measured through health services research reports, with the utilisation of health services measured by the probability of providing an intervention when needed, the probability of requiring it again in the future, and the probability of receiving an intervention based on previous experience [29,31].

3.6. Health workforce. Lastly, 'health workforce', present in 3 methodological frameworks, refers to the reduction in the days of work lost because of a particular illness [2,5,31].

4. Health-related and societal impact. Three subgroups were included in this category: 'health literacy'; 'health knowledge, attitudes, and behaviours'; and 'improved social equity, inclusion, or cohesion'.

4.1. Health knowledge, attitudes, and behaviours. Eight of the 24 frameworks suggested the assessment of 'health knowledge, attitudes, behaviours, and outcomes', which could be measured through the evaluation of levels of public engagement with science and research (e.g., National Health Service (NHS) Choices end-user visit rate) or by using focus groups to analyse changes in knowledge, attitudes, and behaviour among society [2,5,29,33–35,38,43].

4.2. Improved equity, inclusion, or cohesion and human rights. Other methodological frameworks, 4 of the 24, suggested capturing improvements in equity, inclusion, or cohesion and human rights. Authors suggested these could be using a resource like the United Nations Millennium Development Goals (MDGs) (superseded by Sustainable Development Goals [SDGs] in 2015) and human rights [29,33,34,38]. For instance, a cluster-randomised controlled trial in Nepal, which had female participants, has demonstrated the reduction of neonatal mortality through the introduction of maternity health care, distribution of delivery kits, and home visits. This illustrates how research can target vulnerable and disadvantaged groups. Additionally, this research has been introduced by the World Health Organisation to achieve the MDG 'improve maternal health' [16,29,65].

4.3. Health literacy. Some methodological frameworks, 3 of the 24, focused on tracking changes in the ability of patients to make informed healthcare decisions, reduce health risks, and improve quality of life, which were demonstrably linked to a particular programme of research [5,29,43]. For example, a systematic review showed that when HIV health literacy/knowledge is spread among people living with the condition, antiretroviral adherence and quality of life improve [66].

5. Broader economic impacts. Some methodological frameworks, 9 of 24, included aspects related to the broader economic impacts of health research—for example, the economic benefits emerging from the commercialisation of research outputs [2,5,29,31,33,35,36,38,67]. Suggested metrics included the amount of funding for research and development (R&D) that was competitively awarded by the NHS, medical charities, and overseas companies. Additional metrics were income from intellectual property, spillover effects (any secondary benefit gained as a repercussion of investing directly in a primary activity, i.e., the social and economic returns of investing on R&D) [33], patents granted, licences awarded and brought to the market, the development and sales of spinout companies, research contracts, and income from industry.

The benefits contained within the categories 'health and health systems impact', 'health-related and societal impact', and 'broader economic impacts' are considered the expected and final returns of the resources allocated in healthcare research [30,62]. These benefits commonly arise in the long term, beyond 5 years according to some authors, but there was a recognition that this could differ depending on the project and its associated research area [4].

Data synthesis

Five major impact categories were identified across the 24 included methodological frameworks: (1) 'primary research-related impact', (2) 'influence on policy making', (3) 'health and health systems impact', (4) 'health-related and societal impact', and (5) 'broader economic impact'. These major impact categories were further subdivided into 16 impact subgroups. The included publications proposed 80 different metrics to measure research impact. This impact typology synthesis is depicted in 'the impact matrix' (Fig 2 and Fig 3).

Commonality and differences across frameworks

The 'Research Impact Framework' and the 'Health Services Research Impact Framework' were the models that encompassed the largest number of the metrics extracted. The most dominant methodological framework was the Payback Framework; 7 other methodological framework models used the Payback Framework as a starting point for development [8,29,31–35]. Additional methodological frameworks that were commonly incorporated into other tools included the CIHR framework, the CAHS model, the AIHS framework, and the Exchange model [8,33,34,44]. The capture of 'research-related impact' was the most widely advocated concept

across methodological frameworks, illustrating the importance with which primary short-term impact outcomes were viewed by the included papers. Thus, measurement of impact via number of publications, citations, and peer-reviewed articles was the most common. 'Influence on policy making' was the predominant midterm impact category, specifically the subgroup 'type and nature of policy impact', in which frameworks advocated the measurement of (i) changes to legislation, regulations, and government policy; (ii) influence and involvement in decision-making processes; and (iii) changes to clinical or healthcare training, practice, or guidelines. Within more long-term impact measurement, the evaluations of changes in the 'quality of care and service delivery' were commonly advocated.

In light of the commonalities and differences among the methodological frameworks, the 'pathways to research impact' diagram (Fig 4) was developed to provide researchers, funders, and policy makers a more comprehensive and exhaustive way to measure healthcare research impact. The diagram has the advantage of assorting all the impact metrics proposed by previous frameworks and grouping them into different impact subgroups and categories. Prospectively, this global picture will help researchers, funders, and policy makers plan strategies to achieve multiple pathways to impact before carrying the research out. The analysis of the data extraction and construction of the impact matrix led to the development of the 'pathways to research impact' diagram (Fig 4). The diagram aims to provide an exhaustive and comprehensive way of tracing research impact by combining all the impact metrics presented by the different 24 frameworks, grouping those metrics into different impact subgroups, and grouping these into broader impact categories.

Discussion

This review has summarised existing methodological impact frameworks together for the first time using systematic methods (Fig 4). It allows researchers and funders to consider pathways to impact at the design stage of a study and to understand the elements and metrics that need to be considered to facilitate prospective assessment of impact. Users do not necessarily need to cover all the aspects of the methodological framework, as every research project can impact on different categories and subgroups. This review provides information that can assist researchers to better demonstrate impact, potentially increasing the likelihood of conducting impactful research and reducing research waste. Existing reviews have not presented a methodological framework that includes different pathways to impact, health impact categories, subgroups, and metrics in a single methodological framework.

Academic-orientated frameworks included in this review advocated the measurement of impact predominantly using so-called 'quantitative' metrics—for example, the number of peer-reviewed articles, journal impact factor, and citation rates. This may be because they are well-established measures, relatively easy to capture and objective, and are supported by research funding systems. However, these metrics primarily measure the dissemination of research finding rather than its impact [30,68]. Whilst it is true that wider dissemination, especially when delivered via world-leading international journals, may well lead eventually to changes in healthcare, this is by no means certain. For instance, case studies evaluated by Flinders University of Australia demonstrated that some research projects with non-peer-reviewed publications led to significant changes in health policy, whilst the studies with peer-reviewed publications did not result in any type of impact [68]. As a result, contemporary literature has tended to advocate the collection of information regarding a variety of different potential forms of impact alongside publication/citations metrics [2,3,5,7,8,29–47], as outlined in this review.

Time frame	Impact categories	Framework / Impact subgroups	Payback Framework	HTA Organisation Assessment Framework	Research Utilisation Ladder	The social impact of applied research	Exchange model	RAE	CIHR	RIF	PHC RIS	Logic Model	Meagher et al.	RQF
Short-term	1. Research-related impact	Research and innovation outcomes	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
		Dissemination and knowledge transfer	✔		✔	✔		✔		✔	✔	✔	✔	✔
		Capacity building, training and leadership	✔			✔		✔	✔	✔	✔		✔	
		Academic collaborations, research networks and data sharing	✔			✔		✔					✔	
Mid-term	2. Influencing and involvement in policy making	Level of policy- making	✔	✔	✔	✔	✔		✔	✔	✔		✔	✔
		Type and nature of policy impact	✔		✔	✔				✔	✔	✔	✔	✔
		Policy networks	✔		✔	✔				✔			✔	
Long-term	3. Health and health systems impact	Evidence-based practice							✔	✔	✔			
		Quality of care and service delivery	✔			✔			✔	✔	✔	✔		
		Improved information and health services management								✔				✔
		Cost containment and effectiveness	✔						✔	✔				
		Resource allocation	✔	✔						✔	✔			
		Health workforce	✔								✔			
	4. Health related and societal impacts	Health literacy								✔			✔	
		Health knowledge, attitudes, behaviour and outcomes	✔							✔			✔	✔
		Improved social equity, inclusion or cohesion								✔				✔
	5. Broader economic impacts		✔							✔	✔			✔

Fig 2. The impact matrix (1). CIHR, Canadian Institutes of Health Research; HTA, Health Technology Assessment; PHC RIS, Primary Health Care Research & Information Service; RAE, Research Assessment Exercise; RQF, Research Quality Framework.

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The 2014 REF exercise adjusted UK university research funding allocation based on evidence of the wider impact of research (through case narrative studies and quantitative metrics), rather than simply according to the quality of research [12]. The intention was to ensure funds were directed to high-quality research that could demonstrate actual realised benefit. The inclusion of a mixed-method approach to the measurement of impact in the REF (narrative and quantitative metrics) reflects a widespread belief—expressed by the majority of authors of the included methodological frameworks in the review—that individual quantitative impact metrics (e.g., number of citations and publications) do not necessary capture the complexity of the relationships involved in a research project and may exclude measurement of specific aspects of the research pathway [10,12].

Many of the frameworks included in this review advocated the collection of a range of academic, societal, economic, and cultural impact metrics; this is consistent with recent recommendations from the Stern review [10]. However, a number of these metrics encounter research 'lag': i.e., the time between the point at which the research is conducted and when the actual benefits arise [69]. For instance, some cardiovascular research has taken up to 25 years to generate impact [70]. Likewise, the impact may not arise exclusively from a single piece of research. Different processes (such as networking interactions and knowledge and research

Time frame	Impact categories	Framework / Impact subgroups	Canavan et al.	CAHS	The Becker Model	REF	SIAMPI	The Health Services Research Impact Framework	AIHS	Contribution Mapping	Cohen et al.	Brueton et al.	IOM	Research Contribution Framework
Short-term	1. Research-related impact	Research and innovation outcomes		✔	✔	✔		✔	✔	✔	✔	✔	✔	
		Dissemination and knowledge transfer				✔	✔	✔	✔	✔	✔	✔	✔	
		Capacity building, training and leadership		✔	✔	✔	✔	✔	✔		✔		✔	✔
		Academic collaborations, research networks and data sharing				✔		✔	✔	✔		✔		
Mid-term	2. Influencing and involvement in policy making	Level of policy- making	✔					✔	✔					
		Type and nature of policy impact	✔	✔	✔				✔	✔	✔	✔	✔	✔
		Policy networks						✔		✔				
Long-term	3. Health and health systems impact	Evidence-based practice		✔				✔						
		Quality of care and service delivery		✔	✔			✔						
		Improved information and health services management		✔				✔						
		Cost containment and effectiveness		✔	✔			✔						
		Resource allocation		✔				✔						
		Health workforce						✔						
	4. Health related and societal impacts	Health literacy						✔						
		Health knowledge, attitudes, behaviour and outcomes		✔				✔	✔		✔			
		Improved social equity, inclusion or cohesion		✔					✔					
	5. Broader economic impacts			✔	✔			✔	✔		✔			

Fig 3. The impact matrix (2). AIHS, Alberta Innovates—Health Solutions; CAHS, Canadian Institutes of Health Research; IOM, Impact Oriented Monitoring; REF, Research Excellence Framework; SIAMPI, Social Impact Assessment Methods for research and funding instruments through the study of Productive Interactions between science and society.

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translation) and multiple individuals and organisations are often involved [4,71]. Therefore, attributing the contribution made by each of the different actors involved in the process can be a challenge [4]. An additional problem associated to attribution is the lack of evidence to link research and impact. The outcomes of research may emerge slowly and be absorbed gradually. Consequently, it is difficult to determine the influence of research in the development of a new policy, practice, or guidelines [4,23].

A further problem is that impact evaluation is conducted 'ex post', after the research has concluded. Collecting information retrospectively can be an issue, as the data required might not be available. 'ex ante' assessment is vital for funding allocation, as it is necessary to determine the potential forthcoming impact before research is carried out [69]. Additionally, ex ante evaluation of potential benefit can overcome the issues regarding identifying and capturing evidence, which can be used in the future [4]. In order to conduct ex ante evaluation of potential benefit, some authors suggest the early involvement of policy makers in a research project coupled with a well-designed strategy of dissemination [40,69].

Providing an alternate view, the authors of methodological frameworks such as the SIAMPI, Contribution Mapping, Research Contribution, and the Exchange model suggest that the problems of attribution are a consequence of assigning the impact of research to a particular impact metric [7,40,42,44]. To address these issues, these authors propose focusing on the contribution of research through assessing the processes and interactions between

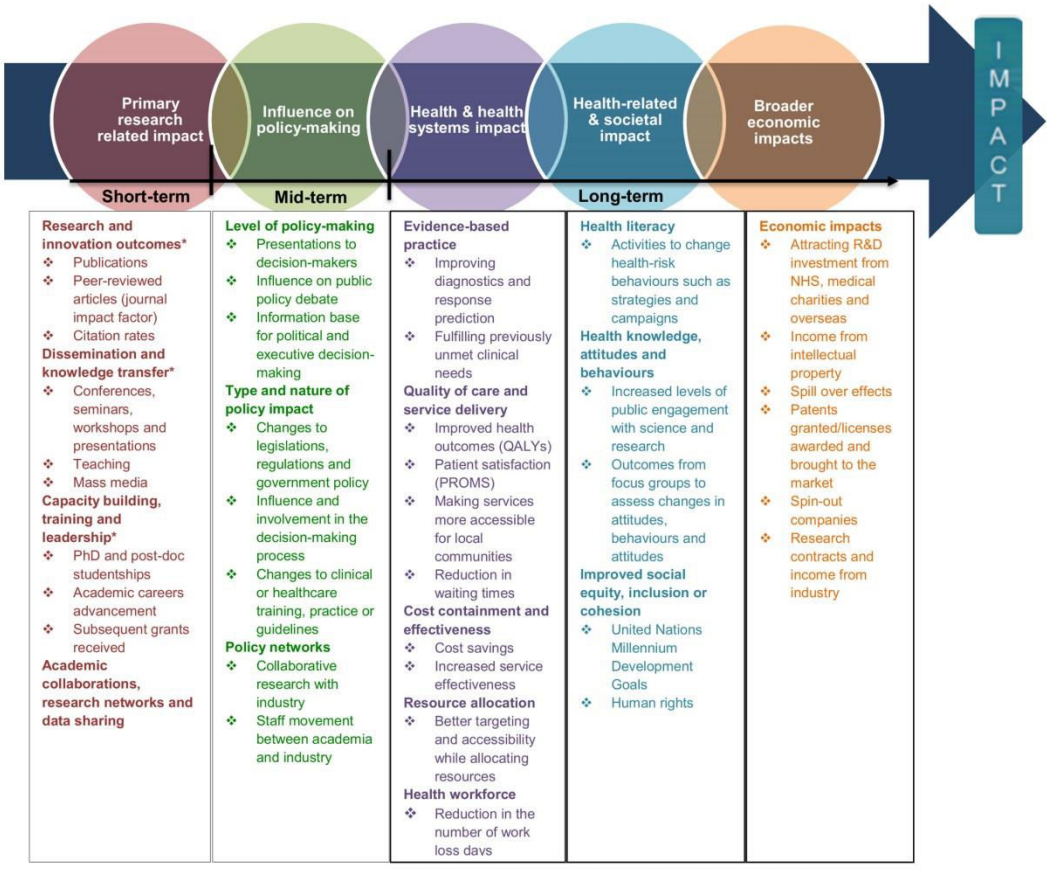

Fig 4. Pathways to research impact. NHS, National Health Service; PROM, patient-reported outcome measure; QALY, quality-adjusted life year; R&D, research and development.

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stakeholders and researchers, which arguably take into consideration all the processes and actors involved in a research project [7,40,42,43]. Additionally, contributions highlight the importance of the interactions between stakeholders and researchers from an early stage in the research process, leading to a successful ex ante and ex post evaluation by setting expected impacts and determining how the research outcomes have been utilised, respectively [7,40,42,43]. However, contribution metrics are generally harder to measure in comparison to academic-orientated indicators [72].

Currently, there is a debate surrounding the optimal methodological impact framework, and no tool has proven superior to another. The most appropriate methodological framework

for a given study will likely depend on stakeholder needs, as each employs different methodologies to assess research impact [4,37,41]. This review allows researchers to select individual existing methodological framework components to create a bespoke tool with which to facilitate optimal study design and maximise the potential for impact depending on the characteristic of their study (Fig 2 and Fig 3). For instance, if researchers are interested in assessing how influential their research is on policy making, perhaps considering a suite of the appropriate metrics drawn from multiple methodological frameworks may provide a more comprehensive method than adopting a single methodological framework. In addition, research teams may wish to use a multidimensional approach to methodological framework development, adopting existing narratives and quantitative metrics, as well as elements from contribution frameworks. This approach would arguably present a more comprehensive method of impact assessment; however, further research is warranted to determine its effectiveness [4,69,72,73].

Finally, it became clear during this review that the included methodological frameworks had been constructed using varied methodological processes. At present, there are no guidelines or consensus around the optimal pathway that should be followed to develop a robust methodological framework. The authors believe this is an area that should be addressed by the research community, to ensure future frameworks are developed using best-practice methodology.

For instance, the Payback Framework drew upon a literature review and was refined through a case study approach. Arguably, this approach could be considered inferior to other methods that involved extensive stakeholder involvement, such as the CIHR framework [8]. Nonetheless, 7 methodological frameworks were developed based upon the Payback Framework [8,29,31–35].

Limitations

The present review is the first to summarise systematically existing impact methodological frameworks and metrics. The main limitation is that 50% of the included publications were found through methods other than bibliographic databases searching, indicating poor indexing. Therefore, some relevant articles may not have been included in this review if they failed to indicate the inclusion of a methodological impact framework in their title/abstract. We did, however, make every effort to try to find these potentially hard-to-reach publications, e.g., through forwards/backwards citation searching, hand searching reference lists, and expert communication. Additionally, this review only extracted information regarding the methodology followed to develop each framework from the main publication source or framework webpage. Therefore, further evaluations may not have been included, as they are beyond the scope of the current paper. A further limitation was that although our search strategy did not include language restrictions, we did not specifically search non-English language databases. Thus, we may have failed to identify potentially relevant methodological frameworks that were developed in a non-English language setting.

Conclusion

In conclusion, the measurement of research impact is an essential exercise to help direct the allocation of limited research resources, to maximise benefit, and to help minimise research waste. This review provides a collective summary of existing methodological impact frameworks and metrics, which funders may use to inform the measurement of research impact and researchers may use to inform study design decisions aimed at maximising the short-, medium-, and long-term impact of their research.

Supporting information

S1 Appendix. Search strategy.
(TIF)

S1 PRISMA Checklist. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.
(PDF)

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Appendices for Chapter 3

Chapter 4: The impact of patient-reported outcome (PRO) data from clinical trials

Determining the impact of PRO trial data

Patient reported outcomes (PROs) are self-completed questionnaires that ask patients about the impact of a disease or treatment on their health, quality of life and symptoms [1, 2]. These questionnaires provide a way of measuring patients' views about their health and wellbeing [2]. PRO data from clinical trials may potentially lead to impact for patients and society. Identifying and measuring the impact of PRO trial data is critical to inform funding allocation and demonstrate accountability to government, stakeholders and society, as discussed in Chapters 1 and 3.

The systematic review reported in this chapter addressed the thesis **objective B:** to determine the range of potential impacts of PRO data collected from clinical trials, **objective C:** to identify potential PRO impact metrics and determine common barriers and facilitators to maximising PRO impact and **objective D:** to assess Research Excellence Framework (REF) impact case studies to explore real-world evidence of PRO trial impact and highlight optimal pathways to such impact. Further information on the methods used in this study can be found in Chapter 2.

Publication 2*:*

Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. **The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis**. *Health Qual Life Outcomes*. 2019;17(1):156. Published 2019 Oct 16.(10.1186/s12955-019-1220-z)

The work has been further disseminated as outlined in Table 1.

Table 1. Dissemination of publication

Year	Conference	Location	Type of presentation
2018	3rd Patient Reported Outcomes Measures Research Conference	Birmingham, UK	Oral
2018	A two-day course hosted by Professor Calvert and the Centre for Patient Reported Outcomes Research (CPROR)	Birmingham, UK	Oral
2019	4th Patient Reported Outcomes Measures Research Conference	Leeds, UK	Poster
	5th ICTMC (International Clinical Trials Methodology Conference)	Brighton, UK	Oral
	ISOQOL (International Society for Quality of Life Research) 26th Annual Conference	San Diego, CA, USA	Poster

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Rivera et al. Health and Quality of Life Outcomes (2019) 17:156
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Health and Quality of Life Outcomes

RESEARCH Open Access

The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis

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Abstract

Background: Patient-reported outcomes (PROs) are commonly collected in clinical trials and should provide impactful evidence on the effect of interventions on patient symptoms and quality of life. However, it is unclear how PRO impact is currently realised in practice. In addition, the different types of impact associated with PRO trial results, their barriers and facilitators, and appropriate impact metrics are not well defined. Therefore, our objectives were: i) to determine the range of potential impacts from PRO clinical trial data, ii) identify potential PRO impact metrics and iii) identify barriers/facilitators to maximising PRO impact; and iv) to examine real-world evidence of PRO trial data impact based on Research Excellence Framework (REF) impact case studies.

Methods: Two independent investigators searched MEDLINE, EMBASE, CINAHL+, HMIC databases from inception until December 2018. Articles were eligible if they discussed research impact in the context of PRO clinical trial data. In addition, the REF 2014 database was systematically searched. REF impact case studies were included if they incorporated PRO data in a clinical trial.

Results: Thirty-nine publications of eleven thousand four hundred eighty screened met the inclusion criteria. Nine types of PRO trial impact were identified; the most frequent of which centred around PRO data informing clinical decision-making. The included publications identified several barriers and facilitators around PRO trial design, conduct, analysis and report that can hinder or promote the impact of PRO trial data. Sixty-nine out of two hundred nine screened REF 2014 case studies were included. 12 (17%) REF case studies led to demonstrable impact including changes to international guidelines; national guidelines; influencing cost-effectiveness analysis; and influencing drug approvals.

Conclusions: PRO trial data may potentially lead to a range of benefits for patients and society, which can be measured through appropriate impact metrics. However, in practice there is relatively limited evidence demonstrating directly attributable and indirect real world PRO-related research impact. In part, this is due to the wider challenges of measuring the impact of research and PRO-specific issues around design, conduct, analysis and reporting. Adherence to guidelines and multi-stakeholder collaboration is essential to maximise the use of PRO trial data, facilitate impact and minimise research waste.

Trial registration: Systematic Review registration PROSPERO CRD42017067799.

Keywords: Patient-reported outcomes, Quality of life, Impact, REF case studies, Clinical trials

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Introduction

Patient-reported outcomes (PROs) are increasingly used in clinical trials to assess the impact of a medical treatment or intervention. PRO assess a range of outcomes including symptoms, functional health, well-being and psychological issues from the patients' perspective, without interpretation by a clinician [1–3]. Between 2007 and 2013, 26,337 (27%) of the clinical trials registered on ClinicalTrials.gov included PROs [4]. However, there is growing evidence that there is substantial research waste in relation to PROs [5, 6]. A recent systematic evaluation of oncology clinical trials determined that PRO protocol items were frequently omitted, non-reporting of PRO trials results was common and PRO publications were considerable delayed and presented suboptimal standards of reporting [5]. Thus, important PRO evidence may not be available to benefit patients and society.

Assessing the impact of research is a complex activity; however, it is important that the impact of PRO data is understood as this may inform funding allocations and demonstrate accountability to government, stakeholders and society [7]. Impact is defined as "*any identifiable benefit to, or positive influence on, the economy, society, public policy or services, culture, the environment or quality of life …" (p.26)* [8]. A number of reviews describe potential pathways (i.e. "*a way of achieving a specified result; a course of action*' [9]) to general research impact [8, 10–33]. However, few studies have investigated the optimal pathway or methods for augmenting or evaluating specific impacts of PRO trial data or the extent to which PRO impact is being realised. It is also not clear which is the most appropriate way to measure PRO impact, or the barriers and facilitators to realising that impact.

One way of assessing real-world impact is via the United Kingdom (UK) Higher Education Funding Council for England Research Excellence Framework (REF) impact case studies. During the REF 2014 exercise, UK higher education institutions submitted impact case studies: narratives that described the impact of research conducted during a specific time-period, including a number of case studies describing clinical trials involving PROs. REF case studies present meaningful, far-reaching and properly articulated impact that is demonstrated through convincing evidence. The impact presented focuses on the benefits of the research rather than on the pathways of research impact, allowing the assessment of real-world impact on society [34]. Examination of these case studies can enhance understanding of the best methods for maximising and measuring PRO research impact, not only in the UK, but also internationally since a number of the studies described in REF are international studies [10, 35].

Therefore, the study had four objectives. First, to conduct a systematic review of the literature to: i) determine the range of potential impact that may arise from clinical trial PRO clinical trial data, ii) identify potential PRO impact metrics iii) identify barriers/facilitators to maximising PRO impact and; iv) to examine REF 2014 impact case studies to explore real-world evidence of PRO trial data impact.

Methods

This systematic review was registered on the PROSPERO database (CRD42017067799) and results are reported in accordance with PRISMA guidelines [36].

Search strategy

Systematic review

Two reviewers (SCR and OLA) systematically and independently searched MEDLINE (Ovid), EMBASE, HMIC and CINAHL+ databases (inception to December 2018) for articles discussing the impact of PRO data collected from clinical trials from inception to December 2018 (see Additional file 1 for the full search strategy). The authors (SCR/MC/DK) designed the search strategy with input from a University of Birmingham Information Specialist. In addition, the keywords 'patient reported outcome measure*', 'PROs', 'PRO', 'PROM', 'PROMS', 'HRQOL', 'HRQL', 'quality of life', 'impact' and 'clinical trial*' were searched on Google Scholar, where the initial 100 results were screened. Only the first 100 results (10 pages) were revised, as article relevance diminishes with each page of results [37]. Lastly, additional publications ($n = 3$) were sought through communication with methodological PRO experts facilitated by MC/DK. Hand-searching of reference lists and citation searches of the included publications was also conducted to identify additional relevant articles.

REF 2014 impact case studies

The keywords "trial*" and "quality of life" or "patient reported outcome*" were introduced in the REF 2014 database. The search strategy was restricted to: i) Unit of assessment: main panel A (see Table 1 for further detail), ii) Summary impact type: 'health' and iii) Research subject area: medical and health sciences.

Eligibility criteria

Systematic review publications were deemed eligible if they discussed research impact in the context of PRO clinical trial

Table 1 REF 2014 – Main panel A

Units of assessment		
Main panel A	1	Clinical medicine
	2	Public Health, Health Services and Primary Care
	3	Allied Health Professions, Dentistry, Nursing and Pharmacy
	4	Psychology, Psychiatry and Neuroscience
	5	Biological Sciences
	6	Agriculture, Veterinary and Food Science

data. In particular, we sought information on the types of impact (and pathways to impact) thought to be associated with PRO findings, proposed methods for measuring such impact and perceived barriers/facilitators to generating PRO-specific research impact. Publications were excluded if: i) solely focused on PROs used in routine clinical practice as the focus of this review was on the proposed PRO impact from trials; ii) trial publications reporting PRO results as the focus was research impact rather than primary results; or iii) conference abstracts. REF 2014 impact case studies were eligible if they included a trial in which PRO data were collected. There were no language restrictions.

Data screening

Systematic review

The screening process was conducted independently by two reviewers (SCR and OLA). Citations were downloaded into Endnote® software (version X7.3.1) and duplicates deleted. Records were screened by title and abstract. Potentially relevant articles were identified for further full-text screening (SCR and OLA). Discrepancies were resolved through discussion with a third reviewer (MC/DK/AS) if required.

REF 2014 impact case studies

The screening process was also conducted independently by SCR and OLA. The case studies were downloaded into a Microsoft Excel spreadsheet. Records were screened by title and summary of the impact. Relevant case studies were selected for further full-text screening (SCR and OLA). Discrepancies were resolved through discussion, with a third reviewer (MC/DK/AS) as necessary.

Data extraction/coding

Systematic review

Data extraction was done after the final selection of the included articles. SCR and OLA independently identified text excerpts that provided information on PRO-specific impact types, pathways, metrics, barriers or facilitators from the systematic review. Both reviewers independently imported text excerpts into a qualitative data analysis software package (QRS NVivo 11). They generated categories independently using descriptive coding under the directed content analysis framework [38]. The 'pathways to research impact' framework [10] was deductively applied to the data in order to identify types of impact and impact metrics. Data which did not fit within the existing framework were added to a 'miscellaneous' category. 'Influence on policy-making' was the only impact category discussed by the articles included in the systematic review. Subsequently, the data coded into this impact category was organised into subgroups. Through deductive coding, the following types of impact were identified: 'inform clinical practice', 'inform clinical guidelines', 'inform clinical decision-making', 'inform health policy' and 'inform shared decision-making'.

Inductive coding was undertaken to describe and interpret more detailed codes within the 'influence on policy-making' and miscellaneous categories. The following types of impact were identified through inductive coding: 'support drug approval', 'support pricing decisions', 'support reimbursement decisions' and 'inform consent for treatment'. In addition, inductive coding was used to identify further impact metrics, and barriers and facilitators to PRO trial impact. Development of overarching themes occurred after the coding process and collation of codes. The following details were also extracted from all the included publications: author, publication year, journal, methodology, study focus and type of PRO data impact.

REF 2014 impact case studies

Deductive and inductive was also undertaken to identify types of impact, impact metrics and barriers and facilitators among the REF case studies. In addition, the following details were extracted from the REF 2014 case studies: name, submitting institution and clinical area; trial name and year of publication, trial design, leading study centre, trial phase, trial primary and secondary outcomes, PRO instrument, significance of primary and secondary trial outcomes and type of impact. Furthermore, type of impact was further classified as either: i) direct PRO impact, where there was evidence of a direct link between PRO trial findings and subsequent impact. ii) Indirect PRO impact, where a trial including PROs subsequently led to impact, but it was not possible to directly attribute this impact to the PRO findings over and above the other trial outcomes; or iii) no evidence of PRO impact, where a trial including PROs failed to lead to impact. SCR and OLA independently piloted the coding frames, following discussion with MC/DK/AS/CM to resolve discrepancies. Finally, systematic review and impact case studies coding frames were validated by the co-authors MC/DK/AS/CM, who possess expertise in PRO clinical trial data, research impact and qualitative data analysis.

Results

Systematic review

Included studies

The search strategy retrieved 11,377 citations from MEDLINE (Ovid), EMBASE, HMIC, and CINAHL+; 100 citations were returned using Google Scholar and 6 through expert communication (PRISMA flow diagram, Additional file 2). Eight thousand eight hundred seventy-seven citations were excluded following review

Type of impact	Informing			Informing			Informing		
Author	Clinical practice	Clinical guidelines	Health policy	Drug approval	Pricing decisions	Reimbursement decisions	Clinical decision-making	Shared-decision making	Consent for treatment
Revicki et al. (2000)				✔					
Bottomley et al. (2003)							✔		
Efficace et al. (2003)							✔		
Goodwin (2003)							✔		
Bjordal (2004)							✔		
Arpinelli and Barnfi (2006)				✔	✔	✔			
Avery and Blazeby (2006)							✔		
Blazeby J. et al. (2006)							✔		✔
Patrick et al. (2007)				✔					
Efficace et al. (2008)							✔		
Gujral et al. (2008)							✔		
Parameswaran et al. (2008)							✔		✔
McNair and Blazeby (2009)	✔						✔	✔	
Doward L. et al. (2010)				✔	✔	✔			
Au H. et al. (2010)							✔		
Snyder and Brundage (2010)							✔		
Brundage et al. (2011)	✔								
Calvert et al. (2011)			✔			✔	✔		
Ganz (2011)							✔		
Lemieux et al. (2011)							✔		
DeMuro (2012)				✔					
Calvert et al. (2013)	✔	✔	✔				✔		
Jacobs et al.(2013)	✔						✔	✔	
Zagadailov E. et al. (2013)						✔			
Anker et al. (2014)				✔		✔			
Dirven et al (2014)							✔		
Efficace et al. (2014)							✔		
Efficace et al. (2014 b)							✔		
Basch et al. (2015)				✔					
Nixon (2015)				✔		✔	✔		
Rees et al. (2015)							✔		
Rouette (2015)							✔		
Gnanasakthy et al. (2016)				✔					
Mercieca-Bebber et al. (2016)	✔		✔				✔		
Coon C (2016)				✔					
Hao Yanni et al. (2016)					✔	✔	✔		
McNair et al. (2016)	✔						✔		
Mott (2017)						✔	✔		
Sztankay et al. (2017)								✔	

Fig. 1 Proposed PRO impact types

31%) identified PRO-specific barriers associated with trial conduct and analysis [40, 41, 56, 57, 62, 63, 70, 72, 73, 75, 78, 83]. The most frequent barriers mentioned by authors were low PRO compliance rates (n = 10, 83%), lack of personnel training on administration of PRO instruments (n = 3, 25%), incomplete follow-up of HRQL assessment (n = 2, 16%), selection of inappropriate statistical methods to handle missing data (n = 2, 16%).

Reporting

Incomplete or suboptimal reporting of PRO trial data was cited by 23 (65%) publications as a barrier to research impact if PRO trial findings and generalisability is not clearly presented [7, 38–43, 45–53, 56, 57, 63, 64, 72, 82, 83]. The most common barriers to impact were failure to report: the rationale for the chosen PRO instrument (n = 10, 43%), mode of administration (n = 10, 43%).

Use of PRO data in practice

Adoption of PRO trial findings into clinical practice was identified as somewhat problematic by 17 (43%) of the publications [39–41, 43, 45, 46, 52, 54–56, 61, 63, 64, 75, 78, 81, 82]. Key issues included lack of training/practice for clinicians on interpreting PRO data (n = 11, 64%) and lack of familiarity with PRO measures (n = 7, 41%).

Facilitators to impact

The review of the included articles identified a number of suggested facilitators purported to enhance the probability of realising PRO specific impact. Two (5%) authors suggested strict adherence to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative to improve the completeness of trial protocols and reduce risk of bias [51, 62]. Eight (18%) authors proposed adherence to the Consolidated Standards of Reporting Trials (CONSORT) PRO Extension statement [7, 51–53, 56, 62, 64, 83] and two (5%) authors to the CONSORT statement [7, 51], in order to enhance transparency and complete reporting of PRO clinical trials. A detailed summary of the barriers and facilitators highlighted by the included publication are presented in Table 2, which includes additional resources identified by communication with methodological PRO experts (MC/DK).

REF 2014 impact case studies

Examples of clinical trial PRO impact were explored using REF2014 case studies. These identified a range of impact metrics.

Included studies

The search strategy yielded 209 REF 2014 impact case studies (PRISMA Flow Diagram, Additional file 3). Case studies were excluded if they did not include a clinical trial or the clinical trials did not incorporate a PRO element, meaning 69 relevant case studies were subsequently included in the analysis.

PRO clinical trials characteristics

The characteristics of the PRO clinical trials included across the eligible REF 2014 case studies are detailed in Table 3.

Full details of the included case studies are available in Additional file 4. The assessment of the PRO trial metrics was considered using the 'pathways to research impact' framework [10]. Following this, two new additional impact metrics were identified, cost-effectiveness and drug/device approval. The summary of the PRO impact metrics is depicted in Fig. 2.

Real-world evidence of PRO impact

Assessment of the 69 eligible case studies determined that (n = 12, 17%) appeared to lead to direct demonstrable PRO impact, (n = 12, 17%) showed evidence of indirect PRO impact and (n = 45, 66%) provided no evidence of PRO impact (Fig. 2). Trials that included PROs as primary outcome (50%) reported a larger number of trials leading to direct impact than those trials that had PROs as secondary outcome (83%).

Direct PRO impact

The most common types of direct PRO impact presented across the case studies included: number of publications (n = 12, 17%), citation rates (n = 12, 17%), changes to international guidelines (n = 5, 7%), contribution to national guidelines (n = 4, 6%), contribution to evidence of cost-effectiveness (n = 3, 4%) and informing drug approval (n = 2, 3%). In addition, several case studies demonstrated more than one type of impact.

Indirect PRO impact

The most common types of indirect PRO impact included: number of publications (n = 12, 17%), citation rates (n = 12, 17%), changes to national guidelines (n = 10, 14%), contribution to international guidelines (n = 9, 13%) and national practice (n = 9, 13%) and contribution to evidence presented in conferences, seminars and workshops (n = 5, 7%).

Absence of evidence around PRO impact

The assessment of the included case studies demonstrated that the impact of PRO trial data is not usually

Table 2 Barriers and facilitators to maximising PRO trial data

Barriers to impact	Impact Facilitators
PRO trial design	
Authors not using/citing guidelines to design PRO trials [69, 75, 76]	●SPIRIT ●SPIRIT-PRO Ext[a]
Selection of inappropriate PRO time frames of assessment [38, 42, 44, 58]	●SPIRIT ●SPIRIT-PRO Ext[a]
Failure to define PRO/HRQL endpoints [47]	●SPIRIT-PRO Ext[a]
Selection of inappropriate or invalid PRO measures [42, 44, 50, 52, 54, 57, 60, 66, 67, 69]	●SPIRIT-PRO Ext[a] ●ISOQOL Minimum Standards for PRO Measures in patient-centered outcomes and comparative effectiveness research[a]
Inappropriate PRO sample size and population [38, 48, 54, 56, 59]	●SPIRIT ●SPIRIT-PRO Ext[a]
Issues of bias due to allocation concealment (selection bias), random sequence generation (selection bias), blinding of participants and personnel (performance bias) and blinding of outcomes assessment (detection bias) [57, 68, 69, 75, 76, 79, 82]	●SPIRIT
Lack of evidence of PRO translation or cross-cultural validation [53, 57]	●SPIRIT-PRO Ext[a]
PRO trial conduct and analysis	
Low PRO compliance rates [38, 39, 42, 44, 50, 60, 61, 77, 79, 82]	●SPIRIT-PRO Ext[a] ●SISAQOL[a]
Lack of personnel training on administration of PRO instruments [44, 57, 61]	●SPIRIT-PRO Ext[a] ●SISAQOL[a]
Lack of communication between researchers and administrators regarding PRO questionnaires involved in the trial [44]	●SPIRIT-PRO Ext[a] ●SISAQOL[a]
Lack of standardisation of the PRO questionnaire administration process [44, 61]	●SPIRIT-PRO Ext[a] ●SISAQOL[a]
Lack of patient adherence to the PRO component of the study due to questionnaire length or irrelevant content [44, 52, 61]	●SPIRIT-PRO Ext[a] ●SISAQOL[a]
PRO trial reporting	
Authors not using/citing guidelines to report PRO trials (e.g. CONSORT PRO Extension) [54, 69, 75, 76]	●CONSORT ●CONSORT-PRO Ext
Failure to report the a priori PRO hypothesis [39, 50, 54, 58, 59, 62, 63, 69]	●CONSORT ●CONSORT-PRO Ext ●SPIRIT-PRO Ext
Failure to report baseline PRO compliance [39, 50, 59, 62, 69]	●CONSORT
Failure to report rationale for the chosen PRO instrument [7, 39, 44, 50, 54, 58, 62, 69, 72, 76]	●CONSORT-PRO Ext ●SPIRIT-PRO Ext
Failure to report mode of administration of the PRO instrument [44, 47, 48, 50, 54, 58, 62, 63, 75, 76]	●CONSORT-PRO Ext ●SPIRIT-PRO Ext
Failure to report timing of PRO assessment [37, 58, 59]	●CONSORT ●SPIRIT-PRO Ext
Failure to report methods of PRO data collection [62, 63]	●CONSORT ●CONSORT-PRO Ext
Failure to report clinical significance of PRO findings [39, 40, 47, 56, 59, 62, 67, 75]	CONSORT-PRO Ext
Reporting levels of missing PRO data [7, 39, 52, 58, 59, 62]	●CONSORT ●CONSORT-PRO Ext
Failure to report statistical methods dealing with missing PRO data [39, 54, 56, 58, 62, 63, 69, 75]	●CONSORT ●SPIRIT-PRO Ext
Failure to report generalisability of PRO trial results in the context of clinical outcomes [54, 56, 69, 76, 82]	CONSORT-PRO Ext
Selective reporting of PRO results [7, 75, 76]	●CONSORT ●SPIRIT-PRO Ext

Table 2 Barriers and facilitators to maximising PRO trial data *(Continued)*

Barriers to impact	Impact Facilitators
Discrepancies between PRO protocol and PRO trial report [44]	•CONSORT •SPIRIT-PRO Ext
Failure to report PRO data in the main trial publication [47, 48, 54, 59, 63, 72]	•Publication of HRQL and other clinical outcomes in the main trial report [48, 67, 69, 72]
Late publication of PRO trial results and in a different journal to the main publication [42, 48, 56, 67, 72, 77]	•Publication of secondary and timely PRO publication [63, 69]
Journal word restrictions [54, 69]	•Journals should allow space to report HRQL data alongside other clinical outcomes [50]
Barriers to uptake of PRO trial results in practice	
Lack of familiarity with PRO measures [42, 44, 45, 50, 60, 67, 71]	•PROlearn[a] •SPIRIT-PRO Ext •Provide training to clinicians to gain confidence regarding the validity and reliability of HRQL instruments [67]
Lack of training/guidance for clinicians on interpreting PRO data [40, 42, 44, 45, 48, 50, 53, 58, 66, 67, 69]	•PROlearn[a] •Training for clinicians to understand clinical interpretation of HRQL data [48, 50] •Clinician's checklist for reading and using an article about patient-reported outcomes[a]
Clinicians concerns about the PRO results being biased by missing data [77]	•PROlearn[a] •Provide training to clinicians to gain confidence regarding the validity and reliability of HRQL instruments [67] •Clinician's checklist for reading and using an article about patient-reported outcomes[a]
Lack of evidence of generalisability of PRO/HRQL results [42, 53, 67, 71]	•CONSORT •Clinician's checklist for reading and using an article about patient-reported outcomes[a]
Concerns that the PRO results were chance findings arising from multiple testing [77]	•PROlearn[a] •Provide training to clinicians to gain confidence regarding the validity and reliability of HRQL instruments [67] •Clinician's checklist for reading and using an article about patient-reported outcomes[a]
Researchers failure to present PRO data in a way that is accessible to patients and clinicians [54, 69]	Use of graphical methods to present PRO results [42, 44, 48, 50] •Stakeholder-driven, evidence-based standards for presenting PROs in clinical practice[a]
Lack of time to discuss PRO outcomes with patients [67]	•PROlearn[a] •Provide consistent and improved HRQL data reports and a summary of the clinical implications of the HRQL results [67] •Provide training to clinicians to gain confidence regarding the validity and reliability of HRQL instruments [67]
Overburden of staff, clinicians, participants and resources [42, 44, 56, 61]	•SPIRIT-PRO Ext[a]

ISOQOL Minimum Standards for PRO Measures in patient-centred outcomes and comparative effectiveness research [83]. CONSORT (Consolidated Standards of Reporting Trials) [84]. CONSORT-PRO Extension [58]. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) [85]. SPIRIT-PRO Extension [3]. SISAQOL (The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data) [86]. Stakeholder-driven, evidence-based standards for presenting PROs in clinical practice [87]. Clinician's checklist for reading and using an article about patient-reported outcomes [88]. PRO Learn [89]. *Ext* Extension

[a]Additional resources identified through expert communication

captured in the long-term, specifically under the impact categories health and health system impacts, health related and social impact and economic impact.

Discussion

This manuscript is the first to present a systematic review aimed at identifying the potential types of PRO trial impact alongside real-world evidence of impact. It will allow researchers, clinicians, funders and policy-makers to consider pathways to research impact before conducting PRO trial research and to identify metrics to assess impact prospectively. In the same way, it will allow PRO stakeholders to consider facilitators at the design, conduct, analysis and reporting stages whilst avoiding recurrent barriers to generating PRO-specific impact and minimising research waste. High quality clinical trials involving PROs may lead to benefits for patients and society.

Table 3 PRO clinical trials characteristics

Trial characteristics	Number of trials, (%)
Trial phase	
I	0
I/II	1 (1.4)
II	1 (1.4)
III	24 (34)
Other	3 (5.7)
Not specified	40 (57)
Leading study centre	
UK	62 (89)
International	7 (11)
Trial design	
International multicentre study	21(30)
PRO outcome	
Primary outcome	17 (24)
Secondary outcome	35 (50)
Both	11 (15)
PRO measures used	
SF-36	17 (24)
EQ-5D	12 (17)
HADS	9 (13)
VAS	9 (13)
EORTC QLQ-C30	3 (4)
Other	70[a]

[a]Number of different PRO measures identified – eCase studies characteristics

Nine types of potential PRO trial impact were identified (Fig. 1): informing clinical practice, informing clinical guidelines, informing health policy, supporting drug approval, supporting pricing and supporting reimbursement decisions, informing clinical and shared decision-making and informing consent for treatment. Only four impact metrics were proposed to measure the impact of PRO data, number of pharmaceutical claims and promotional labelling claims and inform drug/device approval and cost-effectiveness. Further research to formalise PRO-specific impact metrics is required.

Authors suggested that potential barriers to the use of PRO trial findings to inform healthcare decision-making and patient care included poor quality trial design, conduct, analysis, reporting and uptake in practice [55]. Several of the barriers comprised within 'uptake of PRO trial results in practice' (Table 2) are not unique to PRO clinical trials. These challenges are also encountered in the implementation of PRO data collected in routine clinical practice to inform patient care or for audit/benchmarking purposes. For instance, 'high levels of missing data' 'overburden of staff, clinicians, participants and resources', 'lack of training/guidance for clinicians on interpreting PRO data' are challenges commonly faced in routine practice [84, 85]. Furthermore, it is important to note that many of these challenges are not unique to PRO data/trials. Greater efforts are required to improve outcome selection, collection and reporting in both in trials and routine care [86, 87].

Suboptimal reporting of PRO trial data was the most discussed barrier (65%), which might hinder the maximisation of PRO trial findings. Therefore, addressing poor and incomplete reporting is essential, as it is unethical to waste research funding, resources and patients' efforts and time invested during the collection PRO trial data [5, 6]. In recent years, a number of methodological guidelines have been developed to address the different barriers highlighted by this systematic review. These include: the SPIRIT-PRO Extension to improve the completeness of trial protocols [3]; The ongoing work of the SISAQOL Consortium to standardise the analysis and interpretation of PRO and quality of life from oncology clinical trials [88]; CONSORT-PRO Extension to facilitate optimal reporting guidance of trials that include PROs as primary or secondary outcome [46] and; the work carried out by Snyder et al. (2017) to present PRO trial findings [89]. The adoption of these guidelines has the potential to improve the design, conduct, analysis and report of PRO trials thus ensuring that high-quality data that may benefit patients and society are obtained from trials. The uptake of these guidelines is currently being promoted through PROTEUS (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) Consortium, which is funded by the US Patient Centred Outcomes Research Institute (PCORI) [90].

The literature suggests that adherence to guidelines should be endorsed/mandated by journals/editors in order to ensure high quality PRO data through the trial design, implementation, analysis and reporting stages. In addition, the FDA [2] and EMA [91] provide guidance to sponsors on reporting of PRO instrument development, measurement properties, implementation, analysis, and interpretation used to support drug approval and pharmaceutical labelling claims in the United States and Europe, respectively. Additional facilitators identified to maximise the realisation of impact in practice were reporting of PRO results adequately within the main trial publication, whilst considering journals word restrictions [43, 52, 53, 56, 64] and clinicians receiving training/guidance on interpretation of PRO data [41, 43, 52, 63]. Thus, it is essential that funders, ethics committees, journal editors and trial researchers proactively work together to ensure that PRO studies follow optimal design, conduct and analysis and reporting.

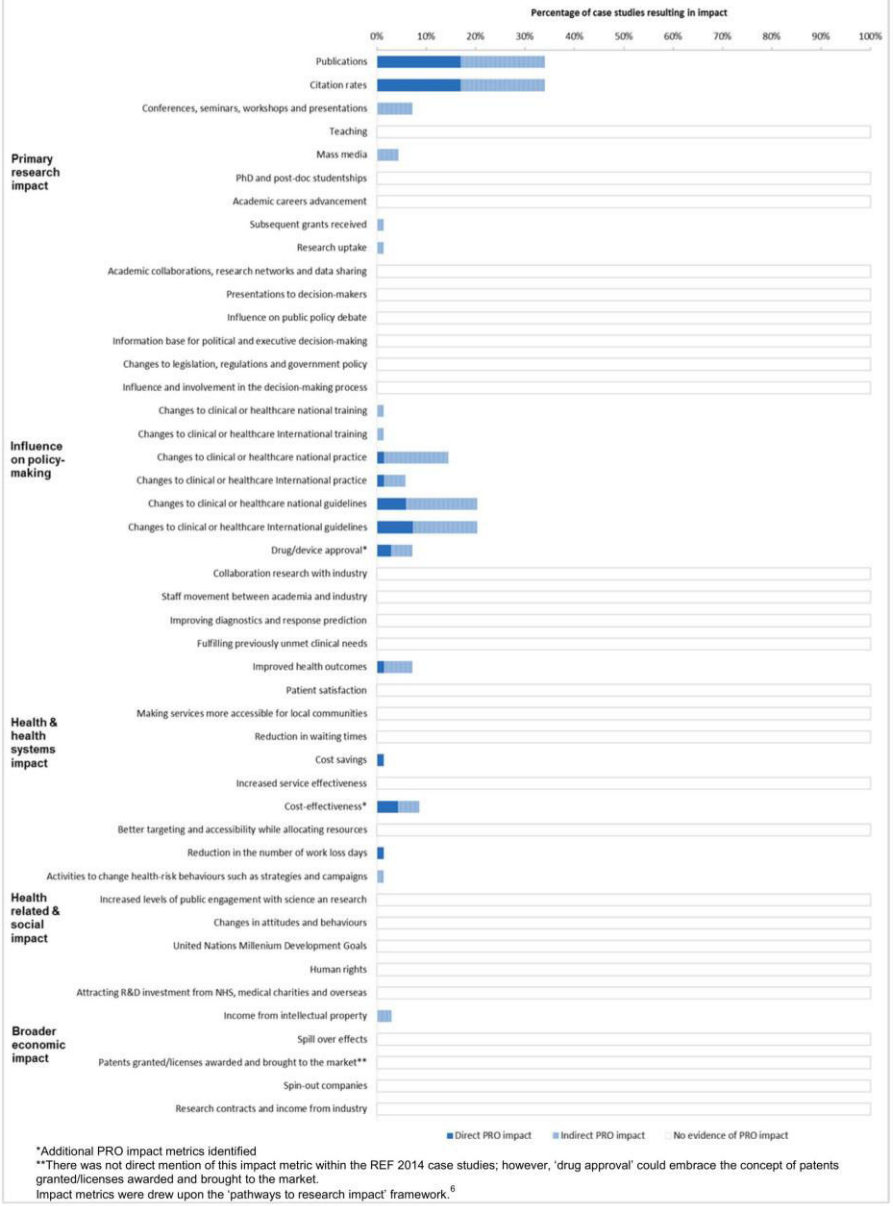

Fig. 2 PRO trial impact metrics. *Additional PRO impact metrics identified. **There was not direct mention of this impact metric within the REF 2014 case studies; however, 'drug approval' could embrace the concept of patents granted/licenses awarded and brought to the market. Impact metrics were drew upon the 'pathways to research impact' framework [6]

Although the systematic review publications may not have included information on PRO trial data impact, we explored whether evidence of impact could be identified from REF 2014 impact case studies as by their nature, they present an opportunity for researchers to highlight the impacts of their research. Sixty-nine REF 2014 case studies included a trial where PRO data were collected. Of these, 24 (34%) presented evidence of PRO trial impact that was classified as direct or indirect impact. Direct attribution of impact to PRO trial data was possible in 12 trials, most commonly informing national and international clinical guidelines. A number of potential impact categories are currently unrealised or under reported. This could be attributed to the fact that some of the PRO trials associated to the case studies have been published in the last years, which limits demonstration of PRO trial impact in the mid and long-term [10]. Furthermore, it was often difficult to unpick the exact contribution of PRO data to this impact as they were commonly combined with 'clinical' outcome data.

The REF 2014 case study 'Heart failure: Improving the quality of life and survival of heart failure patients through Cardiac Resynchronisation Therapy', submitted independently by the University of Birmingham [92] and Hull [93] is described below (Table 4) to illustrate the different facilitators that might help translating PRO findings into clinical practice. This example was chosen, as it is one of the case studies that have led to most varied impact and will provide researchers a useful guide about how to maximise PRO trial data and reduce research waste (Fig. 3).

However, reported barriers and facilitators in the literature focused predominantly on the PRO clinical trial design, conduct and analysis stages. There was a dearth of information on how to address barriers to generating PRO trial impact in practice. Additionally, identified impact was mainly focused on primary research (e.g. publications, citations and conference). There was little attention on policy-making, health & health systems, health related & societal and economic impact, which is generally realised in the mid and long term. Thus, further research in this area is required to identify facilitators to maximise PRO trial impact in the longer term. This will be achieved through interviews with international stakeholders in order to explore in-depth perceived barriers and facilitators to effective dissemination and impact on healthcare decisions and patient care. Work will be conducted to refine the 'pathways to research impact' framework in the context of PRO trial impact. In addition, it is important to mention that it is well established that certain impact categories (e.g. primary research impact via publications) are easier to measure than others (e.g. societal impact), which can limit the number of available impact metrics to measure the impact of PRO trial data.

Table 4 Practical guide for researchers

The Cardiac Resynchronisation — Heart Failure (CARE-HF) trial demonstrated that the cardiac resynchronisation therapy reduced the risk of complications and death among patients with left ventricular systolic dysfunction and cardiac dyssynchrony who had moderate or severe heart failure [85, 86]. In addition, as measured with the EQ-5D and Minnesota Living with Heart Failure Questionnaire (MLWHF), the therapy was associated with quality of life and symptoms improvement [86].

- The main trial publication was characterised for complying with the different facilitators identified by the systematic review and for adhering to the SPIRIT PRO Extension and CONSORT PRO Extension guidelines despite these guidelines being published subsequently.
- Low rates of PRO missing data (8%) and statistical methods for dealing with missing data were reported.
- The PRO data was included in the main RCT report and alongside other clinical data [87]. In addition, there were detailed and timely secondary PRO publications [86, 88, 89].

Attributing impact directly to PRO data is difficult given the survival benefit; however, this well designed, conducted, analysed and reported trial led to impact that could be measured through the following impact metrics:

- In the short term, PRO results were included in the main trial publication, [87] which led to 4927 citations by January 2018. At least 4 additional PRO trial publications are available.
- In the mid-term, PRO trial findings were incorporated in clinical guidelines and health policy at national and international level: NICE in the UK, [90] the European Society of Cardiology, [91] the European Society of Cardiology in Canada, [92] Brazil, [93] and USA [94]. Therefore, the use of CRT influenced the healthcare practice at national and international level by providing the CRT to patients with heart failure and dyssynchrony.
- In the long-term, an additional study assessing the effects of the CARE-HF trial on quality of life demonstrated that the device improved quality of life and symptoms and improved survival among the users [88]. In addition, PRO results informed the cost-effectiveness analysis of the intervention and the production of the device, [89, 95] which led to increased income from industry: *'the world market for CRT devices is projected to grow to $2.8 billion annually by 2015'.* [81] The cost-effectiveness analysis demonstrated that CRT is cost-effective when compared with medical therapy alone (MT). In the same way, CRT plus cardioverter-defibrillator is more cost-effective when compared to CRT + MT.[95]

Limitations

This systematic review summarised the different types of impact thought to be associated with PRO trial findings and proposes metrics to measure impact in practice. The main limitation was that due to poor indexing, over half of the included publications were identified through hand-searching of references lists and citation searches methods rather than databases searching. Therefore, some relevant publications might not be included in this article if they failed to mention a type of impact in the title/abstract. However, we made efforts to identify all the relevant publications. The search strategy adopted did not include the search term 'self-rated health', which could have led to the exclusion of relevant articles. Nonetheless, our search strategy was informed by the Oxford PROM Group Construct & Instrument Type Filter

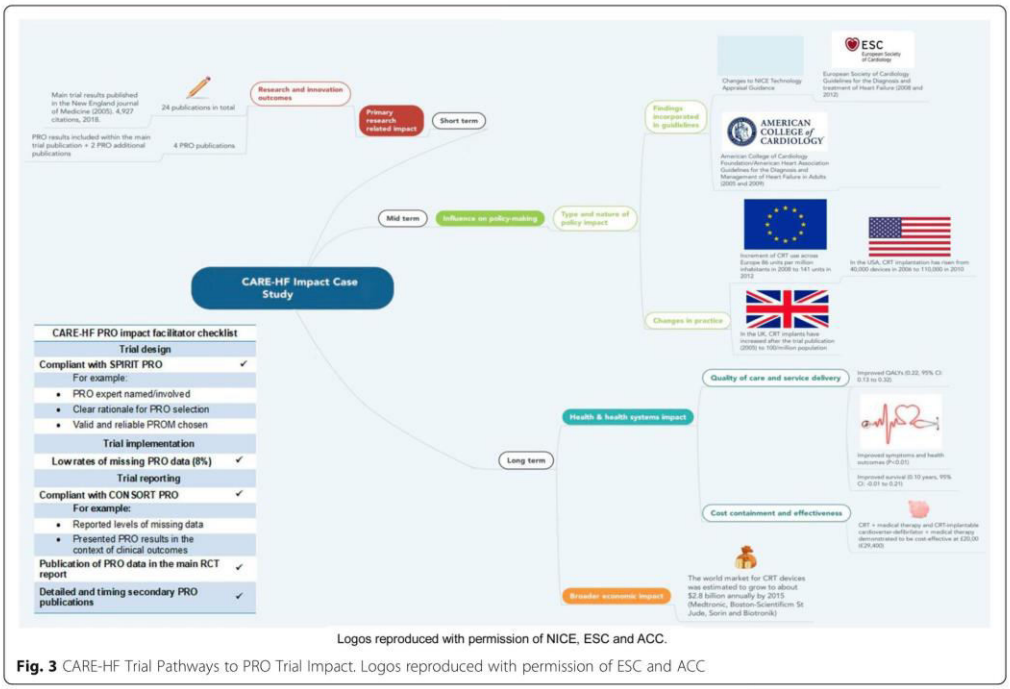

Fig. 3 CARE-HF Trial Pathways to PRO Trial Impact. Logos reproduced with permission of ESC and ACC

[94], which was modified according to the objectives of this systematic review. Although there were no language restrictions, we did not systematically search non-English databases. In addition, a formal quality appraisal was not undertaken to assess the quality of the studies included. We acknowledge that a significant amount of the evidence we found was based on expert opinion, which does not rank highly in the evidence hierarchy. Furthermore, a small number of the included studies were discussed by different authors, which may have influenced the frequency counts. However, this does not affect the conclusions of this systematic review.

The 'pathways to research impact' framework was used to measure the impact of PRO trial data. This framework was selected as it synthetises all the existing types of healthcare research impact and metrics (Fig. 2). However, not all the types of impact outlined by the framework are relevant to PRO trial data (e.g. human rights and United Nation Millennium Development Goals). The REF is an expert review process solely focused on the UK HEIs, which may limit the generalisability of the impact of the PRO data, although 30% of the trials were categorised as international trials. In some instances, it was not possible to confirm the impact described by the REF 2014 impact case studies, as there was no access to some sources provided. It is important to consider that the case studies had word count restrictions, which could have led to under reporting of impact. In addition, the majority of the articles included in the first section of the systematic review focused on oncology. Therefore, the findings presented in this study can only be generalised to oncology PRO clinical trials.

Conclusion

This review provides a summary of the different types of potential PRO impact identified in the literature, supported by real-world examples. The impact of PRO clinical trials can be attributed to PRO results and measured through different impact metrics. It is essential that researchers and authors design, conduct and analyse and report high quality PRO trial results and; proactively tackle barriers to PRO impact in order to maximise the impact of PRO clinical trials in the short, mid and long term to fully realise benefits for society. Adherence to guidance and multi-stakeholder collaboration is essential to maximise the utilisation of PRO trial data, while minimising research waste and maximising future patient care.

Appendix 1

Table 5 Study characteristics of the literature review

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
Revicki et al. (2000) [38]	Quality of Life Research	Guidance paper	Recommendations on use of HRQL data to support labelling and promotional claims	Informing drug approval
Bottomley et al. (2003) [39]	American Society of Clinical Oncology	Systematic review	HRQL in Non-small-cell lung cancer	Influencing clinical decision-making
Efficace et al. (2003) [40]	Journal of Clinical Oncology	Guidance paper	A checklist for evaluating HRQL in prostate cancer trials	Informing clinical decision-making
Goodwin et al. (2003) [41]	Journal of the National Cancer Institute	Literature review	HRQL in breast cancer trials	Informing clinical decision-making
Bjordal (2004) [42]	Annals of Oncology	Literature review	Impact of HRQL assessments within trials on clinical practice	Informing clinical decision-making
Arpinelli and Bamfi (2006) [43]	Health and Quality of Life Outcomes	Commentary	PRO trial data in drug development	Informing drug approval Informing reimbursement decisions Informing pricing decisions
Avery and Blazeby (2006) [44]	World Journal Surgery	Systematic review	HRQL in breast, prostate, lung and colorectal cancer trials	Informing clinical decision-making
Blazeby et al. (2006) [45]	Journal of Clinical Oncology	Literature review	HRQL in surgical oncology trials	Informing clinical decision-making Influencing informed consent
Patrick D. et al. (2007) [46]	Value in Health	Literature review	Use of PRO data to support medical product labelling claims (FDA perspective)	Informing drug approval
Efficace et al. (2008) [47]	European Journal of Cancer	Systematic review	HRQL in leukaemia trials	Informing clinical decision-making
Gujral et al. (2008) [48]	Support Care Cancer	Systematic review	Quality of life after colorectal cancer surgery	Informing clinical decision-making
Parameswaran et al. (2008) [49]	Annals of Surgical Oncology	Systematic review	HRQL in surgery for esophageal cancer	Influencing clinical decision-making Influencing informed consent
McNair and Blazeby (2009) [50]	Expert Reviews Pharmaeconomics Outcomes Research	Literature review	HRQL in gastrointestinal cancer trials	Informing clinical practice Informing clinical decision-making Inform shared decision-making
Au H. et al. (2010) [51]	Expert Review of Pharmacoeconomics & Outcomes Research	Review	HRQL in oncology clinical trials	Informing clinical decision-making
Doward L. et al. (2010) [52]	Health and Quality of Life Outcomes	Commentary	Use of PRO trial data to inform pharmaceutical labelling claims and payers	Informing drug approval Informing pricing decisions Informing reimbursement decisions
Snyder and Brundage (2010) [53]	Expert Reviews Pharmaeconomics Outcomes Research	Commentary	PROs in healthcare policy, research and practice	Informing clinical decision-making
Brundage et al. (2011) [54]	Quality of Life Research	Systematic review	PROs in Phase III randomised clinical trials	Informing clinical practice
Calvert et al. (2011) [7]	The Lancet	Systematic review	Quality of life in clinical trials	Informing clinical decision-making Informing health policy Informing drug approval
Ganz (2011) [55]	Journal of the National Cancer Institute	Commentary	Quality of life measurement in breast cancer trials	Informing clinical decision-making
Lemieux et al. (2011) [56]	Journal of the National Cancer Institute	Systematic review	Quality of life in breast cancer trials	Influencing clinical decision-making
DeMuro et al. (2012) [57]	Value in Health	Literature review	Reasons why PRO label claims were rejected and provide feedback from the regulatory perspective regarding the use of PROs in clinical trials	Informing drug approval

Table 5 Study characteristics of the literature review *(Continued)*

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
Calvert et al. (2013) [58]	Health and Quality of Life Outcomes	Commentary	Implications of the CONSORT PRO extension on clinical trials and practice	Informing clinical practice Informing clinical guidelines Informing health policy Informing clinical decision-making
Jacobs et al. (2013) [59]	Quality of Life Research	Systematic review	HRQL in oesophageal cancer trials	Informing clinical practice Informing clinical decision-making Informing shared decision-making
Zagadailov E. et al. (2013) [60]	American Health & Drug Benefits	Literature review	Challenges and opportunities of incorporating oncology PRO trial data into reimbursement decisions	Informing reimbursement decisions
Anker et al. (2014) [61]	European Heart Journal	Literature review	Cardiovascular PRO clinical trials	Informing drug approval Informing reimbursement decisions
Dirven et al. (2014) [62]	European Journal of Cancer	Systematic review	PROs in brain tumour trials	Influencing clinical decision-making
Efficace et al. (2014) [63]	European Association of Urology	Systematic review	PROs in prostate cancer trials	Informing clinical decision-making
Efficace et al. (2014b) [63]	European Journal of Cancer	Systematic review	PROs in gynaecological cancer trials	Informing clinical decision-making
Basch E. et al. (2015) [64]	JAMA Oncology	Qualitative study	PRO trial data in cancer drugs development	Informing drug approval
Nixon et al. (2015) [65]	Farmeconomia. Health Economics and Therapeutic Pathway	Commentary	PRO data to support drug development decision-making	Informing drug approval Informing reimbursement decisions Informing clinical decision-making
Rees et al. (2015) [66]	Journal of Cancer Research and Clinical Oncology	Systematic review	PROs in colorectal cancer trials	Informing clinical decision-making
Rouette et al. (2015) [67]	Quality of Life Research	Literature review	Oncologists' perspectives on HRQL in trials among countries and specialities	Informing clinical decision-making
Gnanasakthy et al. (2016) [68]	Journal of Clinical Oncology	Literature review	PRO labelling for products approved by the Office of Haematology and Oncology Products of the FDA	Informing drug approval
Mercieca-Bebber et al. (2016) [69]	European Journal of Cancer	Systematic review	PROs in head, neck and thyroid cancer trials	Informing health policy Informing clinical practice Informing clinical decision-making
Coon C (2016) [70]	Clinical Therapeutics	Commentary	PRO oncology clinical trials	Informing drug approval
Hao Yanni et al. (2016) [71]	Clinical Therapeutics	Commentary	PRO oncology clinical trials	Informing reimbursement decisions Informing pricing decisions Informing clinical decision-making
McNair et al. (2016) [72]	PLOS One	Systematic review	PRO and clinical gastro-intestinal cancer data in trials	Informing clinical decision-making Informing clinical practice
Mott (2017) [73]	Oncology and Therapy	Qualitative study	PROs and lung cancer	Informing reimbursement decisions Informing clinical decision-making
Sztankay et al. (2017) [74]	BMC Cancer	Qualitative study	HRQL in patients with advanced non-small cell lung cancer	Informing shared decision-making

Appendix 2

Potential types of PRO impact proposed

Clinical practice, clinical guidelines and health policy

A number of authors discussed the potential influence of PRO data on clinical practice, clinical guidelines and health policy. Several authors felt inclusion of PRO data on clinical guidelines may influence clinical practice, by fulfilling unmet clinical needs and leading to improved patient centre care by helping patients make more informed decisions on their care [44, 48, 51, 58–60, 76]. Three studies suggested that the inclusion of PRO data in clinical guidelines might ensure wider acceptance of guideline recommendations among patients, while enhancing implementation through health policy [5, 51, 60].

Drug and device approval

Authors reported that PRO data is increasingly used to provide evidence for drug and device approval, especially in oncology clinical trials [67, 68]. Eight publications discussed the influence of PRO data on pharmaceutical labelling claims by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) [44, 62, 64–70]. One publication suggested that PRO data may inform drug and device approval through communication of the benefits and harms of the intervention has to clinicians, patients and other consumers [64].

Pricing and reimbursement decisions

Three publications discussed the influence of PRO data on pricing decisions [57, 66, 71] and seven on drug reimbursement decisions [5, 57, 61, 66, 69, 71, 74]. Authors suggested that inclusion of PRO data provided valuable information regarding the risk-benefit of new interventions. Several authors postulated that within the context of oncology treatment, PRO data have the potential to identify costly events reported by the patients in the trials. Hence, interventions with reduced toxicity and added PRO benefit may influence payer decision-makers [72]. Additionally, the inclusion of patient advocacy groups may influence the availability of interventions, enhancing the patient healthcare experience by incorporating the 'patient's voice' throughout payer decision-making [57, 66].

One such example illustrated in the literature, is the decision by NICE (2015) to recommend the use of nintedanib plus docetaxel (Vargatef®) as a treatment option for locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology. The drug approval was primarily based on improved survival, minimal adverse drug effects and fewer detrimental effects on health-related quality of life (HRQL) compared to chemotherapy treatment. PRO data suggested that HRQL, as measured by the EuroQol-5 Dimension (EQ-5D), the European Organization for Research and Treatment core quality of life questionnaire (EORTC QLC-C30) and the lung cancer–specific Quality of Life Questionnaire (EORTC QLQ-LC13) was similar in both groups [57, 96]. However, the PRO measures also demonstrated better pain management in patients randomised to nintedanib plus docetaxel based on information from the pain items [57, 96]. Therefore, additional drug benefits (symptom improvement and tolerability) were demonstrated through incorporation of PRO measurements into the trial, which similarly informed the reimbursement decision. The additional HRQL benefits may have been missed without the supporting PRO data within this trial.

Clinical decision-making

While reducing the impact of intervention toxicity and the impact on HRQL is important for drug labelling claims, it is also an important consideration for choices in clinical decision-making. According to Goodwin et al. (2003), when there is medical treatment equivalence, HRQL data has the potential to inform clinical decision-making by prioritising quality of life outcomes and reduction in toxicity when making clinical decisions [56]. The authors conducted a systematic review of breast cancer clinical trials including PROs and determined that HRQL contributed to clinical decision-making within primary management (surgery, radiation and hormone therapies) and symptom control/supportive care setting of breast cancer.

In total, 26 publications presented evidence that PRO data may help in the selection of optimal treatment, patient's symptom experience and management, satisfaction with care and might predict prognosis, which has the potential to inform clinical decision-making based on the clinicians' critical appraisal and interpretation of the available information [5, 34–36, 38–40, 44–61, 74].

Dirven et al. (2014) conducted a systematic review of PRO clinical trials in patient with brain tumours and demonstrated that HRQL can be used alongside overall and progression-free survival to inform clinical decision-making. One of the clinical trials included determined that the combination of concomitant and adjuvant temozolomide and radiotherapy has become standard care for newly diagnosed patients with glioblastoma [53]. This combination treatment led to significantly prolonged overall and progression-free survival, without negatively impacting HRQL in the long-term as measured with the EORTC QLQ-C30 questionnaire and Brain Cancer Module (BN-20) [53].

Shared decision-making

Shared decision-making is also important and four publications outlined the potential benefits of including PRO findings alongside other outcomes such as survival. This allowed patients and their clinicians to make an informed

joint decision about treatment preferences and symptom management based on mutual understanding of treatment objectives and expectations [44, 58, 59, 73].

Sztankay et al. (2017) assessed HRQL during first-line chemotherapy with pametrexed and maintenance therapy (MT) among patients with advanced non-small cell lung cancer [73]. First-line chemotherapy for patients with advanced non-small cell lung cancer was shown to improve overall progression-free survival. However, as measured with the EORTC QLQ-C30 and EORTC QLQ-LC13, MT compared to first-line chemotherapy was associated with lower HRQL and improvements in nausea, vomiting, appetite loss, constipation and pain. This information presented alongside survival data, allowed patients and clinicians to make real-world informed joint decisions regarding treatment options.

Informed treatment consent

Consent for treatment refers to the authorisation given by a patient to receive a treatment, once the clinician presents a diagnosis, relevant treatment options and respective risks and benefits to the patient [97]. Two publications discussed the influence of PRO trial data on treatment consent [39, 49]. Parameswaran et al. (2008) presented a systematic review of two randomised controlled trials, 9 longitudinal studies and 11 cross-sectional studies. The authors determined that only 11 studies presented data that was capable of effectively informing patient consent. This statement was based on the assessment of the HRQL methodology of the studies, through the HRQL checklist by Efficace et al. (2003) [34]. For instance, as measured with the EORTC-QLQ-C30 and MOS-SF36, one of the eleven studies determined that surgery for oesophageal cancer patients has a detrimental impact on quality of life in the postoperative stage (e.g. anastomic leaks, sepsis and cardiac and pulmonary complications) and in some cases; quality of life among survival patients does not improve in the long term [39]. Therefore, communicating HRQL and clinical data to patients after the intervention could help inform patients about relevant information regarding recovery and outcomes before undergoing an intervention and inform the consent process.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12955-019-1220-z.

Additional file 1. Search strategies

Additional file 2. Systematic Review PRISMA Flow Diagram

Additional file 3. REF 2014 Impact case studies PRISMA flow diagram

Additional file 4. REF impact case studies

Abbreviations

CINALH+: Cumulative Index to Nursing and Allied Health Literature; CONSORT: Consolidated Standards of Reporting Trials; CONSORT-PRO Extension: Consolidated Standards of Reporting Trials-Patient Reported Outcomes Extension; EMA: European Medicine Agency; EMBASE: Excerpta Medica Database; EORTC QLQ-C30: European Organization for Research and Treatment - Core Quality of Life Questionnaire; EQ-5D: European Quality of Life Instrument - 5 Dimension; FDA: Food and Drug Administration; HADS: Hospital Anxiety and Depression Scale; HEIs: Higher Education Institutions; HMIC: Health Management Information Consortium; MEDLINE: Medical Literature Analysis and Retrieval System Online; MFSAF: Myelofibrosis Symptom Assessment Form; PCORI: Patient Centred Outcomes Research Institute; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROs: Patient-reported outcomes; PROSPERO: The International Prospective Register of Systematic Reviews; PROTEUS: Patient-Reported Outcomes Tools: Engaging Users & Stakeholders; REF: Research Excellence Framework; SF-36: Short Form Health Survey 36-item; SISAQOL: The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial; SPIRIT-PRO Extension: Standard Protocol Items: Recommendations for Interventional Trial-Patient Reported Outcomes Extensions; UK: United Kingdom; VAS: Visual Analogue Scale

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Authors' contributions

SCR, MC and DK designed the study, SCR and OLA reviewed and interpreted the data, SCR drafted the manuscript. MC, DK, AS and CM reviewed analysis and substantively revised the manuscript. All the authors read and approved the final manuscript.

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Not Applicable

Competing interests

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Publisher's Note

Appendices for Chapter 4

Chapter 5: The impact of patient-reported outcomes (PROs) from clinical trials: perspectives from international stakeholders

The impact of PRO trial data: perspectives from international stakeholders

The findings of Chapter 4 suggested that patient-reported outcome (PRO) trial data have the potential to inform clinical practice, clinical guidelines, health policy; support drug and pricing decisions and; inform clinical and shared decision-making and consent for treatment. In addition, examination of REF 2014 case studies appeared to demonstrate that a range of impact can be associated with PRO trial data, e.g. changes to international and national guidelines; influencing cost-effectiveness and drug approval. The findings of Chapter 4 also highlighted methodological problems regarding PRO trial design, conduct, analysis and reporting, may impair realisation of potential PRO impact.

It was felt important to explore these findings further in order to gain deeper understanding about the identified topics. Thus, this chapter addresses **objective E** of this doctoral research thesis: to explore in-depth international stakeholders' perspectives about the range of potential impacts of PRO clinical trials and impact metrics and; barriers and facilitators to maximise the impact of PRO trial data.

Further information on the methods used in this study can be found in Chapter 2. This chapter is presented in a paper format ahead of submission to the PLOS Medicine Journal.

Table 1. Dissemination of the research

Year	Conference	Location	Type of presentation
2018	A two-day CPD course hosted by Professor Calvert and the Centre for Patient Reported Outcomes Research (CPROR)	Birmingham, UK	Oral
2019	ISOQOL (International Society for Quality of Life Research) 26th Annual Conference	San Diego, CA, USA	Oral

The impact of patient-reported outcome data from clinical trials: perspectives from international stakeholders

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Abstract

Background Patient-reported outcomes (PROs) are increasingly collected in clinical trials as they provide unique information on the physical, functional and psychological impact of a treatment from the patient's perspective. Recent research suggests that PRO trial data have the potential to inform shared decision-making, support pharmaceutical labelling claims and influence healthcare policy and practice. However, there remains limited evidence regarding the actual impact associated with PRO trial data and how to maximise PRO impact to benefit patients and society. Thus, our objective was to qualitatively explore international stakeholders' perspectives surrounding: **a)** the impact of PRO trial data, **b)** impact measurement metrics, and **c)** barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society.

Methods Informed by a generic qualitative approach, we undertook semi-structured interviews with 24 international stakeholders between May and October 2018. Interviews were audio recorded and transcribed verbatim. Data were coded and analysed using reflexive thematic analysis.

Findings International stakeholders emphasised the impact of PRO trial data to benefit patients and society. Influence on policy-impact, including changes to clinical healthcare practice and guidelines, drug approval and promotional labelling claims were common types of PRO impact reported by interviewees. Interviewees suggested impact measurement metrics including: number of pharmaceutical labelling claims and interviews with healthcare practitioners to determine whether PRO data were incorporated in clinical decision-making. Key facilitators to PRO impact highlighted by stakeholders included: standardisation of PRO tools; consideration of health utilities when selecting PRO measures; adequate funding to

support PRO research; improved reporting and dissemination of PRO trial data by key opinion leaders and patients; and development of legal enforcement of the collection of PRO data.

Conclusion Determining the impact of PRO trial data is essential to better allocate funds, minimise research waste and to help maximise the impact of these data for patients and society. However, measuring the impact of PRO trial data through metrics is a challenging task, as current measures do not capture the total impact of PRO research. Broader international multi-stakeholder engagement and collaboration is needed to standardise PRO assessment and maximise the impact of PRO trial data to benefit patients and society.

Introduction

Patient-reported outcomes (PROs) are questionnaires that capture patients' perspectives about the impact of disease and treatment on their health status, for example quality of life and symptoms, without the interpretation of a clinician, or anyone else [1, 2]. Inclusion of PROs in clinical trials can provide unique patient-centred data, which can be used to help clinicians and patients to make more informed treatment decisions, support pharmaceutical labelling claims and influence healthcare policy [3-6]. However, the lack of scientifically rigorous PRO data collection, analysis and reporting is a waste of resources and hinders the maximisation of PRO trial impact [6-9].

Our recent systematic review (Chapter 4) suggested that PRO trial data have the potential to lead to a range of benefits for patients and society, which can be measured through impact metrics. To date, however, there has been little research exploring how PRO research impact is realised and measured in practice or the barriers and facilitators to realising this impact. Therefore, the purpose of this study was to qualitatively explore international stakeholders' perspectives on: **a)** the impact of PRO trial data, **b)** PRO impact metrics to measure such impact, and **c)** barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society.

Methods

Design

A generic qualitative approach was chosen as it best suited to explore in-depth participants' perspectives, which facilitated a rich description of their perspectives while staying close to the data. In addition, this approached was deemed suitable as no theoretical assumption were made [10, 11]. In order to obtain a broad insight of

the participants the following sampling, data collection and analysis methods were chosen, which were informed by the generic approach. In order to obtain a broad insight of the participants the expert purposeful sampling method was selected [12]. One-to-one semi-structured interviews were chosen as this qualitative data collection method allows obtaining 'rich' data by building a trust relationship with the participants [13]. Finally, the data was analysed using the reflexive thematic analysis method [14-16]. This qualitative study is reported in accordance with the Consolidated criteria for reporting qualitative research (COREQ) [17].

Sampling and recruitment

International stakeholders over the age of 18 years, who spoke English and were willing and able to give informed consent were invited via email to take part in the qualitative interviews. Stakeholders included: policy-makers, representatives from regulatory agencies, funders, journal editors, academic trialists, clinicians and industry trialists. Individuals were eligible for interview if: **a)** they reported experience of using PRO data to inform clinical practice, clinical guidelines and health policy development; to support drug approval, pricing and reimbursement decisions, or to inform clinical decision-making and consent for treatment; or **b)** they reported experience of reviewing the PRO components of clinical trials and/or scientific publications. Initial recruitment approaches were made through personal research networks known to the team (MC/DK/AS) and through the identification of key authors from relevant PRO literature (expert purposive sampling [18]); further participants were identified and recruited through snowball sampling [19].

Data collection

Semi-structured interviews were conducted by SCR between May and October 2018, either by phone or face to face on University premises [20]. SCR, the

interviewer, is a doctoral researcher at the Centre for Patient Reported Outcomes Research within the University of Birmingham, UK. Ethical approval for this study was gained from the University of Birmingham (ERN_16-0806).

All participants gave informed consent prior to each interview. An interview schedule (Appendix 1) was used to guide the discussion. This was initially informed by our systematic review on PRO trial impact (Chapter 4) and subsequently refined after two pilot interviews with two international stakeholders and consultation with the research team (CM/DK/AS/MC). The aim of the pilot interviews was to identify any flaws or limitations within the interview design. As no major changes to the interview schedule were required, these data were included in the cohort of interviews analysed. Table 1 provides further detail on the topics covered by the interview schedule.

Table 1. Summary of interview schedule

Topic area	Summary of subtopics covered
a) The impact of PRO trial results	Exploration of international stakeholders' perceptions of PRO trial impact, specifically: • Impact of PRO trial data on stakeholder's practice • Thoughts, opinions and experience of incorporating PRO trial data in practice • Examples of PRO clinical trials that have led to impact • Examples of PRO clinical trials that have not led to impact
b) Impact measurement metrics	Exploration of stakeholders' perceptions of the most effective ways to identify trials that have led to PRO impact, specifically: • Identify impact measurement metrics • Identify the most effective way to measure PRO trial impact • Thoughts and opinion of developing a framework to measure PRO trial data
c) Perceived barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society	Exploration of stakeholders' perceptions of barriers and facilitators to maximise the impact of PRO trial data, specifically: • Thoughts, opinions and experience of facilitators to that maximise the impact of PRO trial data • Thoughts, opinions and experience of barriers to that maximise the impact of PRO trial data

After the piloting exercise, data collection and analysis were conducted iteratively (i.e. themes identified within early interviews and interpreted within transcripts were included in subsequent interviews) until analytic saturation was reached. Saturation is defined as 'data adequacy' [21], the point when data collection does not contribute any additional information and the data collected provides comprehensive information to answer the research question [21-23]. For the purpose of this study, saturation was reached when no new themes were interpreted from the data [22,

23]. In this qualitative study, saturation was determined at the stakeholder cohort level through review of the data and discussion within the research team.

Data analysis

Interviews were digitally recorded and transcribed verbatim by a professional transcription company. Interview data were managed using a qualitative data analysis software package (QSR NVivo 11). Data analysis was informed by the reflexive thematic analysis approach [16]. In order to support the analysis and interpretation of the data, a multidisciplinary team including methodologists, clinical and non-clinical experts was involved. The analysis process started with reading the transcripts several times to increase familiarity with the data. This was followed by deductive and then inductive coding processes.

Deductive analysis

Initially, deductive coding was undertaken using the 'pathways to research impact' framework [24], developed as part of chapter 3, in order to identify types of PRO trial impact and impact measurement metrics. The framework provided a comprehensive summary of impact categories, impact subgroups and impact metrics across five types of impact: 1) Primary research related impact; 2) Influence on decision-making; 3) Health and health systems impact; 4) Health-related and societal impact, and 5) Broader economic impact [24] (Appendix 2). The five impact categories of the framework were deductively applied to the data. In instances where it was not possible to categorise data into the existing framework, they were added to a 'miscellaneous' coding category. Subsequently, the data coded into each of the impact categories was organised into subgroups.

Inductive coding

More detailed codes were described and interpreted inductively within each of the five categories and the ‘miscellaneous’ category. In addition, inductive coding was also used to identify impact metrics, and barriers and facilitators to PRO trial impact, across the whole dataset. After the coding process, and collation of codes, theme generation continued until the definitive overarching themes were developed [14, 16]. Table 2 presents an example of the inductive coding process.

Table 2. Examples of the inductive coding process

Raw data	Code[1]	Category[2]	Theme[3]	Main topic[4]
"I think its empowering patients and the public to understand what's important to them. So they can go back to their healthcare provider, you know, take the example of that patient who is having treatment for breast cancer will feel empowered to talk to their healthcare provider […]"	Empower patients and the public to understand what's important to them	Patient empowerment, dissemination and communication	Dissemination and uptake of results	Facilitators to PRO impact
"The key things that would help dissemination which we don't make enough of are patients getting up at conferences and talking about the change it has made to their lives."	Patients presenting at conferences	Patient empowerment, dissemination and communication	Dissemination and uptake of results	Facilitators to PRO impact
"Like I said, we tried to put PRO results in the primary manuscript but usually, in most, I get two or three sentences and that's it. Then we always try to do a full manuscript but sometimes it can be very challenging to get those full manuscripts out there."	Lack of detail of PRO data in the main manuscript	PRO data not included or lack of detail within the main trial publication	Suboptimal PRO trial reporting	Barriers to PRO impact

[1] Code: Refers to the most basic element of the dataset that can be assessed in a meaningful way.
[2] Category: Grouping of patterns observed in the coded data in order to start the process of classifying findings.
[3] Theme: Refers to characteristics of participants' accounts describing particular perceptions relevant to the research question.
[4] Main topic: Refers to the four main objectives this qualitative study focused on: types of impact, impact metrics, and barriers and facilitators to PRO impact.

Following inductive coding, the transcripts were again read several times to ensure there were no elements of the dataset missing. During the coding stage, a random sample of interviews (10%, n=3) was additionally coded by an independent researcher (CM) in order to enhance credibility of the analysis of the data collected (analyst triangulation) [19].

After the coding process, data were organised and analysed following descriptive accounts by type of impact, impact metrics and barriers and facilitators to impact [25]. Subsequently, under each code a record of the meaning of the quotes was included. These notes helped grouping together descriptive codes that shared common meaning into categories in order to get a broader sense of the data. The final stage was to group relevant categories into themes to represent broader concepts of the data. The themes identified were either rearranged to create a new theme or collapsed to form a single theme [14]. In addition, the themes were revised to ensure they clearly and concisely described the dataset. Quotes that highlighted the nature of each theme were chosen to demonstrate prevalence. To present commonalities and differences among stakeholders, descriptive tables were created per theme and subsequently grouped by main topic. The tables included quotes that helped describe the key findings from the dataset. The respective coding, categories and themes decisions were discussed with the research team (DK/AS/MC) to inform the final analysis and interpretation of the data.

Results

Of 41 stakeholders invited to participate, 24 semi-structured interviews were conducted with a range of international stakeholders. Reasons for declining participated included lack of availability (n=4), preference to maintain a neutral position regarding the topic (n=1), belief they were ineligible (n=1). In addition, 11

people did not respond to the invitation. Interviews lasted on average 35 minutes (range 24 to 55 minutes). Most of the interviews (n=21) were conducted by phone whilst three took place face-to-face on University premises. Interviewees self-identified with a range of stakeholder groups including academic and industrial trialists, journal editors, clinicians, funders and policy-makers/regulators. Six participants identified with more than one group. Participant summary characteristics are presented in Table 3.

Table 3. Participants' characteristics

Stakeholder group	Country	Type of institution	Participant number
Academic trialists	USA	University	1
	Australia	University	2
	The Netherlands	University	3
	Canada	University	9
	USA	University	10
Industry trialists	USA	Research institute	4
	USA	Research institute	5
	UK	Pharmaceutical company	11
	USA	Pharmaceutical company	16
	USA	Global contract research organisation	17
Journal editors	USA	Peer-reviewed medical journal	7
	UK	Peer-reviewed medical journal	15
	USA	Peer-reviewed medical journal	24
Clinicians	USA	University	1*
	UK	Government	8*
	Canada	University	9*
	UK	Charity	18*
	USA	Funding institute	19*
	UK	University	23
	UK	University	24*
Policy-makers and regulators	USA	Regulatory agency	6
	UK	Regulatory agency	8
	Germany	Reimbursement agency	12
	UK	Regulatory agency	13
	UK	Reimbursement agency	14
Funders	UK	Charity	18

	USA	Funding institute	19
	UK	Government	20
	USA	Funding institute	21
	USA	Funding institute	22

*Participant included in two different stakeholder groups.

Interpretation of four core themes are presented in this section: 1) types of PRO impact 2) PRO impact metrics and 3) barriers to PRO trial impact, and 4) facilitators to PRO trial impact. To explain the dataset in a meaningful way, an informed approach was adopted. The dataset was presented against these four core themes, which relate back to the five types of impact categories as appropriate throughout.

Results are presented below with quotes labelled as shown in Table 4 followed by participant number. Deviant cases were explored and presented were appropriate.

Table 4. Quotes labels

Stakeholder group	Academic trialists	Industry trialists	Journal editors	Clinicians	Policy-makers and regulators	Funders
Label	AT	IT	JE	CL	PM-RE	FU

1. Types of PRO impact

The following section describes the different types of impact identified by stakeholders in which PRO trial data were purported to have an impact.

1.1 Primary research related impact

This is an impact associated with the generation of new knowledge, dissemination of results, building of research capacity, delivery of training and development of new leadership, and academic collaborations and networks. This impact is expected to be generated in the short-term, one year or less [24].

Academic and industry trialists, clinicians and funders were the main stakeholder groups that discussed the potential impact of PRO trial findings on ‘research and

innovation outcomes'. They believed that publications (including press releases and lay summaries), peer reviewed articles and citation rates have the potential to maximise the impact of PRO trial data outcomes by making the PRO data available to patients, clinicians and decision-makers. Another type of PRO impact mentioned was 'dissemination and knowledge transfer', which participants identified as presentation of PRO trial data in conferences by leaders or experts (including patients), mass media, and translation of PRO data to other research areas.

> *"The most impactful thing is when a respected expert gets up on the podium and says, "It's really important that this study showed pain improvements and we should be telling our patients that their pain gets better." That makes a big difference […]"* ***CL1***

See Table 5 for further quotes on primary research related impact.

Table 5. Primary research related impact quotes

Types of impact			Discussed by						Illustrative quotes
			Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Primary research related impact	Research and innovation outcomes	Publications	✓	✓	✓	✓		✓	*"[…] publications are there in the literature to be read. So, I think those are important, and in publication in high ranking journals like New England or Lancet are obviously more important."* ***CL9***
	Dissemination and knowledge transfer	Conferences, seminars, workshops and presentations		✓		✓	✓		*"It needs someone like NCRI or NIHR or Evolve or someone just to put a call out. If you've had a study that's improved something via PRO measures, if PROM's have made an impact tell us what the study was, tell us what it is, and by the way we're looking to do a showcase for you to talk about it at this or that conference on this or that date."****JE15***
		Teaching							
		Mass media	✓		✓	✓			*"It could also be TV, radio; newspaper advertisements and other form of media are also ways to spread the knowledge about the PRO's and to advance the matter so that different people with little understanding of statistics and epidemiology can understand."* ***IT16***
		Translation of PRO data to other research areas	✓				✓		*"It can also be that it will be translated, or that it will be applied in another field or it influences further research."* ***AT3***
	Capacity building, training and leadership								
	Academic collaborations, research networks and data sharing								

1.2 Influence on policy-making

This type of impact refers to the interaction between policy-makers and academics and available knowledge base, which may result in changes to policy. These impacts are generally considered to arise in the mid-term (1 to 3 years) [24].

Several interviewees highlighted the potential impact of PRO trial data on 'type and nature of policy-making', by influencing changes clinical guidelines to practice and providing information to support drug approval, pharmaceutical labelling claims and promotional labelling claims.

> *"[…] to support a drug license, what we would hope in the future is that patient reported outcomes are the patient voices captured in a way, in a robust way, and an objective way that would allow that data to be integrated into the assessment of benefits and risks and then concluding on whether a drug should be given a drug license"* ***PM-RE13***

For instance, some clinicians stated that PRO trial data had influenced their own practice by informing nuanced conversations with patients and supporting careful selection of treatments and giving them confidence to choose the best healthcare treatment while considering toxicity and side effects.

> *"So, for treatments that I discuss with patients, when there are results from trials with information about patient reported outcomes, specifically about symptoms or physical functioning, or overall quality of life I include those in my discussion with patients when they're making a decision about a treatment."* **CL1**

The impact subgroup 'type and nature of policy-making' was mainly discussed by academic trialists, policy-makers and regulators. See Table 6 for further quotes on influence and policy-making impact.

Table 6. Influence on policy-making impact quotes

Types of impact			Discussed by						Illustrative quotes
			Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Influence on policy-making	Level of policy-making								
	Type and nature of policy impact	Changes to legislations, regulations and government policy							
		Influence and involvement in the decision-making process							
		Changes to clinical or healthcare *practice*	✓	✓	✓	✓	✓	✓	*"So there was a study where, if you like, the cancer control outcomes were the same but the PROM's were improved with radiotherapy. That's a trial that's influenced my practice and makes me feel very confident to offer radiotherapy in preference to surgery for those patients based on a PROM outcome."* ***CL18***

	Types of impact		Discussed by						Illustrative quotes
			Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Influence on policy-making	Type and nature of policy impact	Changes to clinical or healthcare *guidelines*	✓			✓		✓	*"When Mitoxantrone was approved in 1996, I think around that time anyway, I mean yes, guidelines for treatment of metastatic prostate cancer changed to include Mitoxantrone as a treatment, a recommended treatment for patients who develop hormone resistant prostate cancer."* ***CL9***
		Drug approval*	✓		✓			✓	*"So when we're weighing up the efficacy data and the safety data, to support a drug license, what we would hope in the future is that patient reported outcomes are the patient voices captured in a way, in a robust way, and an objective way that would allow that data to be integrated into the assessment of benefits and risks and then concluding on whether a drug should be given a drug license"* ***PM-RE13***
		Pharmaceutical labelling claims*	✓			✓		✓	*"In the case of Abiratone Acetate, it was such an important endpoint that it's included in the drug label for the Food and Drug Administration."* ***CL1***
		Promotional labelling claims*		✓				✓	*"Of the labelling and so that's going to be different by country because in the US we have direct consumer advertising, so PRO messaging can go right to the patient, and then patient might go to the doctor and say 'I saw this commercial and it says I would have improved physical function if I take this migraine medication'."* ***IT5***
	Policy networks								

1.3 Health and health systems impact

Health and health systems impact encompasses the benefits of health research outputs on `quality of care and service delivering', ‘evidence-based practice', ‘improved information and health information management', ‘cost containment and effectiveness', ‘resource allocation', and ‘health workforce'. This type of impact is expected to arise in the long-term, beyond five years [24].

Clinicians and funders were the only stakeholder groups who highlighted the impact of PRO trial data on ‘evidence-based practice’, specifically on the subgroup fulfilling previously unmet needs.

> *“Collecting PROMs on a regular basis allowed us to demonstrate that the management of lymphoedema within our organisation was an unmet need, and using that data, we could then use that to influence purchases and commissioners and make that the backbone of a business case which allowed us to provide new services for patients with lymphoedema.”* ***FU18***

The impact subgroup ‘quality of care and service delivery’ was only discussed among academic and industry trialists, clinicians and funders. These stakeholder groups emphasised the impact of PRO trial data on improved health outcomes. The impact subgroup ‘cost containment and effectiveness’ was predominant among all the stakeholder groups but journal editors. Academic and industry trialists and policy-makers and regulators highlighted the impact of PRO trial data on cost effectiveness.

> *“Well, I sub-divide patient reported outcomes into disease specific PROs and generic ones. The generic ones in particular, EQ-5D. All of the trials that we’ve seen that include the EQ-5D have used them to calculate cost effectiveness.”* ***PM-RE14***

Academic and industry trialists, clinicians, funders and policy-makers and regulators thought that PRO trial data can capture improvements in health-related quality of life that can be used in combination with other clinical outcomes to the contribution of health institutions cost savings. Furthermore, industry trialists, clinicians and funders mentioned that the adoption of a healthcare treatment that improves health-related quality of life could have an impact on the reduction in the number of work loss days, which leads to improved work productivity. The impact sub-category 'reduction in the number of work loss days' is encountered within the category 'healthy workforce'.

> *"For irritable bowel syndrome […] patients had less gas and less this and that, but also that led to improvement in work productivity. They went back to work much earlier so that sort of thing certainly has impact in certain segments of the market."* ***IT4***

In general, clinicians and funders primarily highlighted the impact of PRO trial data on the 'health & health systems' type of impact. Moreover, the impact category 'resource allocation' was not discussed by any of the interviewees. See Table 7 for further quotes on health and health systems impact.

Table 7. Health and health systems impact quotes

Types of impact			Discussed by						Illustrative quotes
			Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Health & health systems impact	Evidence-based practice	Improving diagnostics and response prediction							
		Fulfilling previously unmet needs				✓	✓		*"Collecting PROM's on a regular basis allowed us to demonstrate that the management of lymphoedema within our organisation was an unmet need, and using that data, we could then use that to influence purchases and commissioners and make that the backbone of a business case which allowed us to provide new services for patients with lymphoedema."* ***FU18***
	Quality of care and service delivery	Improved health outcomes	✓	✓		✓	✓		*"We looked at enhanced recovery in people undergoing anterior resections of the rectum using laparoscopic surgery and enhanced recovery methodologies […] it was the fact that the patient reported outcomes in the subsequent weeks and months post operatively demonstrated a much quicker return to a high quality of life as opposed to open surgery."****IT4***
		Patient satisfaction					✓		*"How satisfied [patients] are but also more detailed appropriate patient related outcomes. […] We have to find qualitative systematic ways for doing that because what you want to achieve is the same level of satisfaction but the outcome for individuals could be completely different to maintain that level of satisfaction."* ***FU20***
		Making services more accessible for local communities							
		Reduction in waiting times							

1.4 Health-related & societal impact

Health-related and societal impact includes the impact subgroups: ‘health literacy’, health knowledge, attitudes and behaviours’ and ‘improved social equity, inclusion or cohesion’. This type of impact is also expected to be generated in the long-term, beyond five years.

Funders and a small number of clinicians highlighted that PRO trial data can influence health literacy, by providing information on how patients are affected by a health condition. They believed that this information can be used to change the general perception of a disease or de-stigmatise it (e.g. cancer and mental health conditions) and help patients ‘live better’ with that condition. Industry trialists and funders considered the impact of PRO trial data on patient advocacy groups, which is encountered within the impact category health knowledge, attitudes and behaviours. These interviewees mentioned that patient advocacy groups can influence drug development by communicating to health authorities patients’ priorities.

> *“I think PROs can affect the public image of the disease. I think one of the things we’re all hoping for some day, are treatments for cancer that can help turn what, for many people is a fear of even being with somebody who has cancer into something more positive, that cancer becomes something that we treat like arthritis.”* ***F21***

Industry trialists and funders were the only stakeholder groups that mentioned the potential impact of PRO trial data on ‘health-related & societal impact’. Furthermore, the impact category ‘improved social equity, inclusion or cohesion’ was not discussed by the interviewees. See Table 8 for further quotes on health-related and societal impact.

Table 8. Health-related and societal impact quotes

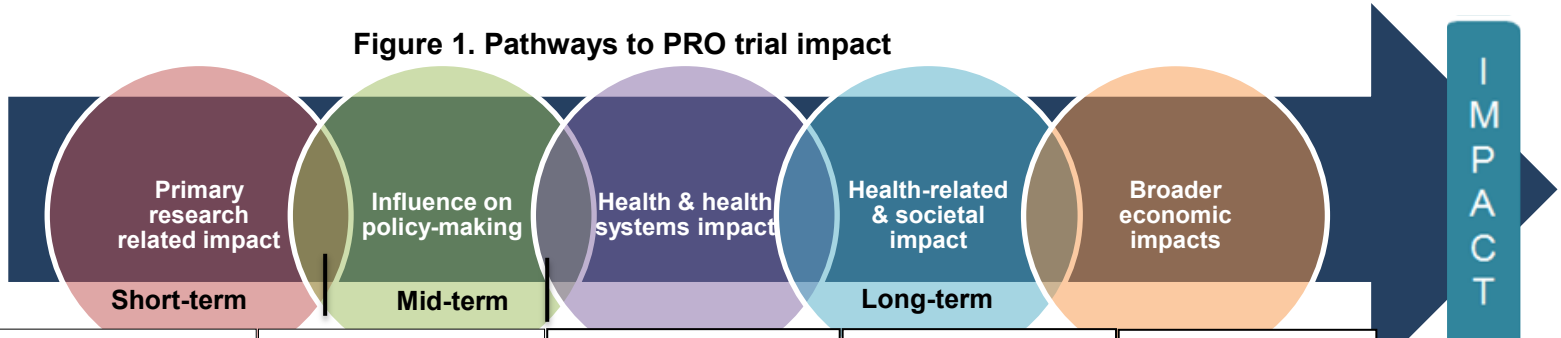
Types of impact			Discussed by						Illustrative quotes
			Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Health-related & societal impact	Health literacy	Activities to change health-risk behaviours	✓				✓		*"A field can be changed in terms of the way in which the impact of the condition is on an individual or on a population or on a health system is conceptualised and patient reported measures can have a huge role to play in that […] I think there's good examples in urinary incontinence therapeutic area that some of the measures that have been developed have changed the way in which the disorder is conceptualised."* ***F21***
	Health knowledge, attitudes and behaviours								
	Improved social equity, inclusion or cohesion	Patient advocacy groups*		✓			✓		*"the efforts being made to translate clinical trial outcomes by patient advocacy groups in terms that a patient can understand. So when they go to their clinician they ask for this information or if they know something about the outcomes for the treatment."* ***IT17***

1.5 Broader economic impacts

This impact category refers to the generation of economic revenue generated from the commercialisation of health research output. This type of impact is also expected to arise in the long term. Industry trialists suggested that PRO trial data can contribute to increasing pharmaceutical companies' sales and revenue. By using PRO trial data to attract income from intellectual property and increased pharmaceutical sales.

> *"Think in the pharmaceutical industry, because we're selling products, one of the main ways they evaluate whether or not it's a success is how much it sells, how frequently it's used and whether or not it becomes part of guidelines, but that's not the only way to understand the value."* ***IT4***

Figure 1. Pathways to PRO trial impact



Research and innovation outcomes*

- Publications
- Peer-reviewed articles (journal impact factor)
- Citation rates

Dissemination and knowledge transfer*

- Conferences, seminars, workshops and presentations
- Teaching
- Mass media

Capacity building, training and leadership*

- PhD and post-doc studentships
- Academic careers advancement
- Subsequent grants received

Academic collaborations, research networks and data sharing

Level of policy-making

- Presentations to decision-makers
- Influence on public policy debate
- Information base for political and executive decision-making

Type and nature of policy impact

- Changes to legislations, regulations and government policy
- Influence and involvement in the decision-making process
- Changes to clinical or healthcare training, practice or guidelines
- **Drug approval**
- **Pharmaceutical labelling/promotional claims**

Policy networks

- Collaborative research with industry
- Staff movement between academia and industry

Evidence-based practice

- Improving diagnostics and response prediction
- Fulfilling previously unmet clinical needs

Quality of care and service delivery

- Improved health outcomes (QALYs)
- Patient satisfaction (PROMS)
- Making services more accessible for local communities
- Reduction in waiting times

Cost containment and effectiveness

- Cost savings
- Increased service effectiveness

Resource allocation

- Better targeting and accessibility while allocating resources

Health workforce

- Reduction in the number of work loss days

Health literacy

- Activities to change health-risk behaviours such as strategies and campaigns

Health knowledge, attitudes and behaviours

- Increased levels of public engagement with science and research
- Outcomes from focus groups to assess changes in attitudes, behaviours and attitudes

Improved social equity, inclusion or cohesion

- United Nations Millennium Development Goals
- Human rights
- **Patient advocacy groups**

Economic impacts

- Attracting R&D investment from NHS, medical charities and overseas
- Income from intellectual property
- Spill over effects
- Patents granted/licenses awarded and brought to the market
- Spin-out companies
- Research contracts and income from industry

Impact metrics highlighted in red were newly identified through the qualitative interviews.

2. Impact measurement metrics

Interviewees proposed different quantitative and qualitative metrics to measure the impact of PRO trial data. These included: the number of citations of PRO publications; journal impact factor; and how often a PRO endpoint was presented in blogs, online communities and social media.

> *"How many times the article on the PRO's has been cited. That's one measure. The standard metrics that the journals and articles have regarding impact."* ***IT16***

Additional impact metrics proposed included: number of clinical trials conducted which included PROs as an endpoint and number of labelling claims. Evaluation of health technology assessment documentation to determine whether PRO data inform drug approval. Surveys and interviews among healthcare practitioners and patients to determine whether PRO data are incorporated into clinical decision-making or used to inform patient shared decision-making.

> *"I think there are experimental methods that could be applied, so sampling, […] there's quantitative survey methods that could be used, but also qualitative methods to be sure to be capturing what it's impact is, for instance, how information from a PRO affected thinking and behaviour on the part of the end user. By end user I mean an individual with a condition or a clinician and even to the level of the health system."* ***FU21***

In contrast, several stakeholders highlighted that measuring PRO trial data through metrics is a challenging task and it might not accurately represent the real impact of PRO trial data.

3. Barriers to PRO impact

Interviewees highlighted a range of perceived barriers that they felt may impair the realisation of impact arising from PRO trial findings, including: 1) poor quality trial

design, 2) suboptimal conduct and analysis, 3) poor reporting quality, and 4) dissemination and uptake of PRO results.

3.1 Poor quality trial design

Poor quality trial design refers to the lack of PRO-specific methodological rigor during the design stage of the clinical trial, which limits the realisation of PRO trial impact in the subsequent stages of the clinical trial. All stakeholder groups, with the exception of industry trialists and funders, mentioned poor quality design as one of the barriers to PRO impact. Interviewees highlighted PRO trial barriers such as lack of detailed PRO protocol and lack of adherence to it.

> *“[PROs are] either exploratory endpoints that are either added in inappropriately, the timings are incorrect, the instrument might not be correct for the particular patient population, the analysis hasn’t been thought through, there’s no hypothesis or objectives listed in the study protocol.”* ***PM-RE13***

Further barriers identified were the inclusion of PROs in the clinical trial as secondary outcome, lack of PRO trial information from phase I and II limiting the design of the PRO component in phase III and; late or not incorporation of PRO experts in the development of the clinical trial protocol.

> *"[…] we would get sent the protocol right at the end, right before the trial was going to be sent to ethics or sometimes even after they had received ethical approval. We would make suggestions to improve the protocol with respect to PRO’s and then some of the investigators would be reluctant to make those changes because it meant they would have to do an extensive protocol amendment"* ***AT2***

See Table 9 for further quotes on poor quality trial design.

Table 9. Poor PRO trial quality design quotes

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Design	Lack of detailed PRO protocol			✓			✓	*"[PROs are] either exploratory endpoints that are either added in inappropriately, the timings are incorrect, the instrument might not be correct for the particular patient population, the analysis hasn't been thought through, there's no hypothesis or objectives listed in the study protocol."* ***PM-RE13***
	Lack of adherence to PRO protocol			✓				
	Inclusion of PRO data as secondary endpoint			✓	✓			*"[…] We don't see very good advanced planning to use PRO in the drug development process; […] patients reported outcome measures are only classed as exploratory endpoints […] then their impact to regulatory decision-making can only be very limited."* ***PM-RE13***
	Lack of PRO information from phase I and II trials limits the design of the PRO component in phase III trials	✓						*"[…] we would get sent the protocol right at the end, right before the trial was going to be sent to ethics or sometimes even after they had received ethical approval. We would make suggestions to improve the protocol with respect to PRO's and then some of the investigators would be reluctant to make those changes because it meant they would have to do any extensive protocol amendment"* ***AT2***
	Late or not incorporation of PRO experts in the trial protocol stage	✓					✓	

3.2 Suboptimal conduct and analysis

The way the trial was conducted and the type of analysis that is implemented were mentioned as barriers to maximise the impact of PRO trial data. Suboptimal conduct and analysis was a predominant theme among all the stakeholders; however, it was discussed to a lesser degree by journal editors and clinicians. This theme included barriers related to high rates of missing data, difficulty collecting PRO data among global trials, patient and staff burden and lack of training for clinicians to optimally conduct a PRO clinical trial and analyse PRO trial data and; lack of expert reviewers to assess PRO trial results.

> *"Medical journals often lack sufficient experts who can review PRO results because the researchers and clinicians who are journal reviewers are not knowledgeable about PRO[s]."* ***IT11***

An additional barrier identified surrounded a perceived lack of understanding and interpretation of PRO data by clinicians, patients and patient advocates.

> *“PRO experts, sometimes assume that the clinicians will understand tables and figures and the interpretation of the clinical trial and I think we know from experience that clinicians don’t always get the message.”* ***IT17***

See Table 10 for further quotes on suboptimal conduct and analysis.

Table 10. Suboptimal PRO trial conduct and analysis quotes

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Conduct and analysis	High rates of missing PRO data	✓				✓	✓	*"So if there is a high number of missing values, then the impact is very intensively lowered […]"* ***PM-RE12***
	Difficulty collecting PRO data among global trials		✓					*"Global trials that involve many countries and languages raise special challenges for PRO where translations are required and collection of PRO may be more challenging to get sites to collect correctly."* ***IT11***
	Patient and staff burden	✓	✓					*"The burden on patients is still an issue and a barrier at times. I think we've been ineffective in trying to develop parsimonious PRO's."* ***PM-RE6***
	Lack of training for clinicians		✓					*"Physicians don't have training in patients reported outcomes unless they have an interest in that area."* ***IT4***
	Lack of expert reviewers to assess PRO trial results		✓					*"Medical journals often lack sufficient experts who can review PRO results because the researchers and clinicians who are journal reviewers are not knowledgeable about PRO."* ***IT11***
	Clinicians, patients, patient advocates and policy makers lack of understanding and interpretation of PRO data		✓	✓	✓	✓		*"PRO experts, sometimes assume that the clinicians will understand tables and figures and the interpretation of the clinical trial and I think we know from experience that clinicians don't always get the message."* ***IT17***

3.3 Poor reporting quality

This theme was primarily highlighted by academic trialists. Barriers emphasised by interviewees included: lack of discussion of PRO outcomes; inclusion or detailed information within the main clinical trial publication; PRO data explanation in view of other clinical endpoints and; publication of PRO trial data many years after publishing the main trial manuscript or its lack of publication.

> *"I came across a few trials where the PRO results hadn't been published […] I saw that certain trials had PRO of secondary endpoint but then when I found the publication that related to it, that was just completely missing and sometimes they would say that the PRO results would be published later but it had been several years down the track."* ***AT2***

Further barriers to PRO impact interpreted included publication of clinical trials manuscripts including PRO data in a technically correct language, but difficult to understand for patients, advocacy groups and patients and; restricted access to PRO publications (paywall restrictions). See Table 11 for further quotes on poor reporting quality.

Table 11. Poor PRO trial reporting quality quotes

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Reporting	**Lack of discussion of PRO outcomes**					✓		*"I think not being published is a big one but also because in the main trial publication, if they are reported then it might just be very minimal information that's not really…not that it's not informative, I mean it's good to know if there are differences between the groups but I think is so much more rich than just that."* ***AT2***
	Lack of inclusion or detailed PRO information within the main trial publication	✓			✓			
	Lack of PRO data explanation in view of other clinical endpoints	✓			✓			
	Lack of journals endorsement	✓						*"I'm not sure that scientific papers have really got their head around the importance of patient reported outcomes."* ***FU20***
	PRO trial data are never published or it is published years after the main trial publication in a low impact journal				✓	✓		*"I came across a few trials where the PRO results hadn't been published […] I saw that certain trials had PRO of secondary endpoint but then when I found the publication that related to it, that was just completely missing and sometimes they would say that the PRO results would be published later but it had been several years down the track."* ***AT2***

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Reporting	**PRO publications in journals report PRO findings in a technically correct language but difficult to understand for patients, advocacy groups and clinicians**		✓					*“There is certainly information that patients want to know about when making a treatment decision and the difficulty is translating those outcomes from the trials into ways that clinicians can understand those outcomes.”* ***IT17***
	Restricted access to PRO publications (paywall restrictions)	✓	✓	✓				*"If you publish it in a very scientific journal and if you are not based in a university, you cannot even read that paper because you don’t have access to those papers. How would you know?"* ***AT3***

3.4 Dissemination and uptake of PRO results

This included PRO-specific issues faced upstream that limited the propagation and adoption of the findings into clinical practice. This theme was common among journal editors, clinicians and policy-makers and regulators, whereas academic trialists commented on this theme to a lesser extent.

Barriers encompassed lack of awareness of PRO data importance between clinicians, researchers, journal editors and sponsors and; prioritisation of clinical outcomes over PRO trial data by researchers and funders.

> *“The main reason is that the high impact journals want survival data and if they’ve got a survival advantage they don’t bother with the quality of life data. […] There’s a study of a drug which has a two-month survival advantage, worse toxicity, quality of life data collected but not published. It’s outrageous.”* ***FU19***

Additional barriers discussed were lack of engagement between academic researchers and research companies with patients to understand patient priorities, collaboration between PRO researchers within same health research areas and law or regulation in the UK to enforce the collection of HRQL in clinical trials.

> *"So we are law enforcers if you like. Now, that doesn’t really incorporate PRO’s, there is no specific law if you like, that they’re going to break if they don’t include a PRO or include it in the wrong context or what have you. So it’s almost, I suppose, supplementary information. It’s not regulated in any way in terms of black and white text."* ***PM-RE8***

Other barriers that reportedly might hinder the maximisation of PRO trial data were the limitation of PROs not automatically becoming health utilities, the different perspective surrounding the inclusion of PROs in clinical trials between the EMA and FDA and the difficulty getting funding for PRO research.

"One of the major funders of research in this country is very unlikely to fund research that has a PROM as a primary outcome. They've made that a strategic intent, so the playing field is already biased against PROM's based research." ***FU18***

See Table 12 for further quotes on dissemination and uptake of PRO results.

Table 12. Dissemination and uptake of PRO results quotes

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Dissemination and uptake of results	**Lack of awareness of PRO data importance among clinicians, researchers, journal editors and sponsors**	✓	✓	✓	✓	✓	✓	*"I think there is still a challenge in the scientific community to see the value of patient reported outcomes as just an important and integral part of our understanding of medicine and medical care and new treatment evaluation".* ***IT11***
	Researchers and funders prioritise clinical outcomes rather than PRO data			✓	✓	✓		*"The main reason is that the high impact journals want survival data and if they've got a survival advantage they don't bother with the quality of life data. […] There's a study of a drug which has a two-month survival advantage, worse toxicity, quality of life data collected but not published. It's outrageous."* ***FU19***
	Lack of engagement between academic researchers and research companies with patients to understand patient priorities		✓	✓	✓	✓		*"The EMA does not permit direct communication from pharma companies to patients, so there are significant challenges sharing more patient-friendly explanations of our PRO research in newsletters, websites, or white papers that could be accessed by patients or clinicians other than with those who participated in the trial or through the Layperson Summary of the trial."* ***IT11***
	Lack of collaboration between PRO researchers within same health research areas						✓	*"One problem is everyone tries to set up their own shop and so instead of trying to say, we're going to develop a great tool for gastrointestinal distress, for example, you have six or seven groups that develop groups for very specific disease areas but they all essentially ask the same questions."* ***PM-RE6***

Trial stage	Barriers	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Dissemination and uptake of results	**Lack of law or regulation in the UK to enforce the collection of HRQL in clinical trials**						✓	*"So we are law enforcers if you like. Now, that doesn't really incorporate PRO's, there is no specific law if you like, that they're going to break if they don't include a PRO or include it in the wrong context or what have you. So it's almost, I suppose, supplementary information. It's not regulated in any way in terms of black and white text."* ***PM-RE8***
	PROs not automatically becoming health utilities						✓	*"[…] [PROs] don't suffer from the problem of not collecting things that will be affected by the disease; they do suffer from the problem that they don't automatically become utilities, although many of them can be mapped."* ***PM-RE14***
	EMA and FDA different perspectives surrounding the inclusion of PROs in clinical trials	✓	✓					*"[…] the EMA seems to be more willing to accept scientific publications and information in the literature than the FDA is, depending on the reviewing decision, it may be easier or harder to get a PRO in the label, so it's not an even playing field across the different divisions."* ***IT17***
	Difficulty getting funding for PRO research				✓	✓		*"One of the major funders of research in this country is very unlikely to fund research that has a PROM as a primary outcome. They've made that a strategic intent, so the playing field is already biased against PROM's based research."* ***FU18***

4. Facilitators to PRO impact

Interviewees highlighted a range of perceived facilitators that they felt may enhance the realisation of PRO trial findings including: 1) improved PRO trial design, 2) optimal conduct and analysis, 3) improved reporting and 4) dissemination and uptake of PRO results.

4.1 Improved PRO trial design

This theme was primarily discussed by policy-makers and regulators. It was not discussed among journal editors and clinicians. Improved PRO trial design facilitators discussed by interviewees included: the production of a clear and detailed PRO protocol; endorsement of the PRO data as a key endpoint in clinical trials; and early incorporation of a PRO expert in the trial team.

> *"There should be a PRO expert on the clinical trial team and at the earliest possibility; if you start thinking about your PROs at the reporting stage it is far too late. You need to be thinking much earlier on."**AT3***

Participants also discussed adherence to PRO guidelines, inclusion of patients and clinicians in the trial design stage, regular meetings with regulatory agencies during the planning period and the end of the trial and; the development of PRO measures while considering health utilities for HTA use.

> *"The patient reported outcomes world could think of utilities at the same time as developing their PRO's. So any patient reported outcome that has got a utility mapping attached to it is very useful."* ***PM-RE14***

See Table 13 for further quotes on improved PRO trial design.

Table 13. Improved PRO trial design quotes

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Design	**Clear and detailed PRO protocol**						✓	*"The protocol is very complete, very detailed about how to interpret the metrics, how to measure them and standardise their use and so on. The findings are more likely to be considered to be valid and reliable."* ***JE7***
	Endorsement of PRO data as key endpoint in clinical trials						✓	*"I think that they have to be key endpoints in clinical trials […] if you look at arthritis where the main endpoint is a symptom, people talk about symptoms more. I think that when you get into diseases where there are other endpoints, like survival, people tend to focus more on those."* ***CL1***
	Early incorporation of a PRO expert in the trial team		✓					*"There should be a PRO expert on the clinical trial team and at the earliest possible,* if you start thinking about your PROs at the reporting stage it is far too late. You need to be thinking much earlier on.***"AT3***
	Adherence to PRO guidelines		✓					*"[...] the SPIRIT PRO guidelines, the CONSORT guidelines, the guidelines coming out of SISAQOL and ISOQOL, the guidelines that have been recommended by the US FDA about what things should be included when you're trying to measure well the patients experience."* ***IT11***
	Inclusion of patients and clinicians in the trial design stage	✓				✓	✓	*"It's really important to speak to clinicians and patients about what issues seem to be most troublesome for patients before they start treatment and then to talk about whether the clinician expects the therapy understudy will have any impact on those particular issues."* ***AT2***

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Design	**Regular meetings with regulatory agencies during the planning period and at the end of the trial**	✓					✓	*"We give comments during the planning period so that there are relatively few questions at the end because we will reanalyse the data and go through everything at the end but that's too late if there is a problem."* ***PM-RE6***
	Development of PRO measures while considering health utilities for HTA use						✓	*"The patient reported outcomes world could think of utilities at the same time as developing their PRO's. So any patient reported outcome that has got a utility mapping attached to it is very useful."* ***PM-RE14***

4.2 Optimal conduct and analysis

Facilitators to achieve optimal conduct and analysis were highlighted by policy-makers and industry trialists, whereas journal editors and clinicians did not contribute to this theme. Facilitators discussed were high completion rates of PRO trial, training sites on the administration, make PRO data more readily understandable and; explanation of PROs and standardisation of PRO tools among therapeutic areas to improve analysis.

> *"Having standardised tools across trials helps us understand the trial results and be able to compare things more easily. [...] Certainly in the US with qualification process for PROs, there's a hope that each of us will not go out and create one off our own tool, instead have some standardisation."* ***IT5***

See Table 14 for further quotes on optimal conduct and analysis.

Table 14. Optimal PRO trial conduct and analysis quotes

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Conduct and analysis	**High completion rates**						✓	*"Try to collect the data from the start until the end of the trial. Also for patients withdrawn from treatment, and also from patients withdrawing from the trials, so there's a possibility to get an observation from these."* ***PM-RE12***
	Training sites on the administration and explanation of PROs		✓					*"So you have to train the sites and the sites have to be comfortable and understand the tools so they can appropriately explain them to patients."* ***IT5***
	Standardisation of PRO tools among therapeutic areas to improve analysis		✓					*"Having standardised tools across trials helps us understand the trial results and be able to compare things more easily. [...] Certainly in the US with qualification process for PROs, there's a hope that each of us will not go out and create one off our own tool, instead have some standardisation."* ***IT5***
	Make PRO data more readily understandable	✓				✓	✓	*"One thing is to do a little bit of interpretation to clinicians, so they can look at it and they don't have to know that a 55 is bad."* ***IT17***

4.3 Improved reporting

Improved reporting was predominant among academic trialists and journal editors; however, this theme was not discussed by industry trialists, policy-makers, and regulators. Facilitators encompassed in this theme were open access publications and PRO trial data reported in the main publication and in a high impact journal.

> *"The studies which have been impactful have been ones where the quality of life data and the survival data has been published together in a high impact journal"* ***FU19***

Further facilitators comprised simple English summary of the trial results for use of patients, availability of more journals to publish PRO trial data and make PRO instruments available through publications. See Table 16 for further quotes on improved reporting.

Table 15. Improved PRO trial reporting quotes

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Reporting	**Open access publications**	✓		✓	✓			*"No paywall, it has to be available. There's no point having a journal that's accessible to patients if they have to pay for it."* ***JE15***
	PRO trial data reported in the main publication and in a high impact journal	✓		✓	✓	✓		*"The studies which have been impactful have been ones where the quality of life data and the survival data has been published together in a high impact journal"* ***FU19***
	Inclusion of a simple English summary of the trial results for use of patients			✓				*"We insist on having a simple English summary of each paper and when authors submit to us, if the simple English summary isn't clear, then we won't read the paper. It goes back to the authors."* ***JE15***
	Availability of more journals to publish PRO trial data	✓						*"So having more PRO clinical trial venues to publish clinical trial results specific for PRO's would be a good thing […]"****AT10***
	Make PRO instruments available through publications	✓						*"It is extremely important that we make tools publicly available […] and then sharing that information through publication to continue to act at the weight of evidence around the validity of the tool. […] sometimes the PRO becomes part of the company's intellectual property."* ***IT5***

4.4 Dissemination and uptake of PRO results

Finally, dissemination and uptake of PRO results was emphasised by all the stakeholders but to a lesser extent by policy-makers and regulators. This theme highlighted facilitators such as adequate funding and the important of funders clearly stating their position around PROs and their expectations of the funded PRO research.

> *“I think funders have a role because they can stipulate, for example, that the work they fund must have some sort of an implementation plan so that work isn’t just completed and then perhaps published in a journal and then never heard from again. Having emphasis on ensuring that there is some pull through into use and impact as a direct requirement of funding would go a long way as well to help the problems.”* ***FU21***

In addition, it was suggested that funders should require an implementation plan in terms of usage and impact of the PRO clinical trial as a direct requirement of funding. Facilitators suggested that might enable the dissemination and uptake of PRO results included: provide PRO training courses for clinicians and drug developers and communicate PRO research widely through the involvement of key opinion leaders, specifically at healthcare conferences.

> *"To allow organisations like the NCRI, ASCO, ESTRO, the organisations that host large healthcare provider conferences to make PROM’s based research a future of their sessions and their main talks and also to improve quality of science communications so that we have skilled science communicators disseminating these results."* ***FU18***

Further facilitators highlighted included empowerment of patients through their involvement in discussions and dissemination of PRO trial results and; endorsement of PRO trial studies by key societies to disseminate results and influence healthcare policy. See appendix 3.5 for additional quotes. See Table 16 for further quotes on dissemination and uptake of PRO results

Table 16. Dissemination and uptake of PRO results quotes

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Dissemination and uptake of results	**Adequate funding**	✓	✓			✓		*"I think as a funder we have an opportunity to assert some leverage about the outcomes that go into the trials that are selected for the trials and if you want our funding then you have to meaningfully incorporate PRO's into the design. You wouldn't want to skip right into practice without some reasonable understanding about what the PRO's can predict, how they can affect other treatment outcomes and research itself on whether patients find them meaningful."* ***FU22***
	Funders should clearly express their position about PROs and what they expect from the funded PRO research					✓		
	Funders should require an implementation plan in terms of usage and impact of the PRO clinical trial as a direct requirement of funding	✓		✓	✓		✓	*"I think funders have a role because they can stipulate, for example, that the work they fund must have some sort of an implementation plan so that work isn't just completed and then perhaps published in a journal and then never heard from again. Having emphasis on ensuring that there is some pull through into use and impact as a direct requirement of funding would go a long way as well to help the problems."* ***FU21***
	Training courses for clinicians and drug developers	✓	✓					*"Having training courses that meet the needs of people, nothing too long, targeting events that are already up and running, like having a PRO session at a conference that's already established rather than having a training day that stands alone."****AT2***

Trial stage	Facilitators	Discussed by						Illustrative quotes
		Academic trialists	Industry trialists	Journal editors	Clinicians	Funders	Policy-makers and regulators	
Dissemination and uptake of results	**Communicate PRO research widely through the involvement of key opinion leaders, specifically at healthcare conferences**	✓			✓	✓		*"[…] so in Brighton and Sussex we have Professor Dame Lesley Fallowfield who has been a champion of PROM's for many years. She is often invited to conferences as a plenary speaker because she speaks very well about PROs and argues vehemently for PROs. [...] She can stand up in front of ten thousand doctors at ASCO and say, you should be measuring PROM's. We need more key opinion leaders like that who can be charismatic and persuade the wide audience of the value of PROM's."* ***FU18***
	Empowerment of patients through their involvement in discussions and dissemination of PRO trial results			✓	✓	✓		*"Let's have a patient standing up saying, my life is better because of this. It's not just got rid of my cancer, but actually I can cope with life, it's given me these things to cope with but actually I can cope with those."* ***JE15***
	Endorsement of PRO trial studies by key societies to disseminate PRO results and influence healthcare policy	✓				✓		*"[...] like the charities, like Macmillan, like Cancer Research UK to be having conversations with government and NHS England to make sure that policy is changed. The biggest changes in healthcare don't come from individuals and from research, they actually come from policy."* ***FU18***

Discussion

For the first time, this study provides international stakeholder perspectives on the types of impact associated with PRO trial results, impact measurement metrics, and barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society.

Stakeholders identified a number of ways in which PRO data from clinical trials can potentially inform/influence primary research, policy-making, health and health systems, health-related and societal impact and broader economic impacts. Although every interviewee was asked similar questions, not all of them discussed each type of impact. It was interpreted from the data that stakeholders appeared to focus on the impact categories that were most relevant to them and did not focus on broader aspects of PRO impact, even when prompted. The dataset provided rich narratives when the interviewee had experience of a particular type of PRO impact. . For instance, academics primarily focused on 'primary research related impact'. Arguably this stakeholder group might be more focused on producing research outcomes and their dissemination, rather than the broader benefits these outcomes may have on patients and society. Nonetheless, PRO stakeholders agreed on the benefit of including PROs in clinical trials and did consider a range of impacts.

The majority of the stakeholders suggested that measuring the impact of PRO trial research can benefit academic researchers, trialists, policy-makers, regulatory authorities, funding bodies, pharmaceutical companies, payers and patients. Measuring the impact of PRO trial findings may help stakeholders understand the importance and value of PRO trial data, broaden their perspectives regarding PRO applicability, and identify the different benefits to society through improved health outcomes and use of resources [26]. For instance, these data would provide a

knowledge base to policy-makers, regulators and funders to justify drug approval and inform funding allocation decisions through demonstrating the potential benefits on patients and society [24, 27]. Moreover, journal editors and academics might be more likely to acknowledge the importance of PRO data and ensure timely, transparent publication of PRO trial data in high impact journals. Considering the impact of PRO trial impact, it has the potential to influence the study design and determine the possible benefits of conducting a particular study.

Stakeholders proposed several qualitative and quantitative metrics to measure the impact of PRO research. Quantitative metrics included number of publications, citations including PROs as an endpoint and number of regulatory approvals including PROs and; surveys among stakeholders and patients to determine how PRO data are being used. Qualitative metrics comprised interviews among people involved in the drug approval process to determine whether PRO trial data inform drug approval appraisal. However, most interviewees highlighted that measuring the impact of PRO trial research is a challenging task as it cannot be captured systematically. Single cross-sectional metrics tend not to represent the overall impact PRO trial data can have, since impact arises at different points in time [24, 28]. In addition, impact is defined by each stakeholder group in a different way. For instance, academics considered impact in terms of number of publications and journal impact factor; policy-makers and regulators in terms of changes to healthcare policy and number of drug approvals. Therefore, further work should be done to determine whether the impact metrics identified capture the full impact of PRO trial data.

Several methodological PRO-specific trial barriers were identified including poor quality trial design, suboptimal trial conduct and analysis and poor reporting quality.

Interestingly, funders did not raise poor quality trial design as an issue in their interviews but arguably should be concerned with the quality of the data collected, as it is considered a crucial barrier to the realisation of PRO trial impact downstream.

Facilitators to maximise the impact of PRO trial data were discussed among stakeholders. Main facilitators highlighted were: mandatory inclusion of PRO data in funded trials and publications where appropriate; and the requirement to provide an implementation plan detailing the proposed use and impact of PRO clinical trial data as a direct requirement of funding. Additional facilitators included the importance of communicating PRO research widely, specifically at healthcare conferences hosted by organisations such as NCRI (The National Research Cancer Institute), ASCO (American Society of Clinical Oncology), and ESTRO (European Society for Radiotherapy & Oncology). It also felt important to empower patients by including them in the dissemination of PRO results at these healthcare conferences. Furthermore, the development of a UK law to enforce the collection of PRO data among clinical trials is considered as essential.

Currently, PRO stakeholders are making concerted efforts to improve the collection of PRO data in oncology and cardiology areas. For instance, the European Society of Cardiology (ESC) has led initiatives to increase the prominence of PROs in cardiovascular research, which can be translated in benefits for patients, clinicians, payers and policy-makers [29]. The Food and Drug Administration (FDA) is currently developing patient-focused drug development (PFDD) guidance to address how stakeholders can collect and include PROs from patients and caregivers in the development and regulation of medical products [30]. In 2016, the EMA (European Medicine Agency) published Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. Appendix 2 provides a general overview of the

use of PRO endpoints in oncology studies and the value of this information from the regulatory perspective [31].

Additional initiatives include PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) [32], which aims to promote the uptake and use of tools to support high quality PRO trial data including tools such as: SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) PRO-Extension [8]; ISOQOL Minimum Standards for PRO Measures in patient-centered outcomes and comparative effectiveness research [33]; SISAQOL (Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data) [34]; CONSORT (Consolidated Standards of Reporting Trials) PRO-Extension [35] Stakeholder-Driven, Evidence-Based Standards for Presenting PROs in Clinical Practice [36]; and Clinician's Checklist for Reading and Using an Article About PROs However, greater work needs to be done to capture PRO data in a rigorous efficient way across disciplines. Furthermore, key societies like Macmillan Cancer Support, ASCO and the NCRI are working on the endorsement of the dissemination of PRO trial studies, which might help to have a wider reach for spreading PRO trial results and consequently a further impact [37, 38].

Strengths and limitations

One of the key strengths of this study was the inclusion of 24 internationally recognised PRO experts. We consider the interviews captured all the core concepts around the impact of PRO trial data, which are presented above in four different themes. SCR, the interviewer, did not have a relationship with the participants; however, the wider team (MC/DK/AS) had previous collaborative links with some of the participants. To reduce the potential misinterpretation of data, the

multidisciplinary team provided support for the analysis and interpretation of the data.

A further limitation was that since participants were recruited from a pool of stakeholders known to the research team, this might have limited the range and experience of stakeholders being interviewed. Moreover, 17 invitees decided not to participate in the research, which could have led to the exclusion of relevant individuals with a different perspective. Nonetheless, we attempted to interview as many participants as possible using purposive and snowball recruitment methods.

Saturation within each stakeholder group would have been ideal but this was not possible. This would have allowed stronger conclusions to be drawn around the similarities and differences between each stakeholder group. Where there was appropriate evidence, similarities and differences were highlighted. Qualitative experts were involved to ensure congruence and structure at each stage of the research.

Finally, the findings drawn from this study may be transferable to other researchers working on PRO clinical trials, who have knowledge of the area. This reflects the need to have a PRO expert as part of the clinical trial team and; make the research accessible and applicable across a broad spectrum of international stakeholders.

Conclusion

In this study, we have presented the perspectives of international PRO stakeholders on the impact of PRO trial data, impact measurement metrics, and barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society. Interviewees highlighted a range of potential impacts associated with PRO trial findings, most notably the influence on policy-making. However, there is a need

to find more comprehensive ways of measuring PRO impact. There a number of barriers that needs to be overcome to facilitate PRO impact. Stakeholders need to come together to address these challenges in order to optimise the uptake of PRO trial findings in practice and maximise the benefit to patients and society.

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Appendices for Chapter 5

Chapter 6: Discussion

Discussion

This chapter summarises the key findings from this thesis, presents an interpretation of the results and their implications, outlines strengths and limitations and offers recommendations for future research. The aims of this thesis were: **a)** to synthesise existing methodological frameworks for healthcare research impact; **b)** determine the range of potential impact associated with PRO data collected in trials, identify potential PRO impact metrics and define common barriers to maximising PRO impact and; **c)** examine real-world evidence of PRO trial data impact and determine common facilitators aimed at maximising PRO trial data impact.

There are a number of existing methodological frameworks used to capture healthcare research impact. However, there is a lack of consensus around the most effective methodological framework and impact metrics to measure the impact of healthcare research. This thesis therefore presents a collective summary of existing methodological impact frameworks and metrics, which funders may use to inform the measurement of healthcare research impact and researchers may use to inform study design decisions aimed at maximising the short-, medium-, and long-term impact of their research [1]. This consolidated framework has been used to underpin this doctoral research investigating common types of PRO trial impact, their measurement, and barriers and facilitators to realising such impact. Whilst a range of PRO-specific types of research impact have been proposed in the literature, real-world evidence of such impact, although available, is currently limited (Chapter 4). Triangulation of both quantitative (Chapter 4) and qualitative (Chapter 5) data suggests there a number of potential barriers that need to be addressed in order to facilitate greater realisation of PRO trial impact in the future.

A mixed-method approach was used to address the aims of the thesis, which contribute to the research fields of research impact and PROs. Initially, a systematic review was conducted to explore existing methodological frameworks used to categorise the impact of healthcare research (Chapter 3; published August 9, 2017; 28,461 views, Altmetric 300 and 15 citations to date). This work presented the novel 'pathways to research impact' framework, which directly informed subsequent chapters.

A second systematic review, informed by the previous framework, was conducted to assess the potential impact of PRO data collected from clinical trials, identify potential PRO impact metrics and identify barriers/facilitators to maximising PRO impact. Additionally, real-world evidence of PRO trial data was assessed based on the Research Excellence Framework (REF) 2014 impact case studies (Chapter 4).

To gain better understanding of the findings in Chapter 4, a qualitative study involving international PRO stakeholders was undertaken. The study explored stakeholders' perceptions on types of PRO trial impact, how to measure such impact and barriers and facilitators to maximise the realisation of PRO trial impact on patients and society (Chapter 5).

Summary of findings

A. Methodological frameworks for measuring the impact of healthcare research

The systematic review (Chapter 3) identified the existence of 24 unique impact frameworks and incorporated these into a unified matrix: the 'pathways to research impact' methodological framework [1]. This framework may be used by funders and researchers to inform the measurement of research impact and study design

decisions to maximise the impact of research. The systematic review emphasised that users do not necessarily need to cover the entire methodological framework as research can impact on different areas. A systematic review (Chapter 4) and qualitative study (Chapter 5) further highlighted the lack of standardised impact metrics to capture PRO trial impact.

B. PRO trial data: potential and real-world impact

A second systematic review of the literature (Chapter 4) identified nine proposed types of PRO trial impact, which may lead to a range of benefits for patients and society. The types of impact identified as potentially attributable to PRO trial data included: informing clinical practice, clinical guidelines and health policy; supporting drug approval, pricing and reimbursement decisions and; informing clinical decision-making, shared decision-making and consent for treatment. The most frequent of these impacts centred around PRO data informing clinical decision-making (69%). In addition, four impact metrics were proposed to measure the impact of PRO data: the number of pharmaceutical and promotional labelling claims, number of drug/device approvals and inform cost-effectiveness. The included publications outlined different barriers and facilitators around PRO trial design, conduct, analysis and reporting that may influence the subsequent impact of PRO trial data.

Sixty-nine out of 209 REF case studies were included for assessment, of which 12 (17%) demonstrated direct measurable PRO-related impact. A further 12 (17%) showed evidence of indirect PRO impact and an additional 45 (66%) provided no evidence of PRO impact. The most common types of direct PRO impact were: number of publications (n=12, 17%), changes to international guidelines (n=5, 7%), contribution to national guidelines (n=4, 6%), contribution to evidence of cost-effectiveness (n=3, 4%) and informing drug approval (n=2, 3%). The lack of evidence

demonstrating directly attributable real-world PRO-related research impact can be attributed to the challenges associated to measuring research impact and PRO-specific issues around design, conduct, analysis and reporting.

International stakeholders were interviewed in order to develop a deeper understanding of the range of potential PRO impacts of clinical trials; barriers and facilitators to maximising the impact of PRO trial data.

C. The impact of PRO trial data - perspectives from international stakeholders: a qualitative study

The aim of the qualitative study (Chapter 5) was to explore the perceptions of PRO international stakeholders around the impact of PRO trial results on **a)** clinical practice, clinical guidelines, health policy, drug approval, pricing and reimbursement decisions, clinical decision-making, shared decision-making and consent for treatment. **b)** PRO impact metrics to measure such impact, and **c)** barriers and facilitators to effectively maximise the impact of PRO trial data upon patients and society.

Based on the 'pathways to research impact' methodological framework [1], developed in Chapter 3, 24 semi-structured interviews were conducted with a range of key stakeholders. These included academic trialists, industry trialists, journal editors, clinicians, policy-makers and regulators, and funders. Interviewees expressed a collective view that PRO trial can influence primary research related impact; policy-making; health & health systems, health-related & societal impact and broader economic impact. Influence on policy-making was the most common type of impact discussed. The results demonstrated that stakeholders should broaden

collaboration in order to effectively tackle barriers to PRO trial impact and maximise the impact of PRO trial research.

Interpretation and implications of findings

A. Measuring healthcare research impact using methodological frameworks

The systematic review presented in Chapter 3 highlighted different approaches to measuring research impact such as 'quantitative' metrics, case studies and approaches focusing on the interactions between stakeholders and researchers. 'Quantitative' metrics are predominately used by funders as they can easily capture the impact of research; however, these metrics focus more on the dissemination of research rather than on the impact of the research findings [2, 3]. Therefore, the use of narrative case studies is required to present a detailed picture of the impact that cannot be attributed to impact metrics, such as the social interactions between stakeholders and researchers [4-8]. A limitation of this approach is that capturing these interactions can be labour-intensive and complex to verify and validate.

These findings align to the narrative review results presented by Greenhalgh et al. [9] and the systematic review conducted by Banzi et al. [10]. The work of Greenhalgh et al. focused on determining the meaning of health research impact, how to measure such impact and reviewed strengths and limitations of different approaches to assess impact. The search strategy of this narrative review included publications between 2005 and 2014 [9]. The systematic review by Banzi et al. focused on identifying common approaches to research impact assessment, categories of impact and their respective indicators. The search strategy was limited to 1990-2009 [10]. This systematic review did not include some relevant methodological frameworks, such as the SIAMPI model, Contribution Mapping, Exchange Model and

Research Contribution Framework, which are essential to measure the impact of healthcare research via interactions between stakeholders and researchers.

Although both reviews presented similar results around methodological impact frameworks, their search strategies were based on earlier dates compared to our systematic review, which was from inception until 2017. Therefore, the systematic review presented in Chapter 3 presented for the first time a collective summary of five major impact categories across the 24 methodological frameworks identified into a single matrix. This matrix led to an exhaustive and comprehensive framework 'pathways to research impact' to measure healthcare research impact. This novel matrix has the potential not to only inform stakeholders involved in healthcare research, but stakeholders involved in other research areas such as socio-economic impact of research. Furthermore, the 'pathways to research impact' framework could be further developed by including new types of impact and impact metrics, associated to a specific research area.

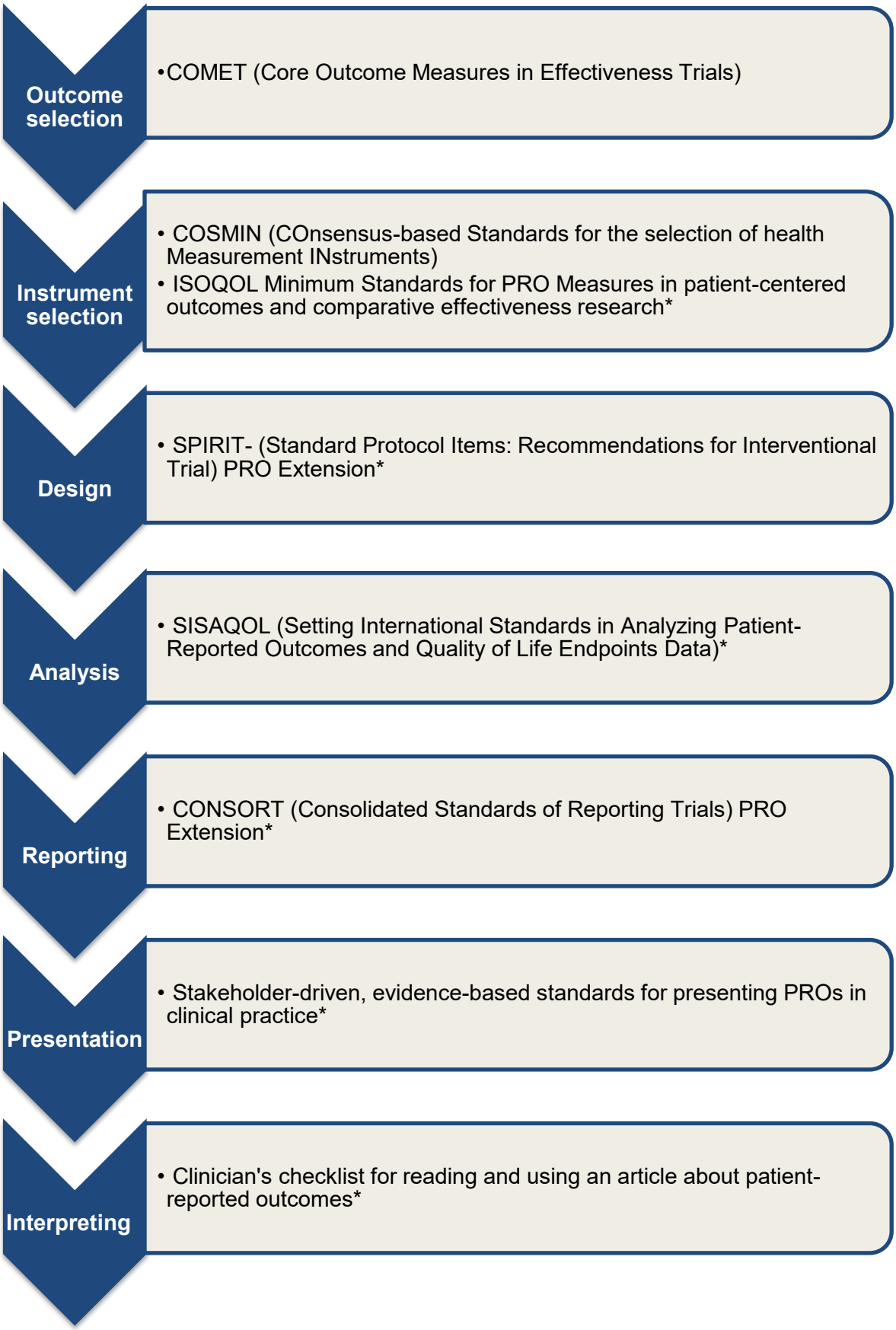
B. PRO trial data: potential and real-world impact

Chapter 4 highlighted methodological barriers and facilitators to realising PRO trial impact. These barriers and facilitators pertained to aspects surrounding PRO trial design, PRO trial conduct and analysis, PRO trial reporting and uptake of PRO trial results in practice. This is the first comprehensive review, which summarises potential PRO trial impact. Moreover, the findings regarding barriers to impact are consistent with a number of papers highlighting challenges with PRO trial design, analysis, reporting and interpretation. These methodological issues have been repeatedly noted in the literature and it is an important area to address to ensure PRO trial impact [11-17].

Challenges associated with PRO data collection and non-reporting of PRO data may potentially lead to significant research waste, including waste of resources, time and patients' efforts expended in PRO data collection, which may hinder the use of PRO data for patients and society [12, 18]. Greater consideration should be given at the design stage of a trial about how to maximise PRO trial data impact. Academic trialists, policy-makers and funders can all play an important role.

In addition, a number of authors have emphasised the importance of adhering to existing PRO guidance, as it may help in the realisation of PRO trial data to benefit patients and society. A recent systematic evaluation of PRO protocol content and reporting in cancer clinical trials demonstrated a positive link between good design and reporting, which suggests that adherence to protocol guidelines could result in improved reporting [19]. In the last decade, PRO researchers have developed initiatives focused on the outcome and instrument selection, design, analysis/interpretation, reporting and presentation of PRO data, rather than focusing on the maximisation of PRO trial research and how to measure such impact. The selection of relevant outcomes, including PROs as appropriate, is an essential consideration in trial design. Figure 1 depicts the existing PRO initiatives, which provide guidance on the use of PROs at the different stages of a clinical trial.

Figure 1. PRO initiatives



* Methodological tools promoted by the PROTEUS Consortium

The COMET (Core Outcome Measures in Effectiveness Trials) initiative has focused on the development and application of standardised core outcomes sets (COS) in clinical trials to provide guidance on the minimum requirements COS should be measured and reported in a clinical trial. Adherence to COMET guidance should lead to improved PRO trial design and selection of outcomes, whilst allowing PRO and clinical outcomes from trials to be compared, contrasted and combined [20].

The COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) initiative provides guidance to researchers and clinicians in the choice of outcomes and outcome measurement instruments [16, 21]. ISOQOL recommendations focus on promoting the use of PRO measures to inform PRO comparative effectiveness research, which has the potential to improve effectiveness and efficiency of healthcare [22].

The SPIRIT- (Standard Protocol Items: Recommendations for Interventional Trial) PRO Extension provides specific guidance around PRO protocol development [23]. SISAQOL (Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data) [24] aims at providing evidence to standardise the analysis and interpretation of PRO and quality of life data from cancer clinical trials, whereas CONSORT PRO Extension provides guidance to facilitate optimal reporting of trials in which PROs are primary or secondary outcomes, which could inform clinical practice and health policy by increasing clinician confidence in published PRO research [25].

Other research initiatives have also set out to provide guidance around presentation and interpretation of PRO trial data. For instance, the stakeholder-driven, evidence-based standards for presenting PRO data provides guidance on how to graphically

present PRO data to patients and clinicians [26], while the clinician's checklist for reading and using a PRO article aim at facilitating a tool for clinicians to assess a PRO clinical trial in order to make practice and treatment decisions for patients. Therefore, adherence to PRO-specific guidance has the potential to maximise real world PRO trial data by facilitating optimal selection of outcomes and instruments, design, analysis, reporting and presentation and interpreting of PRO trial data to PRO stakeholders and patients.

These initiatives have involved a diverse range of international stakeholders (e.g. SPIRIT-PRO Extension involved clinical trial research personnel, PRO methodologists, funders, journal editors, policy makers and patient advocates, among others). However, evidence from Chapters 4 and 5 suggests that simply improving the results and presentation of PRO data through the adoption of the approaches above is unlikely to be sufficient to fully realise PRO impact.

To date, there has been no other research study examining the impact of PRO trial data through the assessment of REF 2014 case studies. In 2015, a study conducted by Greenhalgh and Fahy [27] assessed the REF 2014 case studies submitted under the subpanel A2 (Public Health, Health Services Research and Primary Care) in order to explore the nature and mechanism of community-based health sciences impact. The main type of study examined was clinical trials. Although Greenhalgh and Fahy adopted a different search strategy and had different eligibility criteria to the research undertaken in Chapter 4 of this thesis, similar findings were presented. The research contained within the case studies was said to have mainly influenced clinical guidelines, healthcare policy and clinical practice and to a lesser extent, improvements in health outcomes and support cost savings [27]. Moreover, the structure of the REF 2014 case studies allowed capturing the impact of the research

and demonstrated impact on healthcare policy-making, which arises in the mid-term. However, the case studies did not capture research impact in the long-term such as health & health systems impact, health-related & societal impact and broader economic impact. Therefore, there is a need to assess real-world PRO trial impact and to do it through other methods that will capture such impact in the long-term in order to identify the pathways to PRO trial data impact.

C. The impact of PRO trial data - perspectives from international stakeholders: a qualitative study

While the systematic reviews identified some types of impact, impact metrics and barriers and facilitators associated with PRO impact, it was felt that deeper understanding was required. Therefore, a number of key international stakeholders were interviewed to gain a richer understanding of the issues. In Chapter 5, the international PRO stakeholders identified a number of key areas for PRO trial impact. These included policy-making, including changes to clinical healthcare practice and guidelines, drug approval, pharmaceutical and promotional labelling claims as the most common type of PRO trial impact. Health-related & societal impact and broader economic impact were the least common types of impact discussed by PRO international stakeholders.

Moreover, international stakeholders discussed different PRO-specific methodological barriers and facilitators to maximising the impact of PRO trial results. These related to PRO trial design, PRO conduct and analysis, PRO reporting and dissemination, and uptake of PRO results. Stakeholders identified a number of areas requiring action presented below in Box 1.

Box 1. Key recommendations to maximise the impact of PRO trial data

- Development of a law or regulation to enforce the collection of PRO data*[Participant: 8]
- Adherence to current PRO guidance*[Participant:11] **[12, 17, 28-33]
- Development of PRO measures while considering health utilities for HTA use*[Participant:14]
- Standardisation of PRO tools among therapeutic areas to improve analysis*[Participant:5]
- Open access publications*[Participant:3,15,24]
- Inclusion of a simple English summary of the trial results for use of patients*[Participant:15]
- Availability of more journals publishing PRO trial data*[Participant:10]
- Adequate funding for PRO trial components*[Participant:2,16,22]
- Funders clearly expressing their positions about PROs and what they expect from the funded PRO research*[Participant:20,21,22]
- Communication of PRO research widely through the involvement of key opinion leaders, specifically at healthcare conferences*[Participant:2,18,21]
- Empowerment of patients through their involvement in discussions and dissemination of PRO trial results*[Participant:15,18,21,23,24]
- Endorsement of PRO trial studies by key societies to disseminate PRO results and influence healthcare policy*[Participant:2,18]

*Qualitative study participant numbers, see Chapter 5 for further details.
**Systematic review in Chapter 3. References from the systematic review have been included in the reference list of this Chapter to inform the reader.

Although, several qualitative and quantitative metrics were proposed to measure the impact of PRO trial data; interviewees acknowledged that measuring the impact of PRO trial data through metrics is a challenging task, as it is not always possible to capture the full impact of PRO trial research. Therefore, further work is needed to identify and develop more comprehensive ways of measuring PRO impact. Unfortunately, poor quality PRO clinical trials have hampered the usage of PRO data not only in regulatory decision-making, but also in the use of clinical guidelines, and in clinical decision-making (Chapters 4 and 5). Thus, it is crucial to strengthen national and international collaborations to help in the realisation of PRO trial findings in practice and maximise the benefit to patients and society.

A Policy Review by Kluetz et al. [34] presented the perspectives of three international regulators around opportunities to incorporate PRO trial data in regulatory decision-making. The Policy Review highlighted the importance of improving international stakeholder collaboration and standardisation of PRO concepts, tools, methodology (SPIRIT-PRO extension [23]), analysis, presentation of PRO data and communication of PRO trial results to patients in order to incorporate PRO data into regulatory decision-making rigorously [34]. Although this Policy Review presented similar findings to the qualitative study (Chapter 5), the former did not capture the perspectives of other PRO stakeholders (e.g. academics, policy-makers and funders), who could have emphasised different opportunities to incorporate PRO data into regulatory decision-making. In addition, the same review did not focus on determining PRO impact measurement metrics.

One key stakeholder group that can help drive up standards are regulatory agencies such as the MHRA (The Medicines and Healthcare products Regulatory Agency, EMA (European Medicines Agency) and FDA (The Food and Drug Administration). It is therefore pleasing to see that incorporation of the patient experience into international regulatory decision-making and drug development is becoming of increasing interest [34, 35]. As an example, in 2016 the FDA 21st Century Cures Act (Cures Act) mandated the development and implementation of strategies to incorporate patient input in drug development, biological products, and devices in FDA's decision-making process [36]. Recent FDA initiative, PFDD (patient-focused drug development), is involving a range of stakeholders (patients, researchers, medical product developers and others) to incorporate the ‘voice’ of patient experience data of and other relevant information from patients and caregivers to inform the development of medical product and regulatory decision-making [37]. In

2016, the EMA also published Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man [38], which aims at providing guidance around PRO selection and application in cancer clinical trials.

Additional examples of broader international collaboration includes PROTEUS consortium (Patient-Reported Outcomes in Trials: Engaging Users and Stakeholders), funded by the Patient-Centred Outcomes Research Institute (PCORI) funded. PCORI aims to fund research to help patients and healthcare stakeholders make informed decisions surrounding healthcare treatments and disseminating and implementing research findings [39]. PROTEUS aims to engage key stakeholder groups who design, conduct, report, and benefit from PRO data in clinical trials. The initial work of this consortium is focused on dissemination and uptake of the tools detailed above (Figure 1) [40]; however this multi-stakeholder international consortium may offer opportunities to maximise PRO impact and uptake of data.

Recommendations for future research

The work presented in this thesis has highlighted the need for further research in order to measure and maximise the impact of PRO data from clinical trials.

A. Applicability of methods to other medical research areas

Methods undertaken within this thesis can be applied to further medical research areas (Chapters 3, 4 and 5) to better understand the impact realised by particular disciplines and identify barriers and facilitators to maximise impact. The majority of the literature cited in this thesis focused on oncology; however, PROs are used in multiple disciplines such as rheumatoid arthritis, orthopaedic procedures and cardiovascular conditions. Therefore, there is a need to optimise the use of PROs across medical disciplines, promote multi-stakeholder involvement whilst considering

collaboration across disciplines, especially important given patients with complex needs and multi-morbidities.

B. Adherence to guidelines

Evidence in this thesis suggests that suboptimal PRO trial design/implementation/analysis/reporting may have hampered the arising impact. Therefore, PRO researchers should adhere to existing international consensus guidelines around PROs to maximise the impact of PRO trial data (Box 1). There have been a number of trial guidelines that could be used to improve the quality of PRO use in clinical trials including: COMET [41], COSMIN [42], SPIRIT-PRO Extension [23], SISAQOL [24], CONSORT PRO Extension [25], evidence-based recommendations for PRO data display to improve interpretability among clinicians, patients and PRO researchers [43, 44], clinician's checklist for reading and using an article about patient-reported outcomes [45], the FDA Guidance for Industry [46] and the EMA Appendix 2 [38].

A further important area for research is to evaluate the uptake and use of these guidelines in practice [18]. Preliminary evidence suggests that the use of CONSORT/CONSORT-PRO guidance is associated with improved reporting [47, 48]. However, a 2008 analysis of “Instructions to Authors” among 165 high impact medical journals demonstrated that only 38% included the original CONSORT statement within their instructions. Additionally, no more than 3% of the journals mentioned the CONSORT PRO Extension [47]. Measuring the uptake of PRO guidelines and impact on trial design, conduct and analysis, and reporting could be used by journal editors, funders and other key stakeholders to determine the potential benefits of endorsing and promoting guidelines. Potential methods to measure the uptake of PRO guidance include qualitative interviews among PRO

stakeholders, randomisation of authors or reviewers to the use of checklists or case studies focused on determining the impact of PRO data between trials that adhere and do not adhere to PRO guidance. Adherence to guidance should be adopted and enforced by academic and industry researchers, funders, IRBs (institutional review boards) and ethic committees and journal editors to minimise research waste and maximise the impact of PRO trial data for patients and society. Nonetheless, this is only a first step in generating impact by helping provide high quality PRO data. A further step in the generation of PRO impact is the development of a tool to aid stakeholders planning studies involving PROs to maximise PRO impact.

C. Journals endorsement and enforcement to maximise the impact of PRO trial data

Findings from this thesis (Chapters 4 and 5) suggested that optimal reporting of PRO trial is essential to maximise the uptake of PRO trial results in practice. However, it is essential that journal editors endorse and enforce the publication of PRO trial manuscript by making available more journals that support PRO research; provide open access to publications and include a simple English summary of the trial results specially for the use of patients (Box 1). An important area of research is to determine the number of current journals that endorse PRO trial research and identify those that incorporate patient and public partners in the peer-reviewed process to make PRO trial data more accessible to patients.

D. Assessment of clinical guidelines to determine the impact of PRO trial data

Assessment of clinical guidelines could also be used to determine the impact of PRO trial data in pharmaceutical labelling claims, clinical practice and healthcare outcomes. Although Chapter 4 demonstrated that direct and indirect PRO trial data

can lead to changes in clinical guidelines; the small number of REF impact case studies (n=24), that demonstrated this type of impact, limited the number of clinical guidelines assessed. Therefore, a comprehensive systematic review of clinical guidelines would provide further evidence on the uptake and use of PROs in guideline development, help identify clinical areas which are, or are not using PROs and provide useful case studies to help realise PRO impact.

E. Routine clinical practice

Increasingly, PROs are used in routine clinical practice. In England, the drive to using PROs in clinical practice has been increasing since 2009 with the National Health Service (NHS) PROMs programme, a way of assessing the quality of care delivered in the NHS from the patient's perspective. PROs have been used for assessing the quality of care delivered by a number of elective procedures: hip and knee replacement, and up to September 2017, varicose vain and groin hernia surgery [49]. The availability of PRO tools for use in PROMs specific procedures, alongside the collection of clinical data, may lead to the routine collection of outcomes that matters to patients instead of focusing on functioning or disease specific aspects. Although there are plans to collect patient's data in other procedures like coronary revascularisation, it is important to do more research in this field to improve healthcare services and identify priority healthcare areas that will benefit from the inclusion of PROs in routine clinical practice. The International Society for Quality of Life (ISOQOL) [50] has developed a user-friendly guide, *User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice* [51], to help clinicians in the incorporation of PROs in clinical practice. This guide might be used by other researchers as a step forward in the incorporation of PROs in

clinical practice. Box 2 presents an example of successful incorporation of PRO data in routine clinical practice.

Box 2. Use of PRO data in routine practice

A US single centre randomised controlled trial evaluated whether systematic web based collection of symptoms during chemotherapy treatment improved health-related quality of life (HRQL), survival, quality-adjusted survival, emergency room (ER) visits and hospitalisation, among patients receiving chemotherapy for advanced solid tumours. HRQL improved among the intervention group (34% v 18%), as measured by the EQ-5D. In addition, ER admissions (34% v 41%; P = 0.02) and hospitalisations (45% v 49%; P = 0.08) were less frequent among the intervention group, a longer duration of chemotherapy treatment (mean, 8.2 v 6.3 months; P = 0.002) and superior quality-adjusted survival (mean of 8.7 v. 8.0 months; P = 0.004) [52, 53].

Therefore, the collection of routine care PRO data (see Box 2) has the potential to inform clinical decision making by allowing early detection of problems, providing healthcare according to the patient's needs and; prioritising patients who needed urgent care [54, 55]. Hence, the collection of PROs in routine practice has the potential to generate impact by promoting nuanced conversations between patients and clinicians, symptom management, improving patients' health outcomes and better allocating healthcare resources.

F. PRO impact metrics in routine clinical care

While studies have suggested there is an impact from using PRO in clinical practice, it is important that the extent of that impact can be measured. Therefore, there is a need to identify impact metrics to determine the extent to which collecting PRO in routine clinical practice has an impact. A number of metrics have been identified through the systematic review presented in Chapter 4 and interviews with international stakeholders (Chapter 5). Suggested metrics could include reduced

hospitalisation and length of stay, reduction in the number of outpatient visits and emergency admissions, improvements in quality of life, reduction in the number of work loss days, and cost savings. PRO impact metrics in routine clinical care have the potential to inform hospital performance and patient satisfaction with care, identify unmet needs, inform future funding allocation and set healthcare priorities. Thus, further research is needed to develop a framework that captures the impact of PRO data in routine clinical care, which may benefit patients, funders and healthcare systems.

A. Development of a law or regulation to enforce the collection of PRO data

The development of a governance framework in the UK (Box 1), including legal requirement, to promote routine collection, processing and sharing of PROMs may have the potential to benefit society through the improvement of health outcomes and better use of healthcare resources. The first step to achieve this integrated approach is the establishment of a multi-stakeholder steering group including patients, clinicians, PRO methodologists, regulators, policy-makers and NHS digital to standardise PROM data and to establish good practice [55].

B. Development of PRO measures while considering health utilities for HTA use

Frequently, the data used in HTA often does not include PRO data or includes high levels of missing PRO data. In other instances, HTA increasingly uses generic measures that may not be cover all the dimensions of relevance to some specific health conditions or uses disease specific measures, which require mapping to generate health utility values [56]. Therefore, further work is required to provide high

quality PRO data for HTA. In some instances, new disease specific utility measures may be warranted.

C. Patient empowerment

The involvement of patients and public advocates in the conduct of PRO trial research is essential as PRO data is considered the 'voice of the patient'. Although patient advocacy groups are frequently involved in PRO trial research, it is essential to develop user-friendly tools, training and support for patient advocates in the co-design, conduct and analysis and reporting of PRO clinical trials.

D. Clear funder position and adequate funding

Chapter 5 demonstrated the need to specify the requirements and expectations, in terms of impact, funders have when funding PRO trial research. Funders highlighted the importance of academic and industry trialists to consider the impact of PRO trial research *'a priori'* and beyond primary research related impact. However, there is a lack of guidance by PRO funders. Thus, an important area of research is to determine through qualitative methods, the requirements and expectations funders have when supporting PRO trial research. The findings could inform the development of guidelines for academic and industry trialists, which can help in the maximisation of resources and PRO trial data whilst benefiting patients and society.

Strengths and limitations of the thesis

There has been little previous research investigating the impact of PRO trial research or determining impact measurement metrics or facilitators to maximise PRO-specific research impact. Thus, the research within this thesis contributes novel findings to the research impact and PROs fields. The main strength of this doctoral thesis was the use of a mixed-methods approach to integrate qualitative and

quantitative research. The findings from the qualitative study (Chapter 5) shed additional light on the systematic reviews findings (Chapters 3 and 4) by providing further understanding on how to maximise the impact of PRO trial results to benefit patients and society.

Findings have been disseminated in the following ways:

- One publication in a high impact journal (PLOS Medicine, Chapter 3)
- Publication of Chapter 4 in Health Quality of Life Outcomes Journal, Chapter 4.
- One oral presentation
- Three poster presentations
- Two public engagement activities: 1) 'Research Changes Lives', event hosted by the National Institute of Health Research (NIHR) and 2) Show and Tell event for the Centre for Trauma Sciences Research (CTSR) at the University of Birmingham.
- A radio interview in the programme Practical Theorist by Birmingham Hospitals Broadcasting Network (BHBN) radio.
- A two-day course hosted by Professor Calvert and the Centre for Patient Reported Outcomes Research (CPROR) at the University of Birmingham, November 2018.
- Furthermore, the research was awarded the Michael K. O'Rouke Best PhD Publication for the College of Medical and Dental Sciences, University of Birmingham (Chapter 3).

In addition, the work presented in Chapter 3 has attracted the attention of the Wellcome Trust, who are currently reviewing the socio-economic impact of research.

Their interest in the review has resulted in a number of meetings to discuss the findings from Chapter 3.

A. Measuring healthcare research impact using methodological frameworks

The findings of Chapters 3 and 4 were presented using PRISMA guidelines [57] for systematic reviews. The main strengths of this systematic review (Chapter 3) are adherence to Cochrane [58] and CRD guidelines [59] and development of a comprehensive search strategy, which extended through forwards/backwards citation searching, hand searching reference lists, and expert communication. Furthermore, a second reviewer independently conducted the search strategy, screened the retrieved studies, identified eligible studies and extracted data. The main limitation was the identification of over 50% of the included studies through different methods other than bibliographic database searching, representing poor indexing. Nonetheless, different bibliographic search techniques were adopted to avoid the exclusion of relevant articles. In addition, although the search strategies did not include language restrictions, non-English databases were not searched. Thus, the exclusion of potential articles was a possibility; however, every effort was made to include all the relevant articles.

B. PRO trial data: potential and real-world impact

The main strengths of this systematic review (Chapter 4) are again its rigorous methodology and inclusion of a second researcher at the different stages of the study. The main limitation was poor indexing, which means the exclusion of potential articles despite conducting an exhaustive search strategy. This was also mitigated by adopting different bibliographic search techniques. The systematic review results were limited to the assessment of only UK-based impact case studies, restricting the

generalisability of the results. Nonetheless, 30% of the trials assessed were categorised as international trials. In addition, it was not always possible to demonstrate direct attributable real world PRO-related impact, which can be partly explained by the challenges around measuring research impact. A further limitation was the inclusion of a high number of articles focused on oncology clinical trials, in the first section of the systematic review. The findings may require reproduction in other clinical fields to demonstrate generalisability.

C. The impact of PRO trial data - perspectives from international stakeholders: a qualitative study

In order to gain deeper understanding about types of PRO trial research impact, impact measurement metrics and barriers and facilitators to maximise PRO trial research impact; a qualitative study was conducted (Chapter 5). The qualitative study followed COREQ (Consolidated Criteria for Reporting Qualitative Research) and the ethical standards outlined by the University of Birmingham Code of Practice for Research [60, 61]. The main strength of the study was the inclusion of 24 internationally recognised PRO stakeholders, which allowed exhaustive discussion of the topic. In addition, the conclusions of this qualitative study may be transferable to other stakeholders working on PRO clinical trials, who are knowledgeable about the topic.

The study presented some limitations. Team members (MC/DK/AS) had a previous collaborative relationship with some of the interviewees, which could have limited the range and experience of stakeholders included and; potentially led to the misinterpretation of the data collected. To mitigate this, a multidisciplinary team including methodologists, clinical and non-clinical experts were involved to support the analysis and interpretation of the data. Furthermore, snowballing sampling was

implemented to recruit further participants outside the pool already known to the research team. The lack of saturation at stakeholder cohort level was also considered a limitation, as it would have allowed drawing stronger conclusions around similarities and differences between stakeholder groups. Although several stakeholders highlighted the impact of PRO trial from different clinical conditions such as irritable bowel syndrome, erectile dysfunction and rheumatoid arthritis, the majority of the interviewees discussed the impact of PRO data from oncology clinical trials. This should be taken into account when interpreting the results. Future qualitative work should be undertaken in differing clinical areas to explore alternate perspectives.

Conclusions

The studies presented in this thesis addressed three important topics within the area of PROs: a) the impact of PRO trial data, b) impact measurement metrics and c) barriers and facilitators to maximise the impact of PRO trial research on patients and society.

The findings demonstrated that measuring the impact of PRO trial data is an essential exercise to demonstrate accountability, in terms of efficiency and effectiveness to funders, stakeholders, patients and society; to minimise research waste and; maximise the impact of PRO trial data through understanding the pathways to PRO trial impact. However, measuring PRO trial impact is challenging, as it is difficult to unpick the exact attribution of PRO data when combined with other ‘clinical’ outcomes. Furthermore, to capture the impact of PRO trial data is necessary not to only use ‘quantitative’ metrics but to include qualitative methods and exhaustive case studies.

A key issue in maximising the impact of PRO trial data is the existence of methodological issues regarding the design, conduct, analysis and report of PRO clinical trials. There are a number of barriers that need to be addressed to realise the impact PRO trial data, comprising lack of adherence to PRO guidance, awareness of the importance of PRO and a law or regulation in the UK to enforce the collection of PRO trial data in clinical trials. Therefore, there is a need of a broader collaboration among national and international PRO stakeholders to maximise the benefit of PRO trial data to patients and society.

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Appendices

Appendix 1 - Assessing the impact of healthcare research: A systematic review of methodological frameworks

Appendix 1.1 Supporting information published online for Publication 1 (presented as published)

Cruz Rivera S, Kyte DG, Aiyegbusi OL, Keeley TJ, Calvert MJ. Assessing the impact of healthcare research: A systematic review of methodological frameworks. PLOS Medicine. 2017;14(8):e1002370. doi: 10.1371/journal.pmed.1002370.

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) <1946 to May Week 1 2017>

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1. impact.ti. (141399)
2. (framework or pathway or tool or toolkit or measuring or categori$ing or demonstr*).ti. (223107)
3. research/ or biomedical research/ or health services research/ (290061)
4. 1 and 2 and 3 (63)

Database: Embase <1974 to 2017 May 10>

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1. impact.ti. (229826)
2. (framework or pathway or tool or toolkit or measuring or categori$ing or demonstr*).ti. (290900)
3. health services research/ or medical research/ or research/ (328545)
4. 1 and 2 and 3 (84)

Database: HMIC Health Management Information Consortium <1979 to Jan 2017>

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1. impact.ti. (4716)
2. (framework or pathway or tool or toolkit or measuring or categori$ing or demonstr*).ti. (6295)
3. exp Research/ or exp Health services research/ or exp Medical research/ (6445)
4. 1 and 2 and 3 (9)

Database: CINAHL Plus/Interface - EBSCOhost Research Databases

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1. impact.ti. (60752)
2. (framework or pathway or tool or toolkit or measuring or categori$ing or demonstr*).ti. (48511)
3. research/ health services research/ (11310)
4. 1 and 2 and 3 (16)

PRISMA Checklist

Section/topic	#	Checklist item	Reported on section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Introduction
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, paragraph 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1_Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, paragraph 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction and analysis

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	NA
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on section
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Major impact categories
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	NA

		[see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusions
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 1.2 – Impact metrics to measure healthcare research

Research-related impact	***Research and innovation outcomes***	Publications
		Peer-reviewed articles (journal impact factor)
		Relative download rate and website hit rate
		Citation rates
		Request of reprints
		Reviews and meta-analysis
		Products, patents, medical interventions and translatability
		Research methods/ methodological contributions
	Dissemination and knowledge transfer	Conferences, seminars, workshops and academic presentations
		Teaching
		Number of reads for published articles
		Citations rates in non-journals media such as newspapers, patents and clinical guidelines
		Research uptake by different disciplines
		Mass media and appearances e.g. Twitter and blogs
	Capacity building, training and leadership	PhD and post-doc studenships
		Number of researchers and research-related staff
		Leadership and awards
		Academic careers advancement
		Subsequent grants/funding received
		Follow on research by self or others
		Journal editorships, board or advisory comittees
	Academic collaborations, research networks and data sharing	

Influencing and involvement in policy making	***Level of policy-making***	Presentations to decision-makers
		Influence on public policy debate
		Information base for political and executive decision making
	Type and nature of policy impact	Changes to legislation/ regulations/ governments policy
		Influence and involvement in decision-making processes
		Changes to clinical or healthcare training, practice or guidelines
	Policy networks	Collaborative research with industry (co-authorship)
		Staff movement between academia and industry
Health and health systems impact	***Evidence-based practice***	Improving diagnostics and drug response prediction
		Fullfilling previously unmet clinical needs
	Quality of care and service delivery	Improved health outcomes
		Surveys such as patient satisfaction and PRO instruments
		Making services more accesible for local communities
		Reduce waiting times
	Improved information and health services management	Cost reduction in the delivery of existing services
	Cost containment and effectiveness	Cost savings
		Increased service effectiveness
	Resource allocation	New funding attributed to a research intervention in question
		Equity such as improved allocation of resources at an area level, better targeting and accessibility
	Healthy worforce	Reduction in the days of work lost to a particular illness

Health related and societal impacts	***Health literacy***	Activities to change health-risk behaviours such as campaigns, strategies and establishment of academically-led units
	Health knowledge, attitudes and behaviour	Increased levels of public engagement with science and research
		Focus groups to analyse knowledge, attitudes and bahaviours
	Improved social equity, inclusion or cohesion	Surveys to dertermine social welfare such as reductions in child mortality, improvements in maternal health
Broader economic impacts		Attracting R&D investment from the NHS, medical charities and overseas business
		Income from intellectual property
		Spill over effects
		Patents granted/licences awarded and brought to market
		Spin-out companies such as growth in revenue and number of employees generated in universities or consultancy companies
		Research contracts and income from industry

Appendix 2 - The impact of patient-reported outcome (PRO) data from clinical trials

Appendix 2.1 Supporting information published online for Publication 2 (presented as published)

Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. Health Qual Life Outcomes. 2019;17(1):156. Published 2019 Oct 16. doi:10.1186/s12955-019-1220-z

Appendix 2.1 Search strategies

Database: Ovid MEDLINE(R) <1946 to Dec Week 4 2018>

Search Strategy:

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2 (policy or health policy* or decision making or healthcare policy or policy making or policy initiative or reimbursement decision*).m_titl. (48587)

3 (clinical training or clinical practice or clinical guideline*).m_titl. (25046)

4 (healthcare training or healthcare practice or healthcare guideline*).m_titl. (84)

5 (labeling claims or labelling claims or promotional claims or drug approval).m_titl. (291)

6 2 or 3 or 4 or 5 (73779)

7 1 and 6 (9916)

8 (impact or influence or inform or role or implication* or integrati* or relationship*).m_titl. (1100499)

9 7 and 8 (1231)

****

Database: Embase <1974 to 2019 Jan 04>

Search Strategy:

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3 (clinical training or clinical practice or clinical guideline*).m_titl. (37567)

4 (healthcare training or healthcare practice or healthcare guideline*).m_titl. (116)

5 (labeling claims or labelling claims or promotional claims or drug approval).m_titl. (513)

6 2 or 3 or 4 or 5 (104122)

7 1 and 6 (14192)

8 (impact or influence or inform or role or implication* or integrati* or relationship*).m_titl. (1521903)

9 7 and 8 (1920)

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Database: HMIC Health Management Information Consortium <1979 to January 2017>

Search Strategy:

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1 (HRQL or HRQOL or QOL or quality of life or health index* or health indices or health profile* or health status or PROM* or PRO* or patient reported outcome* or self assessed outcome* or patient assessed outcome* or self report outcome* or health utility or patient report* outcome* or patient report* measure* patient report* assessment* or self report* outcome* or self* report* measure* or self* report* assessment* or self assess*).m_titl. (51093)

2 (policy or health policy* or decision making or healthcare policy or policy making or policy initiative).m_titl. (7457)

3 (clinical training or clinical practice or clinical guideline*).m_titl. (1023)

4 (healthcare training or healthcare practice or healthcare guideline*).m_titl. (16)

5 (labeling claims or promotional claims).m_titl. (14)

6 2 or 3 or 4 or 5 (8485)

7 1 and 6 (1082)

8 (impact or influence or inform or role or implication* or integrati* or relationship*).m_titl. (17743)

9 7 and 8 (140)

****

Database: CINAHL+ <1979 to Dec 2018>

Search Strategy:

S1 TI HRQL or HRQOL or QOL or quality of life or health index* or health indices or health profile* or health status or PROM* or PRO* or patient reported outcome* or self assessed outcome* or patient assessed outcome* or self report outcome* or health utility or patient report* outcome* or patient report* measure* patient report* assessment* or self report* outcome* or self* report* measure* or self* report* assessment* or self assess* (662,953)

S2 TI policy or health policy* or decision making or healthcare policy or policy making or policy initiative (33,355)

S3 TI clinical training or clinical practice or clinical guideline* (17,158)

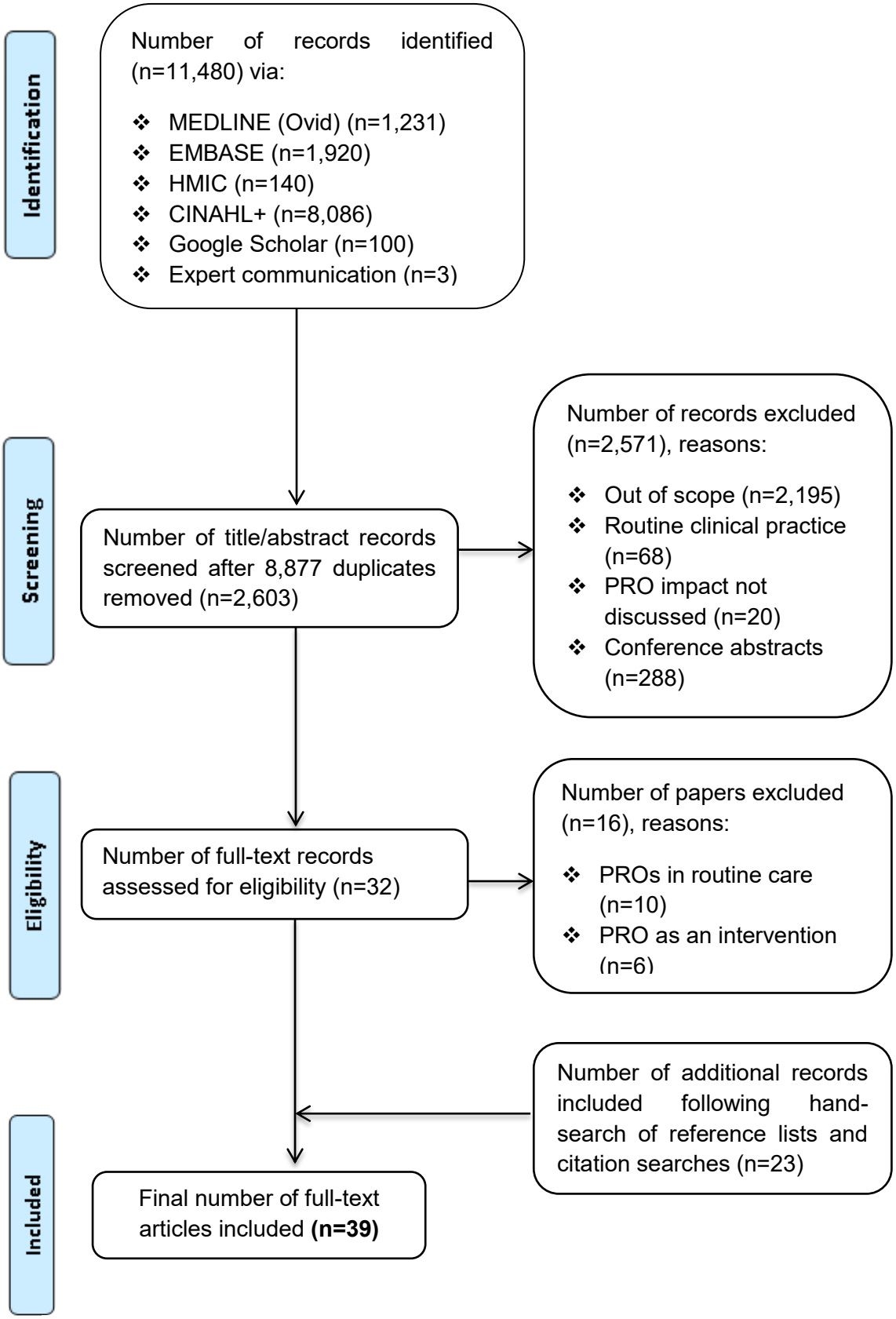
S4 TI healthcare training or healthcare practice or healthcare guideline* (956)

S5 TI labeling claims or promotional claims (20)

S6 S2 OR S3 OR S4 OR S5 (51,160)

S7 S1 AND S6 (8,086)

Appendix 2.2 - Systematic Review PRISMA Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement.

Appendix 2.3 - Study characteristics of the literature review

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
Revicki et al. (2000)[64]	Quality of Life Research	Guidance paper	Recommendations on use of HRQL data to support labelling and promotional claims	Informing drug approval
Bottomley et al. (2003)[52]	American Society of Clinical Oncology	Systematic review	HRQL in Non-small-cell lung cancer	Influencing clinical decision-making
Efficace et al. (2003)[34]	Journal of Clinical Oncology	Guidance paper	A checklist for evaluating HRQL in prostate cancer trials	Informing clinical decision-making
Goodwin et al. (2003)[56]	Journal of the National Cancer Institute	Literature review	HRQL in breast cancer trials	Informing clinical decision-making
Bjordal (2004)[35]	Annals of Oncology	Literature review	Impact of HRQL assessments within trials on clinical practice	Informing clinical decision-making
Arpinelli and Bamfi (2006)[71]	Health and Quality of Life Outcomes	Commentary	PRO trial data in drug development	Informing drug approval Informing reimbursement decisions Informing pricing decisions
Avery and Blazeby (2006)[36]	World Journal Surgery	Systematic review	HRQL in breast, prostate, lung and colorectal cancer trials	Informing clinical decision-making
Blazeby et al. (2006)[49]	Journal of Clinical Oncology	Literature review	HRQL in surgical oncology trials	Informing clinical decision-making Influencing informed consent
Patrick D. et al. (2007)[65]	Value in Health	Literature review	Use of PRO data to support medical product labelling claims (FDA perspective)	Informing drug approval
Efficace et al. (2008)[37]	European Journal of Cancer	Systematic review	HRQL in leukaemia trials	Informing clinical decision-making
Gujral et al.	Support Care Cancer	Systematic	Quality of life after	Informing clinical

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
(2008)[38]		review	colorectal cancer surgery	decision-making
Parameswaran et al. (2008)[39]	Annals of Surgical Oncology	Systematic review	HRQL in surgery for esophageal cancer	Influencing clinical decision-making Influencing informed consent
McNair and Blazeby (2009)[59]	Expert Reviews Pharmaeconomics Outcomes Research	Literature review	HRQL in gastrointestinal cancer trials	Informing clinical practice Informing clinical decision-making Inform shared decision-making
Au H. et al. (2010)[63]	Expert Review of Pharmacoeconomics & Outcomes Research	Review	HRQL in oncology clinical trials	Informing clinical decision-making
Doward L. et al. (2010)[66]	Health and Quality of Life Outcomes	Commentary	Use of PRO trial data to inform pharmaceutical labelling claims and payers	Informing drug approval Informing pricing decisions Informing reimbursement decisions
Snyder and Brundage (2010)[50]	Expert Reviews Pharmaeconomics Outcomes Research	Commentary	PROs in healthcare policy, research and practice	Informing clinical decision-making
Brundage et al. (2011)[76]	Quality of Life Research	Systematic review	PROs in Phase III randomised clinical trials	Informing clinical practice
Calvert et al. (2011)[5]	The Lancet	Systematic review	Quality of life in clinical trials	Informing clinical decision-making Informing health policy Informing drug approval
Ganz (2011)[55]	Journal of the National Cancer Institute	Commentary	Quality of life measurement in breast cancer trials	Informing clinical decision-making
Lemieux et al. (2011)[40]	Journal of the National Cancer Institute	Systematic review	Quality of life in breast cancer trials	Influencing clinical decision-making
DeMuro et al. (2012)[67]	Value in Health	Literature review	Reasons why PRO label claims were rejected and provide feedback from the regulatory perspective	Informing drug approval

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
			regarding the use of PROs in clinical trials	
Calvert et al. (2013)[41]	Health and Quality of Life Outcomes	Commentary	Implications of the CONSORT PRO extension on clinical trials and practice	Informing clinical practice Informing clinical guidelines Informing health policy Informing clinical decision-making
Jacobs et al. (2013)[42]	Quality of Life Research	Systematic review	HRQL in oesophageal cancer trials	Informing clinical practice Informing clinical decision-making Informing shared decision-making
Zagadailov E. et al. (2013)[72]	American Health & Drug Benefits	Literature review	Challenges and opportunities of incorporating oncology PRO trial data into reimbursement decisions	Informing reimbursement decisions
Anker et al. (2014)[69]	European Heart Journal	Literature review	Cardiovascular PRO clinical trials	Informing drug approval Informing reimbursement decisions
Dirven et al. (2014)[43]	European Journal of Cancer	Systematic review	PROs in brain tumour trials	Influencing clinical decision-making
Efficace et al. (2014)[45]	European Association of Urology	Systematic review	PROs in prostate cancer trials	Informing clinical decision-making
Efficace et al. (2014b)[45]	European Journal of Cancer	Systematic review	PROs in gynaecological cancer trials	Informing clinical decision-making
Basch E. et al. (2015)[62]	JAMA Oncology	Qualitative study	PRO trial data in cancer drugs development	Informing drug approval
Nixon et al. (2015)[74]	Farmeconomia. Health Economics and Therapeutic Pathway	Commentary	PRO data to support drug development decision-making	Informing drug approval Informing reimbursement decisions Informing clinical decision-making

Author	Journal	Publication type	Publication focus	Types of PRO impact discussed
Rees et al. (2015)[75]	Journal of Cancer Research and Clinical Oncology	Systematic review	PROs in colorectal cancer trials	Informing clinical decision-making
Rouette et al. (2015)[47]	Quality of Life Research	Literature review	Oncologists' perspectives on HRQL in trials among countries and specialities	Informing clinical decision-making
Gnanasakthy et al. (2016)[70]	Journal of Clinical Oncology	Literature review	PRO labelling for products approved by the Office of Haematology and Oncology Products of the FDA	Informing drug approval
Mercieca-Bebber et al. (2016)[60]	European Journal of Cancer	Systematic review	PROs in head, neck and thyroid cancer trials	Informing health policy Informing clinical practice Informing clinical decision-making
Coon C (2016)[68]	Clinical Therapeutics	Commentary	PRO oncology clinical trials	Informing drug approval
Hao Yanni et al. (2016)[57]	Clinical Therapeutics	Commentary	PRO oncology clinical trials	Informing reimbursement decisions Informing pricing decisions Informing clinical decision-making
McNair et al. (2016)[48]	PLOS One	Systematic review	PRO and clinical gastro-intestinal cancer data in trials	Informing clinical decision-making Informing clinical practice
Mott (2017)[61]	Oncology and Therapy	Qualitative study	PROs and lung cancer	Informing reimbursement decisions Informing clinical decision-making
Sztankay et al. (2017)[73]	BMC Cancer	Qualitative study	HRQL in patients with advanced non-small cell lung cancer	Informing shared decision-making

Appendix 2.4 - Potential types of PRO impact proposed

Clinical practice, clinical guidelines and health policy

A number of authors discussed the potential influence of PRO data on clinical practice, clinical guidelines and health policy. Several authors felt inclusion of PRO data on clinical guidelines may influence clinical practice, by fulfilling unmet clinical needs and leading to improved patient centre care by helping patients make more informed decisions on their care.[44,48,51,58-60,76] Three studies suggested that the inclusion of PRO data in clinical guidelines might ensure wider acceptance of guideline recommendations among patients, while enhancing implementation through health policy.[5,51,60]

Drug and device approval

Authors reported that PRO data is increasingly used to provide evidence for drug and device approval, especially in oncology clinical trials.[67,68] Eight publications discussed the influence of PRO data on pharmaceutical labelling claims by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[44,62,64-70] One publication suggested that PRO data may inform drug and device approval through communication of the benefits and harms of the intervention has to clinicians, patients and other consumers.[64]

An example given by one author was ruxolitinib (Jakafi™): an oral inhibitor to treat intermediate or high risk patients with myelofibrosis. This was the first FDA approved oncology drug that used PROs as an endpoint and followed FDA guidance to support a PRO based labelling claim.[72] The oncology drug was approved based on reduction in spleen volume and improvement in symptom severity (e.g. weight loss, night sweats, itching, abdominal pain/discomfort, bone pain, cough, inactivity, early satiety and fever), as measured with the total symptom score (TSS).

Pricing and reimbursement decisions

Three publications discussed the influence of PRO data on pricing decisions[57,66,71] and seven on drug reimbursement decisions.[5,57,61,66,69,71,74] Authors suggested that inclusion of

PRO data provided valuable information regarding the risk-benefit of new interventions. Several authors postulated that within the context of oncology treatment, PRO data have the potential to identify costly events reported by the patients in the trials. Hence, interventions with reduced toxicity and added PRO benefit may influence payer decision-makers.[72] Additionally, the inclusion of patient advocacy groups may influence the availability of interventions, enhancing the patient healthcare experience by incorporating the 'patient's voice' throughout payer decision-making.[57,66]

One such example illustrated in the literature, is the decision by NICE (2015) to recommend the use of nintedanib plus docetaxel (Vargatef®) as a treatment option for locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology. The drug approval was primarily based on improved survival, minimal adverse drug effects and fewer detrimental effects on health-related quality of life (HRQL) compared to chemotherapy treatment. PRO data suggested that HRQL, as measured by the EuroQol-5 Dimension (EQ-5D), the European Organization for Research and Treatment core quality of life questionnaire (EORTC QLC-C30) and the lung cancer–specific Quality of Life Questionnaire (EORTC QLQ-LC13) was similar in both groups.[57,96] However, the PRO measures also demonstrated better pain management in patients randomised to nintedanib plus docetaxel based on information from the pain items.[57,96] Therefore, additional drug benefits (symptom improvement and tolerability) were demonstrated through incorporation of PRO measurements into the trial, which similarly informed the reimbursement decision. The additional HRQL benefits may have been missed without the supporting PRO data within this trial.

Clinical decision-making

While reducing the impact of intervention toxicity and the impact on HRQL is important for drug labelling claims, it is also an important consideration for choices in clinical decision-making. According to Goodwin et al. (2003), when there is medical treatment equivalence, HRQL data has the potential to inform clinical decision-making by prioritising quality of life

outcomes and reduction in toxicity when making clinical decisions.[56] The authors conducted a systematic review of breast cancer clinical trials including PROs and determined that HRQL contributed to clinical decision-making within primary management (surgery, radiation and hormone therapies) and symptom control/supportive care setting of breast cancer.

In total, 26 publications presented evidence that PRO data may help in the selection of optimal treatment, patient's symptom experience and management, satisfaction with care and might predict prognosis, which has the potential to inform clinical decision-making based on the clinicians' critical appraisal and interpretation of the available information.[5,34-36,38-40,44-61,74]

Dirven et al. (2014) conducted a systematic review of PRO clinical trials in patient with brain tumours and demonstrated that HRQL can be used alongside overall and progression-free survival to inform clinical decision-making. One of the clinical trials included determined that the combination of concomitant and adjuvant temozolomide and radiotherapy has become standard care for newly diagnosed patients with glioblastoma.[53] This combination treatment led to significantly prolonged overall and progression-free survival, without negatively impacting HRQL in the long-term as measured with the EORTC QLQ-C30 questionnaire and Brain Cancer Module (BN-20).[53]

Shared decision-making

Shared decision-making is also important and four publications outlined the potential benefits of including PRO findings alongside other outcomes such as survival. This allowed patients and their clinicians to make an informed joint decision about treatment preferences and symptom management based on mutual understanding of treatment objectives and expectations.[44,58,59,73]

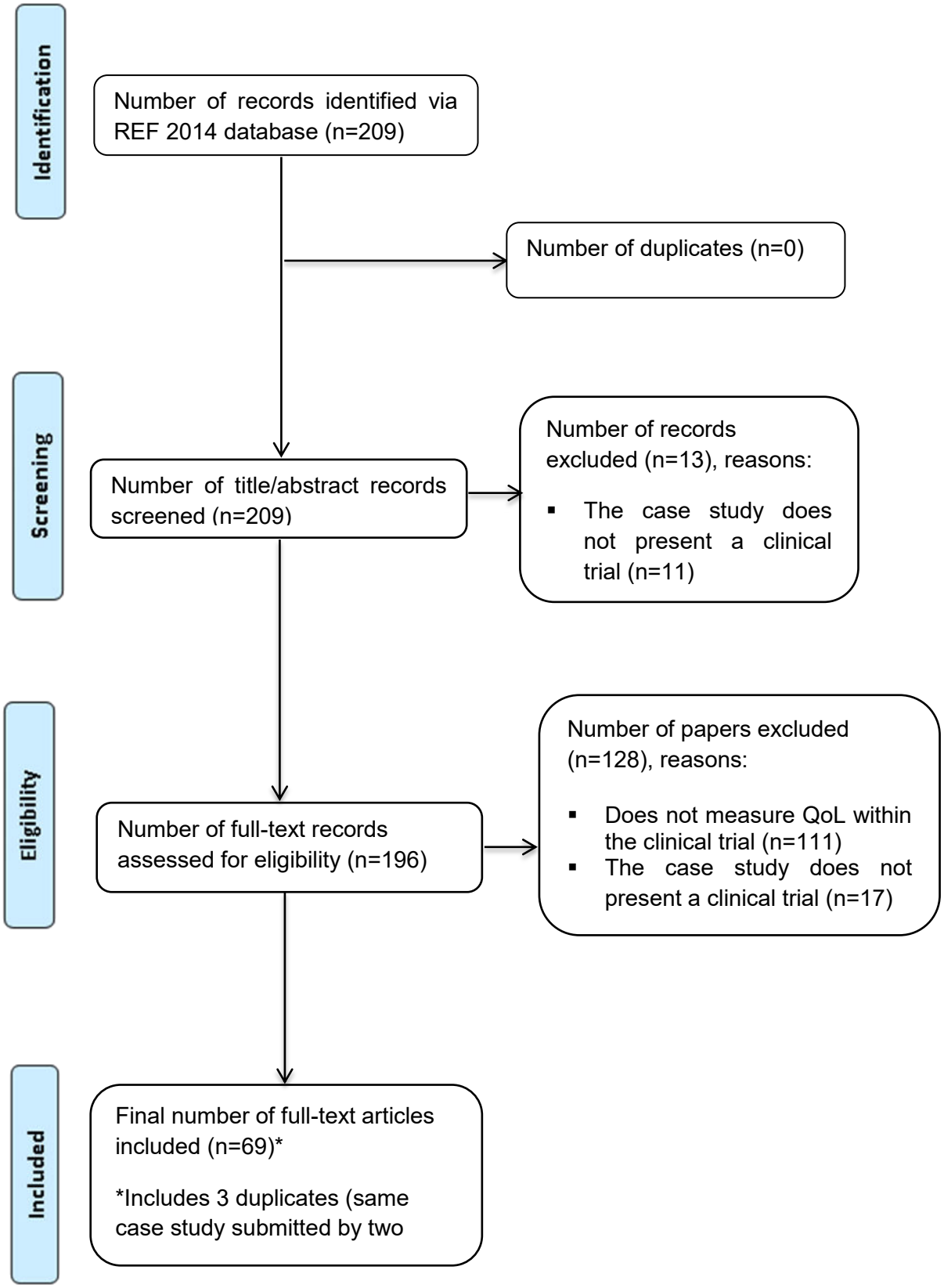
Sztankay et al. (2017) assessed HRQL during first-line chemotherapy with pametrexed and maintenance therapy (MT) among patients with advanced non-small cell lung cancer.[73] First-line chemotherapy for patients with advanced non-small cell lung cancer was shown to

improve overall progression-free survival. However, as measured with the EORTC QLQ-C30 and EORTC QLQ-LC13, MT compared to first-line chemotherapy was associated with lower HRQL and improvements in nausea, vomiting, appetite loss, constipation and pain. This information presented alongside survival data, allowed patients and clinicians to make real-world informed joint decisions regarding treatment options.

Informed treatment consent

Consent for treatment refers to the authorisation given by a patient to receive a treatment, once the clinician presents a diagnosis, relevant treatment options and respective risks and benefits to the patient.[97] Two publications discussed the influence of PRO trial data on treatment consent.[39,49] Parameswaran et al. (2008) presented a systematic review of two randomised controlled trials, 9 longitudinal studies and 11 cross-sectional studies. The authors determined that only 11 studies presented data that was capable of effectively informing patient consent. This statement was based on the assessment of the HRQL methodology of the studies, through the HRQL checklist by Efficace et al. (2003).[34] For instance, as measured with the EORTC-QLQ-C30 and MOS-SF36, one of the eleven studies determined that surgery for oesophageal cancer patients has a detrimental impact on quality of life in the postoperative stage (e.g. anastomic leaks, sepsis and cardiac and pulmonary complications) and in some cases; quality of life among survival patients does not improve in the long term.[39] Therefore, communicating HRQL and clinical data to patients after the intervention could help inform patients about relevant information regarding recovery and outcomes before undergoing an intervention and inform the consent process.

Appendix 2.5 - REF 2014 impact case studies PRISMA flow diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement.

Appendix 2.6 – REF case studies characteristics

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Heart failure: Improving the quality of life and survival of heart failure patients through Cardiac Resynchronisation Therapy (CARE-HF)	University of Birmingham	Public Health, Health Services and Primary Care	The effect of cardiac resynchronization on morbidity and mortality in heart failure	2005	Multi-centre, international randomised controlled trial	UK	Phase III	Time of death from any cause or unplanned hospitalisation as a consequence of a major cardiovascular event
Addressing a priority of people with rheumatoid arthritis: Managing fatigue	University of West England, Bristol	Allied Health Professions, Dentistry, Nursing and Pharmacy	Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therap	2011	Two-arm, parallel randomised controlled trial	UK	Not specified	Impact of fatigue at 18 weeks among group cognitive behavioural therapy (CBT) for fatigue self-management
Living with Multiple Sclerosis: development and use of effective self-management strategies	Brunel University	Allied Health Professions, Dentistry, Nursing and Pharmacy	Evaluation of the effectiveness of professionally guided self-care for people with multiple sclerosis living in the community: a randomized controlled trial	2002	Single-blind randomised controlled trial	UK	Not specified	Performance in activities of daily living, quality of life and independece among multple sclerosis participants, comparing the use of a self-care booklet with placebo

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Heart failure: Improving the quality of life and survival of heart failure patients through Cardiac Resynchronisation Therapy (CARE-HF)	Death from any cause Composite of death from any cause Unplanned hospitalization with heart failure The New York Heart Association (NYHA) class Quality of life at 90 days	Minnesota Living with Heart Failure questionnaire and EQ-5D	In the cardiac-resynchronization group, 82 patients died, as compared with 120 patients who had been assigned to medical therapy alone (20 percent vs. 30 percent; hazard ratio, 0.64; 95 percent confidence interval, 0.48 to 0.85; P<0.002)	Cardiac resynchronization reduced the risk of the composite end point of death from any cause or hospitalization for worsening heart failure (hazard ratio, 0.54; 95 percent confidence interval, 0.43 to 0.68; P<0.001). Patients in the cardiac-resynchronization group had less severe symptoms (P<0.001) and a better quality of life (P<0.001) at 90 days. At 18 months, 105 of the patients in the cardiac-resynchronization group were in NYHA class I, 150 were in NYHA class II, and 80 were in NYHA class III or IV; the respective values in the medical-therapy group were 39, 112, and 152.	Indirect PRO impact
Addressing a priority of people with rheumatoid arthritis: Managing fatigue	Severity of fatigue, coping, pain, perceived disease activity and disability	Multi-dimensional Assessment of Fatigue (MAF; VAS), the Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire, Hospital Anxiety and Depression Scale (HDAS), Arthritis Helpssness Index, Arthritis Self-Efficacy Scale (RASE, 28-140)	MAF 28.99 versus 23.99 (adjusted difference −5.48, 95% CI −9.50 to −1.46, p=0.008); VAS 5.99 versus 4.26 (adjusted difference −1.95, 95% CI −2.99 to −0.90, p<0.001)	There were improvents on fatigue coping, perceived severity, disability, depression, helplesness, self-efficacy and sleep on the CBT group. There was no effect on disease activity, pain, anxiey, quality of life or disability impact	No Evidence of PRO Impact
Living with Multiple Sclerosis: development and use of effective self-management strategies	Not specified	Short Form-36 (SF-36) and Standard Day Dependency Record (SDDR)	Improvements in health status were small. However, at follow-up the intervention group had better SF-36 health scores, in mental health (p = 0.04), and vitality (p = 0.05) and considered help with daily activities to be less essential, as measured by the SDDR (p = 0.04), than the control group. Participants in the intervention group had maintained levels of independence at follow-up (p = 0.62) while the control group showed a signicant decrease in independence (p = 0.001).	Not specified	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Anastrozole for oestrogen receptor positive breast cancer (ATAC trial)	Queen Mary University of London	Clinical Medicine	Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer	2005	Multi-centre, international randomised controlled trial	UK	Not specified	Disease-free survival and occurrence of adverse events
Sentinel lymph node biopsy in breast cancer	Queen Mary University of London	Clinical Medicine	Morbidity after sentinel lymph node biopsy in primary breast cancer: Results from a randomized controlled trial	2005	Randomised controlled trial	UK	Phase III	Assessment of physical morbidity (numbness and paresthesia, arm swelling, shoulder mobility, and seroma formation) and psychological morbidity

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Anastrozole for oestrogen receptor positive breast cancer (ATAC trial)	Time to recurrence, which included new contralateral tumours, but not deaths from non-breast-cancer causes before recurrence; time to distant recurrence; censoring at deaths without recurrence; contralateral breast cancer; death after recurrence; and overall survival.	NA	Disease-free survival at 3 years was 89.4% on anastrozole and 87.4% on tamoxifen. Results with the combination were not significantly different from those with tamoxifen alone.	There was no major difference in the number of patients who died from any cause before a breast-cancer recurrence. Anastrozole also showed a greater benefit for this endpoint in comparison with the combination treatment. However, no difference was seen between the tamoxifen-alone group and the combination group.	No Evidence of PRO Impact
Sentinel lymph node biopsy in breast cancer	Not specified	Short Form-36 (SF-36) and the visual analogue QOL scale	**QOL scale:** The QOL scores were usually higher (better) in the study group, and significantly so immediately postoperatively (P = .01). **SF-36:** In the immediate postoperative period, the physical combined score (P = .001), physical functioning score (P = .003), and vitality score (P = .004) were significantly higher (better) in the study group. In node-negative patients, the study group had significantly higher scores for vitality (P = .001) in the immediate postoperative period (baseline)	Not specified	Indirect PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Dementia friendly care & support in extra care housing and acute hospital settings	University of Worcester	Allied Health Professions, Dentistry, Nursing and Pharmacy	Enriched Opportunities Programme: A cluster randomised controlled trial of a new approach to living with dementia and other mental health issues in extra care housing schemes and villages	2011	Cluster randomised trial	UK	Phase III	To assess whether the Enriched Opportunity Programme enabled individuals with dementia to remain in extra care housing scheme over time and whether their quality of life improve
Self-management intervention for men with lower urinary tract symptoms: development, phased evaluation and global adoption	University College London	Clinical Medicine	Self management for men with lower urinary tract symptoms: randomised controlled trial	2007	Randomised controlled trial	UK	Phase III	Treatment failure at 3, 6, and 12 months.
Targeting endothelin in systemic sclerosis - improved survival in pulmonary arterial hypertension (PAH) in systemic sclerosis and licensing of the first drug specifically for digital ulcers in systemic sclerosis	University College London	Clinical Medicine	Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases	2008	Prospective single-arm trial, conducted in 23 centres in 8 European countries	UK	Not specified	WHO class, clinical worsening, quality of life (week 16 and 48) and survival (week 48 only). Safety and tolerability were monitored throughout the study.

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Dementia friendly care & support in extra care housing and acute hospital settings	Perceived levels of social support and quality of relationships and impact on diversity of occupation and observed well-being in public areas	Alzheimer disease-related quality of life scale (QOL-AD), geriatric depression scale (GDS); and Duke Social Support Index (DSSI)	Better quality of life over time (4.0 (SE 0.6) units; 14% p < 0.001) than the active control (1.3 (SE 0.6) units; 4% p = 0.003).	At baseline the mean score in the control group was 18.6, compared to 17.0 in the intervention group. This difference, though small, was statistically significant (p = 0.002)	No Evidence of PRO Impact
Self-management intervention for men with lower urinary tract symptoms: development, phased evaluation and global adoption	Severity of symptoms, troublesomeness of symptoms, and disease specific quality of life	International prostate symptom score (I-PSS), benign prostatic hypertrophy impact index; and American Urological Association quality of life score (AUASS)	At three months, treatment failure had occurred in 7 (10%) of the self-management group and in 27 (42%) of the standard care group (difference=32%, 95% confidence interval 18% to 46%). Corresponding differences in the frequency of treatment failure were 42% (27% to 57%) at six months and 48% (32% to 64%) at 12 months. At three months, the mean international prostate symptom score was 10.7 in the self-management group and 16.4 in the standard care group (difference=5.7, 3.7 to 7.7). Corresponding differences in score were 6.5 (4.3 to 8.7) at six months and 5.1 (2.7 to 7.6) at 12 months.	At 3, 6, and 12 months, patients who were randomised to self management had less severe symptoms than patients randomised to standard care alone (table 2⇑). The differences in international prostate symptom score increased only slightly when we adjusted them for baseline characteristics. For example, the difference at six months increased from 6.5 (4.3 to 8.7) without adjustment to 7.5 (5.7 to 9.4) with adjustment. Patients who were randomised to self management were also less troubled by their symptoms and had a better quality of life than patients who were randomised to standard care alone	Direct PRO impact
Targeting endothelin in systemic sclerosis - improved survival in pulmonary arterial hypertension (PAH) in systemic sclerosis and licensing of the first drug specifically for digital ulcers in systemic sclerosis	Not specified	Short-Form Health Survey-36 (SF-36) and health assessment questionnaire (HAQ) modified for scleroderma	At week 48, WHO class improved in 27% of patients (95% CI 16–42%) and worsened in 16% (95% CI 7–29%). Kaplan–Meier estimates were 68% (95% CI 55–82%) for absence of clinical worsening and 92% (95% CI 85–100%) for survival. Overall changes in quality of life were minimal. There were no unexpected side effects observed during the study.	Not specified	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Increased range and adoption of evidence-based treatments for refractory moderate-to-severe atopic eczema	Newcastle University	Clinical Medicine	Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial	2006	Parallel-group, double-blind, placebo-controlled trial	UK	Not specified	Change in disease activity from baseline to 12 weeks
Cognitive stimulation - an effective intervention to improve quality of life and cognition in people with mild to moderate dementia	Bangor University	Psychology, Psychiatry and Neuroscience	Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial	2003	Single-blind, multi-centre, randomised controlled trial	UK	Not specified	Changes in cognitive function
Impact on policy and practice in the provision of cochlear implants to deaf children and adults	University of York	Psychology, Psychiatry and Neuroscience	Self-reported benefits from successive bilateral cochlear implantation in post-lingually deafened adults: randomised controlled trial	2006	Randomised controlled trial	UK	Not specified	Self-reported measure skills in spatial hearing in everyday life

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Increased range and adoption of evidence-based treatments for refractory moderate-to-severe atopic eczema	Itch score, body area affected, quality of life, loss of sleep due to eczema, soluble CD30	SASSAD (six area six sign atopic dermatitis) and dermatology life quality index (DLQI)	At week 12, there was a 37% (12·0 unit) improvement in mean disease activity with azathioprine compared with a 20% (6·6 unit) improvement with placebo (17% [5·4 unit] difference, 95% CI 4·3–29%). This finding was accompanied by significant improvements in patient-reported itch, area of involvement, global assessment, and quality of life.	Itch score, body area affected, quality of life (DLQI), and global response assessed by both investigator (p=0·01) and participant (p=0·05) all improved significantly with azathioprine compared with placebo. There were improvements in loss of sleep score and soluble CD30, but these failed to reach significance, with both CIs just crossing zero.	No Evidence of PRO Impact
Cognitive stimulation - an effective intervention to improve quality of life and cognition in people with mild to moderate dementia	Changes in cognitive function (short-term memory) and quality of life	Quality of Life – Alzheimer's Disease (QL-AD), and Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog)	The intervention group had significantly improved relative to the control group on the MMSE (P=0.044)	The ADAS–Cog (P=0.014) and QL – AD scales (P=0.028) in the intervention group showed a significant improvement compared to the control group	Direct PRO impact
Impact on policy and practice in the provision of cochlear implants to deaf children and adults	Not specified	GHSI, HUI3, VAS, and EQ-5D	Receipt of a second implant led to improvements in self-reported abilities in spatial hearing, quality of hearing, and hearing for speech, but to generally non-significant changes in measures of quality of life. Multivariate analyses showed that positive changes in quality of life were associated with improvements in hearing, but were offset by negative changes associated with worsening tinnitus. Even in a best-case scenario, in which no worsening of tinnitus was assumed to occur, the gain in quality of life was too small to achieve an acceptable cost-effectiveness ratio.	Not specified	Direct PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
The Whole Systems Demonstrator Study (WSD) - an evaluation of tele-assistive devices in health and social care systems, to guide the roll-out of telecare and telehealth systems in the UK Health and Social Care services	City University London	Allied Health Research	Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial	2012	Pragmatic, cluster randomised controlled trial	UK	Not specified	Number of patients admitted to hospital during 12 month trial period
Use of non-invasive ventilation to improve survival and quality of life in patients with motor neuron disease	Newcastle University	Clinical Medicine	Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial	2006	Randomised controlled trial	UK	Not specified	The effect of NIV on quality of life and survival. Symptoms, lung function, and quality of life were assessed at randomisation, at 1 and 3 months, then at intervals of 3 months.
Diagnostics and novel life-saving therapies for aspergillosis (FAST study)	The University of Manchester	Clinical Medicine	Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitisation (SAFS), the FAST study	2009	Randomised controlled trial	UK	Not specified	Changes in the Asthma Quality of Life Questionnaire (AQLQ) score at 32 weeks, while evaluating the response of severe asthma with fungal sensitisation to oral itraconazole
Thrombolysis for acute ischaemic stroke is effective for a wide range of patients, including those over 80 years, and improves long-term function and quality of life (IST-3)	The University of Edinburgh	Psychology, Psychiatry and Neuroscience	Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial	2013	Open-label, international, multicentre, randomised, controlled trial	UK	Not specified	The proportion of patients alive and independent with an Oxford handicap scale score of 0–2 at 6 months

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
The Whole Systems Demonstrator Study (WSD) - an evaluation of tele-assistive devices in health and social care systems, to guide the roll-out of telecare and telehealth systems in the UK Health and Social Care services	Mortality over 12 months, number of inpatient bed days, emergency admissions, elective admissions, outpatient attendances, and emergency department visits, as well as the notional cost of hospital activity to commissioners of care based on national tariff costs	Not specified	Intervention group had a lower admission proportion within 12 month follow-up (odds ratio 0.82, 95% confidence interval 0.70 to 0.97, P=0.017)	Telehealth does not improve HRQoL for patients with chronic obstructive pulmonary disease, diabetes, or heart failure over 12 months.	No Evidence of PRO Impact
Use of non-invasive ventilation to improve survival and quality of life in patients with motor neuron disease	Not specified	Short-Form Health Survey-36 (SF-36), the sleep related SAQLI and the chronic respiratory disease questionnaire (CRQ)	Improvement in several measures of quality of life and a median survival benefit of 205 days (p=0·006) with maintained quality of life for most of this period. NIV improved some quality-of-life indices in those with poor bulbar function, including sym (p=0·018), but conferred no survival benefit.	NA	Direct PRO impact
Diagnostics and novel life-saving therapies for aspergillosis (FAST study)	Changes in rhinitis score, total IgE, and respiratory function	AQLQ	The improvement (95% CI) in AQLQ score was 0.85 (0.28, 1.41) in the antifungal group, compared with a -0.01 (-0.43, 0.42) change in the placebo group (P = 0.014).	Rhinitis score improved (-0.43) in the antifungal, and deteriorated (+0.17) in the placebo group (P = 0.013). Morning peak flow improved (20.8 L/minute, P = 0.028) in the antifungal group. Total serum IgE decreased in the antifungal group (-51 IU/ml) but increased in placebo group (+30 IU/ml) (P = 0.001).	No Evidence of PRO Impact
Thrombolysis for acute ischaemic stroke is effective for a wide range of patients, including those over 80 years, and improves long-term function and quality of life (IST-3)	Survival, Oxford handicap scale score, health-related quality of life, overall functioning, and living circumstances.	Oxford handicap scale (OHS) and EQ-5D	391 (35·0%) of 1117 patients versus 352 (31·4%) of 1122 had an OHS score of 0–2 (adjusted odds ratio [OR] 1·28, 95% CI 1·03–1·57; p=0·024). Treatment was associated with a favourable shift in the distribution of OHS grades (adjusted common OR 1·30, 95% CI 1·10–1·55; p=0·002). The differences between the groups in visual analogue scale score and the proportion living at home were not signifi cant.	Treatment was associated with signifi cant improvements in mobility, self-care, ability to do usual activities, and pain or discomfort, with no evidence of an effect on anxiety or depression. Treatment was also associated with a gain in health-related quality of life that was significant for four of the five dimensions of the EQ-5D and the overall EQ utility index.	Direct PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Detailed analysis of trial of lapatinib in combination with capecitabine in advanced, HER2+ breast cancer leads to marketing authorisation worldwide	The University of Edinburgh	Clinical Medicine	A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses	2008	Phase III randomised contr olled trial	International	Phase III	Time-to-progession (TTP)
Improving outcome measurement in pulmonary and cardiac rehabilitation	Coventry University	Allied Health Professions, Dentistry, Nursing and Pharmacy	Can low risk cardiac patients be 'fast tracked' to Phase IV community exercise schemes for cardiac rehabilitation? A randomised controlled tria	2011	Single blinded randomised controlled trial	UK	Phase III	Incremental Shuttle Walking Test
Evidence-based identification and cost-effective treatment of depression in cancer patients - Symptom Management Research Trial (SMaRT)	The University of Edinburgh	Psychology, Psychiatry and Neuroscience	Management of depression for people with cancer (SMaRT oncology 1): a randomised trial	2008	Randomised trial	UK	Not specified	Difference in mean score on Symptom Checklist-20 (SCL-20) depression scale at 3 months among patients allocated in usual care
Lung cancer research at UCL/UCLH sets standards of care	University College London	Clinical Medicine	Comparison of gemcitabine and carboplatin versus cisplatin and etoposide for patients with poor-prognosis small cell lung cancer	2009	Multi-centre randomised trial	UK	Phase III	Overall survival

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Detailed analysis of trial of lapatinib in combination with capecitabine in advanced, HER2+ breast cancer leads to marketing authorisation worldwide	Progression-free survival (PFS), overall survival (OS), overall response rate, clinical benefit rate, and safety as measured by the National Cancer Institute's Common Terminology Criteria for Adverse Events	NA	A total of 184 TTP events were identified by independent review (82 in the combination-therapy group and 102 in the monotherapy group); the corresponding HR was 0.57 (95% CI, 0.43–0.77; P < 0.001), demonstrating a significant reduction in the relative risk of progression when lapatinib is added to capecitabine therapy. This corresponded to an improvement in median TTP from 4.3 to 6.2 months	Consistent results were seen for PFS; HR was 0.55 (95% CI, 0.4–0.74; P < 0.001). The HR for PFS for the combination relative to monotherapy in the 117 patients who initiated protocol therapy within 8 weeks from the last dose of trastuzumab was 0.59 (95% CI, 0.40–0.86) compared with 0.56 (95% CI, 0.35–0.91) in the 79 patients who began protocol therapy greater than 8 weeks from the last dose of trastuzumab.	No Evidence of PRO Impact
Improving outcome measurement in pulmonary and cardiac rehabilitation	HRQoL (SF36) and the MacNew quality of life after myocardial infarction questionnaire. Additionally, blood pressure, BMI and dietary habits were captured	MacNew and Short-Form Health Survey-36 (SF-36)	ISWT distance statistically significantly increased over time (f = 26.80, p < 0.001) for both groups. Participats undertaking Phase IV showed an improvent compared to no-natendees (mean difference 40.38 m, 95%CI 4.20 to 76.57, p = 0.03).	HRQoL showed improvements over time (p<0.05)	No Evidence of PRO Impact
Evidence-based identification and cost-effective treatment of depression in cancer patients - Symptom Management Research Trial (SMaRT)	Response to treatment, remission and SCL-20 depression score at 6 and 12 months' follow-up. Addtionally, anxiety, pain, fatigue, and physical functioning; and quality of life were measured	Symptom Checklist-20 (SCL-20) depression scale. Anxiety - a ten-item subscale of the SCL-90 questionnaire. Pain, fatigue, and physical functioning - EORTC QLQ C30 and quality of life - EQ-5D	The adjusted difference in mean score on SCL-20 was 0·34 (95% CI 0·13–0·55). In other words, the intervention improved the symptoms of depression	The intervention group showed improved anxiety and fatigue but not improvement in pain or physical functioning.	Indirect PRO impact
Lung cancer research at UCL/UCLH sets standards of care	Progression-free survival, tumour response, toxicity and quality of life	EORTC QLQ-C30 questionnaire, lung cancer module LC-17 and LLCG daily diary card (DDC)	There was no difference in overall survival (HR 1.01, 95% CI 0.77 to 1.32)	Median progression-free survival was 5.9 months with GC and 6.3 months with PE. Grade 3 or 4 myelosuppressions were more frequent with GC (anaemia: 14% GC vs 2% PE; leucopenia: 32% GC vs 13% PE; thrombocytopenia: 22% GC vs 4% PE), but these were not associated with increased hospital admissions, infections or fatalities. Grade 2–3 alopecia (68% PE vs 17% GC) and nausea (43% PE vs 26% GC) were more frequent with PE. Patients given GC received more chemotherapy as outpatients (89% GC vs 66% PE of treatment cycles). In QoL questionnaires, more patients receiving PE reported being upset by hair loss (p = 0.004) and impaired cognitive functioning (p = 0.04)	No evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
A safer and shorter treatment for thyroid cancer (HiLo trial)	University College London	Clinical Medicine	Ablation with Low-Dose Radioiodine and Thyrotropin Alfa in Thyroid Cancer	2012	Randomised noninferiority trial	UK	Phase III	The success rate for ablation at 6 and 9 months, comparing low-dose and high-dose radioiodine, each in combination with either thyrotropin alfa or thyroid hormone withdrawal before ablation
Establishing the evidence for treatment to improve outcomes in patients with lung cancer	The University of Manchester	Clinical Medicine	Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma	2003	Randomised Phase III trial	UK	Phase III	Difference in survival between gemcitabine and carboplatin (GC) with mitomycin, ifosfamide, and cisplatin (MIC) AND mitomycin, vinblastine, and cisplatin (MVP)
Improving patient care experience and staff well-being: The application of novel methodological advances (PRaCTICAL study)	University of Dundee	Allied Health Professions, Dentistry, Nursing and Pharmacy	The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial	2009	Pragmatic, non-blinded, multicentre, randomised controlled trial	UK	Not specified	Health related quality of life at 12 months after randomisation

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
A safer and shorter treatment for thyroid cancer (HiLo trial)	The number of days of hospitalization; adverse events during ablation and 3 months after ablation, tumor recurrence, quality of life, and socioeconomic factors	Short-Form Health Survey-36 (SF-36)	Low-dose radioiodine plus thyrotropin alfa was as effective as high-dose radioiodine, with a lower rate of adverse events.	More patients in the high-dose group than in the low-dose group were hospitalized for at least 3 days (36.3% vs. 13.0%, P<0.001). The proportions of patients with adverse events were 21% in the low-dose group versus 33% in the high-dose group (P=0.007) and 23% in the thyrotropin alfa group versus 30% in the group undergoing thyroid hormone withdrawal (P=0.11)There were no significant	Indirect PRO impact
Establishing the evidence for treatment to improve outcomes in patients with lung cancer	Time to disease progression, response rates, toxicity, disease-related symptoms, World Health Organization performance status (PS), and quality of life	EORTC QLQ-C30 scale and the HADS depression scale	There was no significant difference in median survival between the arms	Nonhematologic toxicity was comparable for patients with Grade 3–4 symptoms, except there was more alopecia among patients in the MIC/MVP arm. GC appeared to produce more hematologic toxicity and necessitated more transfusions. There was no difference in performance status, disease-related symptoms, or QoL between patients in the two treatment arms. Fewer inpatient stays for complications were required with GC.	No evidence of PRO Impact
Improving patient care experience and staff well-being: The application of novel methodological advances (PRaCTICAL study)	HRQoL at six months, quality adjusted life years (QALYs) at 12 months, incidence and severity of post-traumatic stress disorder, and anxiety and depression at six and 12 months, cost effectiveness at 12 months, primary and secondary healthcare costs in the year after hospital discharge, and mortality in the 12 months after discharge	Short-Form Health Survey-36 (SF-36), Davidson truama score (incidence and severity of post-traumatic stress disorder) and HADS questionnaire (anxiety and depression)	At 12 months, there was no evidence of a difference in the SF-36 physical component score (mean 42.0 (SD 10.6) v 40.8 (SD 11.9), effect size 1.1 (95% CI −1.9 to 4.2), P=0.46) or the SF-36 mental component score (effect size 0.4 (−3.0 to 3.7), P=0.83).	There were no statistically significant differences in secondary outcomes or subgroup analyses. Follow-up programmes were significantly more costly than standard care and are unlikely to be considered cost effective.	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Tocilizumab - a new treatment for Rheumatoid Arthritis in adults and Juvenile Idiopathic Arthritis in children	University College London	Clinical Medicine	Therapeutic benefit of blocking interleukin-6 activity with an anti–interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: A randomized, double-blind, placebo-controlled, dose-escalation trial	2002	Randomised, double-blind, placebo-controlled, dose-escalation trial	International	Phase III	The proportion of patients who had a JIA ACR 30 response
Influencing national policy to improve service delivery and patient care in gastroenterology (MINuET trial)	Swansea University	Allied Health Professions, Dentistry, Nursing and Pharmacy	Open access follow up for inflammatory bowel disease: pragmatic randomised trial and cost effectiveness study	2000	Pragmatic randomised controlled trial.	UK	Not specified	Gastrointestinal symptoms
Targeted intraoperative radiotherapy at the time of lumpectomy for patients with early breast cancer as an alternative to conventional 3-6 weeks of postoperative radiotherapy (TARGIT-A trial)	University College London	Clinical Medicine	Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial	2010	Randomised, non-inferiority trial	UK	Phase III	Local breast carcinoma recurrence in the conserved breast, comparing intraoperative radiotherapy with conventional policy of whole breast external beam radiotherapy

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Tocilizumab - a new treatment for Rheumatoid Arthritis in adults and Juvenile Idiopathic Arthritis in children	Percentage of Participants With JIA Core Set ACR 30/50/70/90 Response at Week 12; Physician's Global Assessment of Disease Activity; Parent/Patient Global Assessment of Overall Well-being; Maximum Number of Joints With Active Arthritis; Number of Joints With Limitation of Movement; Erythrocyte Sedimentation Rate; Childhood Health Assessment Questionnaire Disability Index [...]	Disability Index of the Childhood Health Assessment Questionnaire [CHAQ-DI],	At week 12, significantly more patients who received tocilizumab than those who received placebo met the primary outcome of a JIA ACR 30 response and an absence of fever (85% vs. 24%, P<0.001)	All 22 predefined secondary end points reached statistical significance. Significantly more patients in the tocilizumab group than in the placebo group had a JIA ACR 70 response (71% vs. 8%, P<0.001) or a JIA ACR 90 response (37% vs. 5%, P<0.001). Systemic symptoms (fever and rash) and laboratory abnormalities (anemia, thrombocytosis, and hyperferritinemia) significantly improved with tocilizumab.	Direct PRO impact
Influencing national policy to improve service delivery and patient care in gastroenterology (MINuET trial)	Quality of life, patient satisfaction, anxiety, cost-effectiveness, immediate and delayed complications, quality of examination by blinded assessment of endoscopic video recordings, quality of procedure reports, patients' preferences for operator 1 year after endoscopy, and new diagnoses at 1 year.	Gastrointestinal Symptom Rating Questionnaire (GSRQ), EQ-5D, Gastrointestinal Endoscopy Satisfaction Questionnaire (GESQ), State-Trait Anxiety Inventory (STAI)	There was no significant difference between the two groups in the primary or secondary outcome measures at 1 day, 1 month or 1 year after endoscopy, with the exception of patient satisfaction at 1 day, which favoured nurses. Nurses were significantly more thorough in the examination of stomach and oesophagus, but no different from doctors in the examination of duodenum and colon.	There was no significant difference in costs to the NHS or patients, although doctors cost slightly more. Although quality of life measures showed improvement in some scores in the doctor group, this did not reach traditional levels of statistical significance.	No Evidence of PRO Impact
Targeted intraoperative radiotherapy at the time of lumpectomy for patients with early breast cancer as an alternative to conventional 3-6 weeks of postoperative radiotherapy (TARGIT-A trial)	Local toxicity or morbidity, which was assessed with a pre-specified checklist with the following elements: haematoma, seroma, wound infection, skin breakdown, delayed wound healing, Radiation Therapy Oncology Group (RTOG version 2.0) toxicity grade 3 or 4 for dermatitis, telangiectasia, pain in irradiated field, or other.	NA	At 4 years, there were six local recurrences in the intraoperative radiotherapy group and five in the external beam radiotherapy group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1·20% (95% CI 0·53–2·71) in the targeted intraoperative radiotherapy and 0·95% (0·39–2·31) in the external beam radiotherapy group (difference between groups 0·25%, –1·04 to 1·54; p=0·41).	The frequency of any complications and major toxicity was similar in the two groups (for major toxicity, targeted intraoperative radiotherapy, 37 [3·3%] of 1113 vs external beam radiotherapy, 44 [3·9%] of 1119; p=0·44). Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted intraoperative radiotherapy group (six patients [0·5%]) than in the external beam radiotherapy group (23 patients [2·1%]; p=0·002).	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Establishing an evidence-based therapeutic approach to ANCA-associated vasculitis	University of Cambridge	Clinical Medicine	Mycophenolate mofetil vs. azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled tria	2010	Open-label randomized controlled trial	International	Phase III	Sustained remission and rates of severe adverse events at 12 months. Death and malignant conditions occuring after 12 months
Preventing the gastroduodenal hazards of non-steroidal anti-inflammatory drugs and aspirin through widespread adoption of proton pump inhibitors	University of Nottingham	Clinical Medicine	Famotidine for the Prevention of Gastric and Duodenal Ulcers Caused by Nonsteroidal Antiinflammatory Drugs	1996	Double-blind, parallel-group, randomised trial	UK	Not specified	Cumulative incidence of gastric or duodenal ulceration at 24 weeks
Threefold Increase in the Use of Anti-TNF in the Treatment of Common Chronic Inflammatory Conditions	Imperial College London	Clinical Medicine	Infliximab and Methotrexate in the Treatment of Rheumatoid Arthritis	2000	Randomised Phase III trial	UK	Not specified	Clinical responses with use of the criteria of the American College of Rheumatology, the quality of life with a health-status questionnaire, and the effect on joint damage radiographically

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Establishing an evidence-based therapeutic approach to ANCA-associated vasculitis	Time to remission, change in the BVAS between 0 and 3 months, change in the GFR, prednisolone dose, quality of life, and score on the Vasculitis Damage Index (scores for this index range from 0 to 64, with higher scores indicating more severe damage) between 0 and 12 months.	Short-Form Health Survey-36 (SF-36	Sustained remission occurred in 25 of 33 patients in the rituximab group (76%) and 9 of 11 patients in the control group (82%). The absolute difference in sustained remission with rituximab as compared with cyclophosphamide was –6 percentage points (95% CI, –33 to 21; P=0.68). Six patients in the rituximab group and 1 patient in the control group died within the first 12 months. Among the patients who survived, 93% of the patients in the rituximab group and 90% of the patients in the control group had sustained remission (P=0.80)	The median change in the score on the Vasculitis Damage Index did not differ significantly between the two treatment groups; the score changed by 2 points (interquartile range, 0 to 3) in the rituximab group and by 1 point (interquartile range, 0 to 2) in the control group (P=0.38). The change in the score on the physical component of the SF-36 also did not differ significantly between the two groups (P=0.36). The control group had a significantly better outcome than the rituximab group with respect to the change in the score on the mental component of the SF-36 (P=0.04), but this difference was accounted for by	No Evidence of PRO Impact
Preventing the gastroduodenal hazards of non-steroidal anti-inflammatory drugs and aspirin through widespread adoption of proton pump inhibitors	Lanza scores for lesser degrees of gastroduodenal injury, abdominal pain, pain scores, and antacid consumption	Health Assessment Questionnaire	The cumulative incidence of gastric ulcers was 20 percent in the placebo group, 13 percent in the group of patients receiving 20 mg of famotidine twice daily (P0.24 for the comparison with placebo), and 8 percent in the group receiving 40 mg of famotidine twice daily (P0.03 for the comparison with placebo)	Pain similar among three groups	No Evidence of PRO Impact
Threefold Increase in the Use of Anti-TNF in the Treatment of Common Chronic Inflammatory Conditions	Not specified	Short-Form Health Survey-36 (SF-36)	Reduction in the symptoms and signs of rheumatoid arthritis that was significantly greater than the reduction associated with methotrexate therapy alone (clinical response, 51.8 percent vs. 17.0 percent; P<0.001). The quality of life was also significantly better with infliximab plus methotrexate than with methotrexate alone. Radiographic evidence of joint damage increased in the group given methotrexate, but not in the groups given infliximab and methotrexate (mean change in radiographic score, 7.0 vs. 0.6; P<0.001). Radiographic evidence of progression of joint damage was absent in infliximab-treated patients whether or not they had a clinical response.	NA	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Improving tolerability, convenience and cost of bowel cancer chemotherapy	University of Glasgow	Clinical Medicine	Capecitabine as adjuvant treatment for stage III colon cancer.	2005	Randomised Phase III trial	UK	Phase III	Equivalence in disease-free survival between capecitabine and bolus fluorouracil plus leucovorin
Cognitive Stimulation Therapy - a new therapy for dementia	University College London	Psychology, Psychiatry and Neuroscience	Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: Randomised controlled trial	2003	Single-blind, multi-centre, randomised Phase III controlled trial	International	Not specified	Changes in cognitive function
Mood Disorders Centre – Improving Psychological Treatments for Depression	University of Exeter	Psychology, Psychiatry and Neuroscience	Rumination-focused cognitive behaviour therapy for residual depression: phase II randomized controlled trial.	2011	Phase II randomised controlled trial	UK	Phase II	Severity of residual depressive symptoms
Natalizumab: a potent treatment for highly active relapsing-remitting multiple sclerosis (AFFIRM study)	University College London	Psychology, Psychiatry and Neuroscience	A controlled trial of natalizumab for relapsing multiple sclerosis	2003	Randomised double-blind trial	UK	Not specified	The number of new gadolinium-enhancing lesions over the six-month treatment period, defined as the period following the first infusion (month 1) to one month after the last infusion (month 6)

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Improving tolerability, convenience and cost of bowel cancer chemotherapy	Relapse-free survival, overall survival, safety and quality of life	The Quality of Life Questionnaire (QLQ-C30)	Disease-free survival in the capecitabine group was at least equivalent to that in the fluorouracil-plus-leucovorin group (in the intention-to-treat analysis	Capecitabine improved relapse-free survival (hazard ratio, 0.86; 95 percent confidence interval, 0.74 to 0.99; P=0.04) and was associated with significantly fewer adverse events than fluorouracil plus leucovorin (P<0.001). In the two groups, the scores remained relatively constant over time. However, at week 25 of treatment, the mean scores for global health status in the two groups showed similar small increases from baseline (<5 percent in raw scores), indicating improvement in the quality of life.	Indirect PRO impact
Cognitive Stimulation Therapy - a new therapy for dementia	Changes in cognitive function (short-term memory) and quality of life	Quality of Life – Alzheimer's Disease (QL-AD), and Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog)	The intervention group had significantly improved relative to the control group on the MMSE (P=0.044)	The ADAS–Cog (P=0.014) and QL–AD scales (P=0.028) in the intervention group showed a significant improvement compared to the control group	Direct PRO impact
Mood Disorders Centre – Improving Psychological Treatments for Depression	Rumination-focused CBT reduces rumination significantly more than treatment as usual	Beck Depression Inventory, Ruminative Response Scale of the Response Styles Questionnaire	The rumination-focused CBT group reported significantly fewer residual depressive symptoms postintervention compared with the treatment as usual group, after covarying initial level of baseline symptoms, for both BDI-II and HRSD	Depressive rumination post-intervention, covarying for baseline levels, was significantly lower in the ruminationfocused CBT group than the TAU group	No Evidence of PRO Impact
Natalizumab: a potent treatment for highly active relapsing-remitting multiple sclerosis (AFFIRM study)	The frequency of relapse, changes in the scores on the Kurtzke Expanded Disability Status Scale, and patients' own assessments of well-being.	Visual-analogue scale	The placebo group had a mean of 9.6 new gadolinium-enhancing lesions per patient during the treatment period. The corresponding means were 0.7 in the group given 3 mg of natalizumab per kilogram (P<0.001) and 1.1 in the group given 6 mg of natalizumab per kilogram (P<0.001). There was no significant difference in values between the two natalizumab groups.	The visual-analogue scores of well-being at month 6 were compared with base-line scores. The placebo group reported a slight worsening (mean decrease of 1.38 mm on a 100-mm scale), whereas the group given 3 mg of natalizumab per kilogram and that given 6 mg of natalizumab per kilogram reported an improvement (mean increase, 9.49 mm [P=0.04] and 6.21 mm [P=0.03], respectively). No significant changes in the scores on the Expanded Disability Status Scale were observed in any group during the six-month treatment period (mean increase of 0.03 in the placebo group and mean decrease of 0.14 and 0.03 in 3-mg and 6-mg groups, respectively).	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Reducing blood transfusions in intensive care and surgery saves precious blood, reduces costs and decreases patient risk	The University of Edinburgh	Clinical Medicine	Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial	2013	Parallel-group randomized multicenter pilot trial.	UK	Pilot trial	Mean difference in hemoglobin concentration (Hb) at 14 days and RBC (at 60 days)
Innovations in the treatment of chronic myeloid leukemia have almost doubled 5-year survival rates.	Newcastle University	Clinical Medicine	Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia	2003	Prospective, multicenter, open-label, phase 3, randomized, controlled trial	International	Phase III	Progression under imatinib or interferon alfa plus low-dose cytarabine treatment
Transforming Treatment for Balance Disorders: Booklet-Based Balance Retraining	University of Southampton	Psychology, Psychiatry and Neuroscience	Effectiveness of nurse-delivered vestibular rehabilitation for chronic dizziness in primary care: a randomized controlled trial	2004	Single-blind randomized, controlled trial.	UK	Not specified	Self-reported spontaneous and provoked symptoms of dizziness, dizziness-related quality of life, and objective measurement of postural stability with eyes open and eyes closed at 3 and 6 months
Enhancing quality of life after acquired brain injury	Goldsmiths, University of London	Psychology, Psychiatry and Neuroscience	Community-based rehabilitation after TBI: A randomised controlled trial	2002	Randomised controlled trial	UK	Not specified	Comparison of outreach treatment in community settings

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Reducing blood transfusions in intensive care and surgery saves precious blood, reduces costs and decreases patient risk	Mortality (at 30, 60, and 180 days); antibiotic-and ventilation-free during 60 days follow-up; prevalence of predefined adverse events; HRQoL and physical function at 60 and 180 days postrandomisation	SF-12 and Rivermead Mobility Index (RMI) questionnaires	The Hb difference among groups was 13.8g/L (95% CI,11.5-16.0 g/L), p<0.0001); mean Hb during intervention was 81.9 vs 95.7 g/L	Mortality at 180 days postrandomisation was higher in the liberal group (55%) compared to the restricitive group (37%); relative risk was 0.68 (95% CI, 0.44-1.05; p=0.073). RMI and SF-12 showed severe functional impairment and reduced HRQoL ar 60 days. At 180 days, there were not no statistically significant differences in RMI or SF-12 physical function component scores. The mental component scores of the SF-12 indicated outcomes improvements for surviving patients in the restricitve group	No Evidence of PRO Impact
Innovations in the treatment of chronic myeloid leukemia have almost doubled 5-year survival rates.	The rate of complete hematologic response, the rate of major cytogenetic response, safety and tolerabily	NA	At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 96.7% in the imatinib group and 91.5% in the combination-therapy group (P<0.001). Imatinib was better tolerated than combination therapy	After a median follow-up of 19 months, the estimated rate of a major cytogenetic response at 18 months was 87.1% (95% CI, 84.1 to 90.0) in the imatinib group and 34.7% (95% CI, 29.3 to 40.0) in the group given interferon alfa plus cytarabine (P<0.001). The estimated rates of complete cytogenetic response were 76.2% (95% CI, 72.5 to 79.9) and 14.5% (95% CI, 10.5 to 18.5), respectively (P<0.001)	No Evidence of PRO Impact
Transforming Treatment for Balance Disorders: Booklet-Based Balance Retraining	Anxiety, depression and physical functioning	Vertigo Symptom Scale–Short Form, Dizziness Handicap Inventory, Hospital Anxiety and Depression Scale (HADS) and Short-Form Health Survey-36 (SF-36)	At 3 months, all the primary outcomes presented a significant imporvement in the vestibular rehabilitation group compared to usual care; this improvement was maintained at 6 months. Of 83 treated patients, 56 (67%) reported clinically significant improvement compared with 33 of 87 (38%) usual care patients (relative risk, 1.78 [95% CI, 1.31 to 2.42])	Secondary outcomes did not present significant changes between both groups. At six months, physical functioning presented a decrease	No Evidence of PRO Impact
Enhancing quality of life after acquired brain injury	Functional independence (disability); and anxiety and depression in a subgroup of patients	The brain injury community rehabilitation outcome-39 (BICRO-39), the functional independence/assessment measure (FIM+FAM), the hospital anxiety and depression scale (HADS)	Outreach participants were showed significant improvements in the BI and the BICRO-39 total score and self organisation and psychological wellbeing subscales	Total FIM+FAM scores had similar improvement in both groups (mean ranks: outreach 46.5, information 47.4; U=1058.5, NS). However, the maximum gain index was higher in the outreach group. The HADS index did not show a change (71% fell into the normal range for anxiety and 65% for depression, and in both cases only 15% of participants scored above 13) between groups from intake to follow up for either anxiety or depression.	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Improving outcomes for people with cystic fibrosis through evidence based clinical trials	Queen's University Belfast	Clinical Medicine	A CFTR potentiator in patients with cystic fibrosis and the G551D mutation	2011	Randomised, double-blind, placebo-controlled trial	International	Phase III	The primary efficacy end point was the absolute change from baseline through week 24 in the percent of predicted FEV1.
Cataract Surgery – Quality of Life Benefits and Improved Access to Treatment in the UK and beyond	University of Bristol	Public Health, Health Services and Primary Care	Randomised trial of effectiveness of second eye cataract surgery	1998	Randomised controlled trial	UK	Not specified	The effects of second eye surgery in terms of patient perceptions as well as through visual acuity, contrast sensitivity, and stereoacuity tests
Improving clinical decision making and patient outcomes in severe limb ischaemia (BASIL trial)	University of Birmingham	Clinical Medicine	Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: Analysis of amputation free and overall survival by treatment received	2010	Multi-centre randomised trial	UK	Not specified	To determine amputation-free survival (AFS) while comparing 'bypass-surgery-first' with a 'balloon-angioplasty-first' revascularisation strategy in patients with severe limb ischaemia (SLI) due to infrainguinal disease requiring immediate/early revascularisation
Personalising asthma care for children	University of Brighton	Allied Health Professions, Dentistry, Nursing and Pharmacy	Tailored second-line therapy in asthmatic children with the Arg(16) genotype	2013	Pragmatic randomised controlled trial, open-label	UK	Not specified	School absence over a year, while receiving salmeterol (50 µg, b.i.d.) or montelukast (5 or 10 mg, once daily) plus inhaled fluticasone for 1 year

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Improving outcomes for people with cystic fibrosis through evidence based clinical trials	The change from baseline through week 48 in the percent of predicted FEV1; the time to the first pulmonary exacerbation through week 24 and week 48; subject-reported respiratory symptoms through week 24 and week 48, as assessed with the use of the respiratory domain of the (CFQ-R); the change in weight from baseline to week 24 and week 48; and the change from baseline in the concentration of sweat chloride, a measure of CFTR channel function, through week 24 and week 48.	Cystic Fibrosis Questionnaire–revised (CFQ-R)	Through week 24, there was an increase from baseline of 10.4 percentage points in the percent of predicted FEV1 in the ivacaftor group, as compared with a decrease of 0.2 percentage points in the placebo group — a treatment effect of 10.6 percentage points (P<0.001)	Subjects treated with ivacaftor, as compared with those receiving placebo, had an improvement in scores on the CFQ-R respiratory domain (indicating a reduction in respiratory symptoms). From baseline to week 48, the scores increased by 5.9 points in the ivacaftor group, as compared with a decrease of 2.7 points in the placebo group (treatment effect, 8.6 points; P<0.001).	Direct PRO impact
Cataract Surgery – Quality of Life Benefits and Improved Access to Treatment in the UK and beyond	Health status	PRO tool does not have an assigned name within the trial. From 2003 the PRO instrument is known as Visual Symptoms and Quality Life (VSQ) Short-Form Health Survey-36 (SF-36)	ifferences in self-reported vision related difficulties between the two groups ranged from 11% (95% CI 4·4–17%, activities) to 30% (19–41%, reading). Stereoacuity was better in the expedited surgery group, the difference between the groups for the proportions with stereoacuity of 3000 s of arc or worse was 58% (47–69%).	There were no significant differences for any of the three reading speed assessments. Analysis of covariance led to no significant differences for any of the eight SF-36 health-profile dimensions. In all cases in which significance was attained, the difference was in favour of the expedited-surgery group.	No Evidence of PRO Impact
Improving clinical decision making and patient outcomes in severe limb ischaemia (BASIL trial)	Overall survival (OS), health-related quality of life (HRQoL) and cost-effective use of hospital resources.	EQ-5D and the Short-Form Health Survey-36 (SF-36), used along with theVascular Quality of Life Questionnaire-6 (VascuQoL)	AFS at 1 and 3 years was not significantly different for surgery and angioplasty. Considering the follow-up period as a whole, AFS and OS did not differ between treatments but for patients surviving beyond 2 years from randomisation, bypass was associated with reduced HRs for AFS (HR 0.85; 95% CI 0.50 to 1.07; p = 0.108) and OS (HR 0.61; 95% CI 0.50 to 0.75; p = 0.009), equating to an increase in restricted mean OS of 7.3 months (p = 0.02) and AFS of 5.9 months (p = 0.06) during the subsequent follow-up period. Vein bypasses and angioplasties performed better than prosthetic bypasses.	HRQoL was non-significantly better in the surgery group; amputation was associated with a significant reduction in HRQoL. Over the first year, hospital costs for bypass were significantly higher (difference 5420 pounds; 95% CI 1547 pounds to 9294 pounds) than for angioplasty. However, by 3 and at 7 years the differences in cost between the two strategies were no longer significant. Patients randomised to surgery lived, on average, 29 days longer at an additional average cost of 2310 pounds. A 36-month perspective showed not significantly different mean quality-adjusted life times for angioplasty and surgery.	No Evidence of PRO Impact
Personalising asthma care for children	Asthma-related hospitalizations, requirement of courses of oral steroids, total asthma exacerbations, the use of inhaled bronchodilator as reliever, daily asthma symptoms as reported by the participants, quality of life and spirometry	Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	School absences were reduced with montelukast, difference in score= −0.40 (95% CI −0.22 to −0.58]; P=0.005). Salbutamol use was also reduced with montelukast compared with salmeterol [difference in score=−0.47 (95% CI, −0.16 to −0.79); P<0.0001].	Quality of life and symptoms scores presented an improvement in the montelukast intervention group. There was no difference in FEV1 (forced expiratory volume in 1 s).	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Better diagnosis and treatment for patients with myeloproliferative neoplasms (COMFORT II trial)	King's College London	Clinical Medicine	AK inhibition with ruxolitinib versus best available therapy for myelofibrosis	2012	Open label, randomised controlled trial	UK	Phase III	Reduction of 35% or more in spleen volume at week 48
Novel treatment for psoriatic arthritis receives regulatory approval (PSUMMIT 1 trial)	University of Glasgow	Clinical Medicine	Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study	2009	Multicenter, randomised, double-blind, placebo-controlled trial	International	Phase III	Proportion of patients with at least 20% improvement in ACR response criteria (ACR20) at week 24
Systemic therapies for ovarian cance	University of Glasgow	Clinical Medicine	Phase III randomized trial of docetaxel-carboplatin versus paclitaxelcarboplatin as first-line chemotherapy for ovarian carcinoma.	2004	Phase III Randomised Contorlled Trial	UK	Phase III	Progression-free survival while comparing the combination of docetaxel–carboplatin with the combination of paclitaxel–carboplatin in women with ovarian cancer
Stroke Units: Research driven excellence in quality stroke care	King's College London	Psychology, Psychiatry and Neuroscience	Training care givers of stroke patients: Randomised controlled trial	2004	Single blind, randomised controlled trial.	UK	Not specified	Cost to health and social services, caregiving burden, patients' and care givers' functional status, psychological state, quality of life and patients' institutionalisation or mortality at one year

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Better diagnosis and treatment for patients with myeloproliferative neoplasms (COMFORT II trial)	Reduction of 35% or more in spleen at week 24. The length of time that a reduction in spleen volume of at least 35% was maintained, the time to a reduction in spleen volume of 35% or more, progression-free survival, leukemia-free survival, overall survival, and change in marrow histomorphologic features.	QLQ-C30 and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scale	At week 48, 28% of the patients in the intervention group had at least a 35% reduction in spleen volume, compared to 0% in the usual care group (P<0.001)	At week 24, 32% of the patients in the intervention group had at least a 35% reduction in spleen volume compared to 0% in the usual care group (P<0.001). Patients in the ruxolitinib group had an improvement in overall quality of life and a reduction in symptoms associated with myelofibrosis	Indirect PRO impact
Novel treatment for psoriatic arthritis receives regulatory approval (PSUMMIT 1 trial)	Change in scores on the Health Assessment Questionnaire Disability Index (HAQ-DI), the proportion of patients achieving at least 75% improvement in the psoriasis area severity index, at least 50% improvement in ACR response criteria (ACR50), and at least 70% improvement in ACR response criteria (ACR70) at week 24	HAQ-DI	More ustekinumab-treated (87 of 205 [42·4%] in the 45 mg group and 101 of 204 [49·5%] in the 90 mg group) than placebo-treated (47 of 206 [22·8%]) patients achieved ACR20 at week 24 (p<0·0001 for both comparisons); responses were maintained at week 52. At week 16, proportions of patients with adverse events were similar in the ustekinumab and placebo groups (171 of 409 [41·8%] vs 86 of 205 [42·0%]).	Overall median HAQ-DI score was 1·3 (IQR 0·8–1·8) and serum CRP concentration 10·3 mg/L (6·0–20·7).	Direct PRO impact
Systemic therapies for ovarian cance	Global health status, functional scales, symptom scales, and neurotoxicity score (NScore)	European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30, and EORTC QLQ-OV28	The progression-free survival median was 23 months, and 98% of living patients had a minimum 1 year's follow-up. The median progression-free survival for the docetaxel–carboplatin arm was 15 months (95% CI = 13.3 to 16.6) and for the paclitaxel–carboplatin arm was 14.8 months (95% CI = 13.5 to 16.1)	Treatment with docetaxel–carboplatin was associated with statistically significantly lower incidences of neurosensory (45% versus 78%; P <.001) and neuromotor (9% versus 16%; P = .001) toxicity than treatment with paclitaxel–carboplatin. Quality of life scores did not differ between treatment arms during either therapy or follow-up, with scores increasing from baseline in both arms. For neurotoxicity, the score decreased and the NScore increased more in the paclitaxel–carboplatin arm than in the docetaxel–carboplatin arm	No Evidence of PRO Impact
Stroke Units: Research driven excellence in quality stroke care	Not specified	Frenchay activities index (FAI), hospital anxiety and depression score (HADS), EQ-5D	The costs of care over one year for patients whose care givers had received training were significantly lower (£10 133 vs £13 794; P = 0.001). Trained care givers experienced less caregiving burden (care giver burden score 32 vs 41; P = 0.0001), anxiety (anxiety score 3 vs 4; P = 0.0001) or depression (depression score 2 vs 3; P = 0.0001) and had a higher quality of life (EuroQol score 80 vs 70; P = 0.001). Patients' mortality, institutionalisation, and disability were not influenced by caregiver training. However, patients reported less anxiety (3 vs 4.5; P < 0.0001) and depression (3 vs 4; P < 0.0001) and better quality of life (65 vs 60; P = 0.009) in the caregiver training group	Not specified	Indirect PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Developing and disseminating conformal radiotherapy and intensity modulated radiotherapy (PARSPORT trial)	The Institute of Cancer Research	Clinical Medicine	Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial	2011	Multi-centred randomised controlled trial	UK	Phase III	The proportion of patients with xerostomia of grade 2 or worse by the LENT SOMA subjective side-effect scale 1 year after treatment
Change in practice of stroke practitioners due to the Bridges stroke self-management programme	Kingston University	Allied Health Professions, Dentistry, Nursing and Pharmacy	Bridges self-management programme for people with stroke in the community: feasibility randomised controlled trial.	2015	Feasibility randomised controlled trial	UK	Feasibility trial	Health-related quality of life and self-efficacy
Lower risks to patients, advances in international practice and substantial resource savings result from 'beating heart' off-pump coronary artery bypass surgery (BHACAS 1 and 2 trials)	University of Bristol	Clinical Medicine	Early and mid-term outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials	2002	Randomised controlled trial	UK	Not specified	All-cause mortality or a cardiac-related event at midterm follow-up (1–3 years)
Sublingual Allergen Immunotherapy in the Treatment of Hayfever	Imperial College London	Clinical Medicine	Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis	2006	Longitudinal, double-blind, placebo-controlled, parallel-group trial	UK	Not specified	Rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score as primary endpoints

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Developing and disseminating conformal radiotherapy and intensity modulated radiotherapy (PARSPORT trial)	The proportion of patients with any measurable salivary flow after radiotherapy, acute and other late radiation side-effects, QoL that included xerostomia-related QoL as measured by the modified xerostomia questionnaire, locoregional progression-free survival (PFS), and overall survival	QLQC30 instrument, the associated head and neck specific module HN35 and the modified xerostomia questionnaire	At 12 months xerostomia side-effects were reported in 73 of 82 alive patients; grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group (25 [74%; 95% CI 56–87] of 34 patients given conventional radiotherapy vs 15 [38%; 23–55] of 39 given IMRT, p=0·0027).	At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (20 [83%; 95% CI 63–95] of 24 patients given conventional radiotherapy vs nine [29%; 14–48] of 31 given IMRT; p<0·0001). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.	No Evidence of PRO Impact
Change in practice of stroke practitioners due to the Bridges stroke self-management programme	Functional independence, activity, mood and community integration	EQ-5D and SSQOL instruments	Participants who received the Bridges stroke self-management program presented a greater change in self-efficacy and quality of life over the six-week intervention period. Quality of life had a reduction at 3 months follow-up	The control group had an improvement in functional activity, social integration over the six-week intervention period. The mood score showed an decrease at three-month follow-up	No Evidence of PRO Impact
Lower risks to patients, advances in international practice and substantial resource savings result from 'beating heart' off-pump coronary artery bypass surgery (BHACAS 1 and 2 trials)	Not speficied	NA	Off-pump coronary surgery significantly lowers in-hospital morbidity without compromising outcome in the first 1–3 years after surgery compared with conventional on-pump coronary surgery.	NA	No Evidence of PRO Impact
Sublingual Allergen Immunotherapy in the Treatment of Hayfever	Not specified	Patients rated their rhinoconjunctivitis symptoms on a scale (not named) and on a visual analog scale (VAS). Additionally, relief medication score was measured too	Patients in the control group presented 30% reduction in rhinoconjunctivitis symptom score (P < .0001) and a 38% reduction in rhinoconjunctivitis medication score (P < .0001) compared with placebo. There were no serious local side effects and no severe systemic adverse events	Not specified	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Positive Impact of Non-invasive Ventilation on Survival in Duchenne Muscular Dystrophy and Related Neuromuscular Disorders	Imperial College London	Clinical Medicine	Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia	2005	Randomised controlled trial	UK	Not specified	Peak TcCO2
Managing hypoglycaemia to improve quality of life in people with diabetes (DAFNE trial)	King's College London	Allied Health Professions, Dentistry, Nursing and Pharmacy	Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial	2002	Randomised controlled trial	UK	Not specified	Glycated haemoglobin (HbA1c) and quality of life among patients receiving dose adjustment for normal eating (DAFNE) training or usual care
Early pulmonary rehabilitation reduces re-admissions and improves survival of patients admitted to hospital with acute flare-ups of chronic obstructive pulmonary disease (COPD)	King's College London	Clinical Medicine	Outpatient pulmonary rehabilitation following acute exacerbations of COPD.	2010	Randomised, parallel assigment, open-label trial	UK	Phase III	Hospital re-admission rate for an exacerbation of COPD of patients treated with post-exacerbation PR (PEPR) or usual care

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Positive Impact of Non-invasive Ventilation on Survival in Duchenne Muscular Dystrophy and Related Neuromuscular Disorders	Number of patients who met criteria to initiate NIV in the control group Changes in pulmonary function Respiratory muscle strength Quality of life	Short-Form Health Survey-36 (SF-36)	Peak nocturnal transcutaneous carbon dioxide tension (TcCO2) did not differ between the groups, but the mean (SD) percentage of the night during which TcCO2 was >6.5 kPa decreased in the NIV group (−57.7 (26.1)%) but not in controls (−11.75 (46.1)%; p=0.049, 95% CI −91.5 to −0.35). Mean (SD) arterial oxygen saturation increased in the NIV group (+2.97 (2.57)%) but not in controls (−1.12 (2.02)%; p=0.024, 95% CI 0.69 to 7.5). Nine of the 10 controls failed non-intervention by fulfilling criteria to initiate NIV after a mean (SD) of 8.3 (7.3) months.	Compared with the control patients, a gain in the SF-36 general health score was seen in group 2 patients by 18 months (p = 0.035, 95% CI 51.35 to 2.31) but there were no changes in other domains in groups 1 and 2. In group 3, vitality and social function scores improved (p = 0.017 and p = 0.031, respectively) and there was a trend to improvement in general health (p = 0.06) and mental health	Indirect PRO impact
Managing hypoglycaemia to improve quality of life in people with diabetes (DAFNE trial)	Satisfaction with treatment, psychological wellbeing, weight, blood pressure, cholesterol, triglycerides, and high density lipoprotein cholesterol. The number of insulin injections, total insulin dose, and blood glucose monitoring	Diabetes-dependent quality of life (ADDQoL) questionnaire, diabetes treatment satisfaction questionnaire (DTSQ), 12-item well-being questionnaire (W-BQ12)	At 6 months, HbA1c was significantly better in immediate DAFNE patients (mean 8.4%) than in delayed DAFNE patients (9.4%) (t=6.1, P < 0.0001). The impact of diabetes on dietary freedom was significantly improved in immediate DAFNE patients compared with delayed DAFNE patients (t= − 5.4, P < 0.0001), as was the impact of diabetes on overall quality of life (t=2.9, P < 0.01).	General wellbeing and treatment satisfaction were also significantly improved, but severe hypoglycaemia, weight, and lipids remained unchanged. Improvements in "present quality of life" did not reach significance at 6 months but were significant by 1 year	No Evidence of PRO Impact
Early pulmonary rehabilitation reduces re-admissions and improves survival of patients admitted to hospital with acute flare-ups of chronic obstructive pulmonary disease (COPD)	Physiological functioning (exercise capacity and quadriceps strength)	EQ-5D, Chronic Respiratory Disease Questionnaire (CRDQ) and St George's Respiratory Questionnaire (SGRQ)	The proportion of patients re-admitted to hospital with an exacerbation was 33% in the UC group compared with 7% in those receiving PEPR (OR 0.15, 95% CI 0.03 to 0.72, p=0.02). The proportion of patients that experienced an exacerbation resulting in an unplanned hospital attendance (either admission or review and discharge from the emergency department) was 57% in the UC group and 27% in those receiving PEPR (OR 0.28, 95% CI 0.10 to 0.82, p=0.02).	PEPR was associated with an improved SGRQ total and activities score as well as increased CRDQ dyspnoea and emotion scores.	Indirect PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Informing the policy and implementation of screening for abdominal aortic aneurysms (AAA - MASS study)	Brunel University	Public Health, Health Services and Primary Care	The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial.	2002	Randomised controlled trial	UK	Not specified	Abdominal aortic aneurysm related mortality
A New Standard of Care for Locally Advanced Prostate Cancer	Cardiff University	Clinical Medicine	Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial	2011	Randomised controlled trial	International	Phase III	Overall survival in men with locally advanced prostate cancer managed with androgen deprivation therapy (ADT) and addition of radiotherapy (RT)
Cardiff research yields evidence for benefits of sentinel node biopsy and spearheads training in the technique as a standard of care in breast cancer surgery (ALMANAC trial)	Cardiff University	Clinical Medicine	Randomised multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer	2006	Multicenter, randomised, controlled trial	UK	Phase III	Arm and shoulder morbidity and quality of life between patients with clinically node-negative invasive breast cancer who received sentinel lymph node biopsy and patients who received standard axillary treatment

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Informing the policy and implementation of screening for abdominal aortic aneurysms (AAA - MASS study)	All cause mortality, frequency of ruptured abdominal aortic aneurysm, and effect of screening and surgery on quality of life	Hospital anxiety and depression scale (HADS), Spielberger state-trait anxiety scale, Short-Form Health Survey-36 (SF-36) and the EQ-5D	There were 65 aneurysm-related deaths (absolute risk 0·19%) in the invited group, and 113 (0·33%) in the control group (risk reduction 42%, 95% CI 22–58; p=0·0002), with a 53% reduction (95% CI 30–64) in those who attended screening. 30-day mortality was 6% (24 of 414) after elective surgery for an aneurysm, and 37% (30 of 81) after emergency surgery.	All cause of moratlity and frequency of ruptured abdominal aortic aneurysm were substantially greater frequently in the group that did not attend screening. There were no differences in anxiety or depression between groups. Ther were small difference in the physical and mental subscales (EQ-5D) and self-rated health (SF-36). 12 months after screening or surgery, there were no differences between the groups in mood, the physical or mental subscale of	No Evidence of PRO Impact
A New Standard of Care for Locally Advanced Prostate Cancer	Disease-specific survival, time to disease progression, symptomatic local control measured, health-related quality of life (HRQoL) and toxicity	QLQ-C30 (version 3) with the PR13 prostate-specific module, or Functional Assessment of Cancer Therapy–Prostate (FACT-P)	The addition of RT to ADT improved overall survival at 7 years (74%, 95% CI 70–78 vs 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033)	Both toxicity and health-related quality-of-life results showed a small effect of RT on late gastrointestinal toxicity (rectal bleeding grade >3, three patients (0·5%) in the ADT only group, two (0·3%) in the ADT and RT group; diarrhoea grade >3, four patients (0·7%) vs eight (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups)	No Evidence of PRO Impact
Cardiff research yields evidence for benefits of sentinel node biopsy and spearheads training in the technique as a standard of care in breast cancer surgery (ALMANAC trial)	Axillary recurrence rate	Functional Assessment of Cancer Therapy-Breast + 4 questionnaire (FACT-B+4)	The relative risks of any lymphedema and sensory loss for the sentinel lymph node biopsy group compared with the standard axillary treatment group at 12 months were 0.37 (95% confidence interval [CI] = 0.23 to 0.60; absolute rates: 5% versus 13%) and 0.37 (95% CI = 0.27 to 0.50; absolute rates: 11% versus 31%), respectively. Drain usage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery were statistically significantly lower in the sentinel lymph node biopsy group (all P <.001), and axillary operative time was reduced (P = .055). Overall patient-recorded quality of life and arm functioning scores were statistically significantly better in the sentinel lymph node biopsy group throughout (all P ≤.003). These benefits were seen with no increase in anxiety levels in the sentinel lymph node biopsy group (P >.05)	At 12 months after surgery, four patients in the standard treatment group and one patient in the sentinel node biopsy group had an axillary local recurrence (difference = 2.7%, 95% CI = −1.5% to 7.8%).	Indirect PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Psycho-education following trauma: Impact on international clinical guidelines and education of health professionals	University of Sheffield	Psychology, Psychiatry and Neuroscience	Effectiveness of providing self-help information following acute traumatic injury: randomised following acute traumatic injury: randomised controlled trial controlled trial	2005	Randomised controlled trial	UK	Not specified	the efficacy of We assessed the efficacy of providing such self-help information through the Post-Traumatic Diagnostic Scale (PDS)
Transforming severe asthma therapy	University of Southampton	Clinical Medicine	Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma	2004	Randomised, double-blind, placebo-controlled trial	UK	Not specified	Percentage reduction from baseline in fluticasone dose after 32 weeks' treatment.
Artificial cervical joint improves patient outcome, reduces healthcare costs worldwide and benefits business	University of Bristol - However the PRO trial was not carried out by the University of Bristol	Psychology, Psychiatry and Neuroscience	Long-term clinical and radiographic outcomes of cervical disc replacement with the Prestige disc: results from a prospective randomized controlled clinical trial	2010	Open-label randomized controlled trial	UK	Not specified	Clinical outcome measures, the NDI, the SF-36 PCS, neck and arm pain scores, and return-to-work status were self-administered preoperatively and at 1.5, 3, 6, 12, 24, 36, and 60 months postoperatively in patients undergoing anterior cervical surgery in which a cervical disc prosthesis was used to treat single-level degenerative cervical disc disease

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Psycho-education following trauma: Impact on international clinical guidelines and education of health professionals	The Hospital Anxiety and Depression Scale (HADS)	Post-Traumatic Diagnostic Scale (PDS) and Hospital Anxiety and Depression Scale (HADS)	Post-traumatic stress disorder (PTSD), anxiety and depression (PTSD), anxiety and depression decreased (decreased (P50.05) with time but there were no group differencesin PTSD or were no group differencesin PTSD or anxiety.The controls wereless depressed anxiety.The controls wereless depressed (P50.05) atfollow-up.There was a 0.05) atfollow-up.There was a reductionin PTSD caseness within the control (50%) compared with the control (50%) compared with the intervention (20%) group which was almost significant (almost significant (P50.06)		No Evidence of PRO Impact
Transforming severe asthma therapy	Absolute reduction in fluticasone dose compared to baseline, asthma exacerbation episodes, use of rescue medication, asthma symptom score, peak expiratory flow (PEF) and post-bronchodilator spirometry. Daily diary cards recorded nocturnal (0–4) and daytime (0–4) asthma scores, morning asthma symptoms (yes=1; no=0), morning and evening PEF, number of puffs of rescue medication used during the day and night, plus number of puffs of fluticasone. The asthma symptom score was computed as (daytime+nocturnal+morning score), giving a maximum score of 9. A decrease in symptom score therefore reflects an improvement.	Asthma Quality of Life Questionnaire (AQLQ)	Median reductions in fluticasone dose were significantly greater with omalizumab than placebo: 60% vs. 50% (P=0.003). Some 73.8% and 50.8% of patients, respectively, achieved a geqslant R: gt-or-equal, slanted50% dose reduction (P=0.001). Fluticasone dose reduction to leqslant R: less-than-or-eq, slant500 µg/day occurred in 60.3% of omalizumab recipients vs. 45.8% of placebo-treated patients (P=0.026). Through both phases, omalizumab reduced rescue medication requirements, improved asthma symptoms and asthma-related quality of life compared to placebo.	Changes in QoL scores from baseline to the end of the corticosteroid-reduction phase of geqslant R: gt-or-equal, slanted0.5 and geqslant R: gt-or-equal, slanted1.5 were considered to be clinically detectable and large improvements in asthma-related QoL, respectively [19, 20]. Overall, 58% of patients treated with omalizumab had a clinically detectable improvement in asthma-related QoL compared to 39% of patients treated with placebo (P<0.01), and 16% had a large improvement compared to 6% with placebo (P<0.05) (Fig. 4). These differences were also reflected in various QoL domain scores (Fig. 4).	No Evidence of PRO Impact
Artificial cervical joint improves patient outcome, reduces healthcare costs worldwide and benefits business	Not specified	Neck Disability Index (NDI) and Short-Form Health Survey-36 (SF-36)	Significant improvements in NDI scores, Physical Component Summary scores of the SF-36, and neck and arm pain scores were achieved by 1.5 months in both groups and sustained at 5 years. The SF-36 PCS scores improved significantly in all groups from preoperative scores by 6 months, which was the first postoperative period for SF-36 evaluation, and these improvements were maintained out to 5 years ($p < 0.001$). The overall rates of maintenance or improvement in neurological status in the investigational group were 91.6%, 92.8%, and 95.0%, respectively, at 24, 36, and 60 months compared with 83.6%, 83.2%, and 88.9% in the control group ($p = 0.006$, 0.004, and 0.051, respectively)	Not specified	Direct PRO impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Improving well-being and outcome for patients with heart failure using Cardiac Resynchronisation Therapy (CRT)	University of Hull	Allied Health Professions, Dentistry, Nursing and Pharmacy	The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure	2005	Multicenter, international, randomised trial	UK	Phase III	Time of death from any cause or unplanned hospitalisation as a consequence of a major cardiovascular event, comparing cardiac resynchronisation vs medical therapy alone
Improved clinical management of lysosomal disorder	University of Manchester	Clinical Medicine	Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo controlled, multinational study of recombinant human α-L-iduronidase (laronidase)	2004	randomised, double-blinded, multinational study	UK	Phase III	Median change from baseline to week 26 between groups in percentage of predicted normal forced vital capacity (FVC) and in 6-minute walk test (6MWT) distance through the use of the Wilcoxon rank sum test.
Uterine artery embolisation is superior to surgery in the short term, for the treatment of symptomatic uterine fibroids	University of Edinburgh	Clinical Medicine	Uterine-artery embolisation versus surgery for symptomatic uterine fibroids	2007	Randomised controlled trial	UK	Not specified	Quality of life at 1 year of follow-up
Health and economic benefits of a self-management training programme for Type I diabetes	University of Sheffield	Allied Health Professions, Dentistry, Nursing and Pharmacy	Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial	2002	Randomised controlled trial	UK	Not specified	Glycated haemoglobin (HbA1c) and quality of life among patients receiving dose adjustment for normal eating (DAFNE) training or usual care

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Improving well-being and outcome for patients with heart failure using Cardiac Resynchronisation Therapy (CRT)	Death from any cause, composite of death from any cause and unplanned hospitalization with heart failure. The New York Heart Association (NYHA) class and quality of life at 90 days	Minnesota Living with Heart Failure questionnaire and EQ-5D	In the cardiac-resynchronization group, 82 patients died, as compared with 120 patients who had been assigned to medical therapy alone (20 percent vs. 30 percent; hazard ratio, 0.64; 95 percent confidence interval, 0.48 to 0.85; P<0.002)	Cardiac resynchronization reduced the risk of the composite end point of death from any cause or hospitalization for worsening heart failure (hazard ratio, 0.54; 95 percent confidence interval, 0.43 to 0.68; P<0.001). Patients in the cardiac-resynchronization group had less severe symptoms (P<0.001) and a better quality of life (P<0.001) at 90 days. At 18 months, 105 of the patients in the cardiac-resynchronization group were in NYHA class I, 150 were in NYHA class II, and 80 were in NYHA class III or IV; the respective values in the medical-therapy group were 39, 112, and 152.	Indirect PRO impact
Improved clinical management of lysosomal disorder	Urinary GAG excretion; sleep study apnea/hypopnea index (AHI, events/hour of sleep); active shoulder flexion (mean of both shoulders); and the Disability Score Index of the Childhood Health Assessment Questionnaire (CHAQ) for patients ≤18 years of age and of the Health Assessment Questionnaire (HAQ) for older patients	Disability Score Index of the Childhood Health Assessment Questionnaire (CHAQ) and the Health Assessment Questionnaire (HAQ)	After 26 weeks, patients receiving laronidase compared with placebo showed mean improvements of 5.6 percentage points in percent of predicted normal FVC (median, 3.0; P=.009) and 38.1 meters in 6MWT distance (median, 38.5; P=.066; P=.039, analysis of covariance). Laronidase also significantly reduced hepatomegaly and urinary glycosaminoglycans, and, in more severely affected patients, improved sleep apnea/hypopnea and shoulder flexion. Laronidase was well-tolerated.	Baseline CHAQ/HAQ Disability Index scores were 1.9 for the placebo group and 2.0 for the laronidase group (scale of 0 to 3, with 3 themost disabled). Changes in theDisability Index after treatment were small and did not differ between groups.	No Evidence of PRO Impact
Uterine artery embolisation is superior to surgery in the short term, for the treatment of symptomatic uterine fibroids	Assessment of findings on the EuroQol-5D questionnairethe time until the resumption of usual activities; a satisfaction score measuring whether patients would recommend the procedure to a friend; a linear-analogue pain score at 24 hours; the presence or absence of complications; and treatment failure, defined as the need for subsequent intervention for symptom control, including hysterectomy or repeated embolization	Short-Form General Health Survey SF-36 and EQ-5D	There were no significant differences between groups in any of the eight components of the SF-36 at 12 months, although at 1 month, the embolization group had significantly greater improvement in scores than the surgery group for the physical function, social function, and physical-role components.	Women in the surgical group had a significantly higher pain score at 24 hours. Symptom scores at 1 and 12 months after the procedure were significantly better in the surgical group. At 12 months, the percentage of women who reported that they would recommend their treatment to a friend was high in both treatment groups (93% in the surgical group and 88% in the embolization group) (P=0.32).	Direct PRO impact
Health and economic benefits of a self-management training programme for Type I diabetes	Satisfaction with treatment, psychological wellbeing, weight, blood pressure, cholesterol, triglycerides, and high density lipoprotein cholesterol. The number of insulin injections, total insulin dose, and blood glucose monitoring	Diabetes-dependent quality of life (ADDQoL) questionnaire, diabetes treatment satisfaction questionnaire (DTSQ), 12-item well-being questionnaire (W-BQ12)	At 6 months, HbA1c was significantly better in immediate DAFNE patients (mean 8.4%) than in delayed DAFNE patients (9.4%) (t=6.1, P < 0.0001). The impact of diabetes on dietary freedom was significantly improved in immediate DAFNE patients compared with delayed DAFNE patients (t= − 5.4, P < 0.0001), as was the impact of diabetes on overall quality of life (t=2.9, P < 0.01).	General wellbeing and treatment satisfaction were also significantly improved, but severe hypoglycaemia, weight, and lipids remained unchanged. Improvements in "present quality of life" did not reach significance at 6 months but were significant by 1 year	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Occupational Therapy and self-management for people with arthritis	University of Salford	Allied Health Professions, Dentistry, Nursing and Pharmacy	Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy	2011	Two-arm, parallel randomised controlled trial	UK	Not specified	Fatigue impact at 18 weeks
Development and Demonstration of the First Effective Therapy for Chronic Fatigue Syndrome (PACE trial)	University of Oxford	Psychology, Psychiatry and Neuroscience	Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial	2011	Parallel-group randomised trial	UK	Not specified	Fatigue, physical function up to 52 weeks after randomisation. Additionally, safety including serious adverse reactions to trial treatments were assessed
Inhaled heparin, a novel therapeutic approach with clinical benefits in the treatment of obstructive airways diseases	University of Portsmouth	Allied Health Professions, Dentistry, Nursing and Pharmacy	Inhaled heparin in cystic fibrosis	2006	Randomised, double-blind, placebo-controlled crossover trial	UK	Pilot trial	Change in FEV1, comparing heparin and placebo treatments

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Occupational Therapy and self-management for people with arthritis	Fatigue severity, coping, pain and perceived disease activity, disability, depression, helplessness, self-effi cacy and sleep were also better in CBT participants	Multi-Dimensional Assessment of Fatigue scale (MAF) and VAS. Health Assessment Questionnaire (HAQ), Impact HAQ, Rheumatoid Srthritis Quality-of-Life scale, Hospital Anxiety and Depression Scale, Arthritis Helplessness Index, Rheumatoid Arthritis Self-Efficacy scale	There were no major baseline differences between the 65 CBT and 62 control participants. At 18 weeks CBT participants reported better scores than control participants for fatigue impact: MAF 28.99 versus 23.99 (adjusted difference −5.48, 95% CI −9.50 to −1.46, p=0.008); VAS 5.99 versus 4.26 (adjusted difference −1.95, 95% CI −2.99 to −0.90, p<0.001). Standardised effect sizes for fatigue impact were MAF 0.59 (95% CI 0.15 to 1.03) and VAS 0.77 (95% CI 0.33 to 1.21), both in favour of CBT	Secondary outcomes of perceived fatigue severity, coping, disability, depression, helplessness, self-efficacy and sleep were also better in CBT participants.	No Evidence of PRO Impact
Development and Demonstration of the First Effective Therapy for Chronic Fatigue Syndrome (PACE trial)	Overall health, disability, disturbed sleep, distance in m untes walked, hospital anxiety and depression scale score,29 number of chronic fatigue syndrome symptoms, and individual symptoms of postexertional malaise and poor concentration or memory	Chalder fatigue questionnaire (CFQ-11) and Short-Form Health Survey-36 (SF-36), hospital anxiety and depression scale score (HADS)	Compared with SMC alone, mean fatigue scores at 52 weeks were 3·4 (95% CI 1·8 to 5·0) points lower for CBT (p=0·0001) and 3·2 (1·7 to 4·8) points lower for GET (p=0·0003), but did not differ for APT (0·7 [−0·9 to 2·3] points lower; p=0·38). Compared with SMC alone, mean physical function scores were 7·1 (2·0 to 12·1) points higher for CBT (p=0·0068) and 9·4 (4·4 to 14·4) points higher for GET (p=0·0005), but did not differ for APT (3·4 [−1·6 to 8·4] points lower; p=0·18). Compared with APT, CBT and GET were associated with less fatigue (CBT p=0·0027; GET p=0·0059) and better physical function (CBT p=0·0002; GET p<0·0001).	Secondary post-hoc analysis compared the proportions of participants who had improved between baseline and 52 weeks by 2 or more points of the Chalder fatigue questionnaire, 8 or more points of the short form-36, and improved on both. In another post-hoc analysis, we compared the proportions of participants who had scores of both primary outcomes within the normal range at 52 weeks	No Evidence of PRO Impact
Inhaled heparin, a novel therapeutic approach with clinical benefits in the treatment of obstructive airways diseases	Changes in sputum levels of neutrophil elastase activity, IL-8, terminal complement complex (TCC) and myeloperoxidase (MPO); serum CRP; weight; symptom scores; quality of life and exercise capacity	VAS for the following symptoms: general well-being, energy, appetite, sleep quality, shortness of breath, cough, sputum volume and sputum colour. In addition, subjects also completed the teen–adult version of	There was no significant effect of heparin upon the primary outcome measure, FEV1 (treatment effect −0.008 L; p=0.90; 95% CI −0.15–0.13. In addition, there was no significant effect of heparin upon VAS (including those pertaining to sputum clearance; table), overall quality of life on the CFQ, or any of the three quality-of-life modules	There was no significant effect of heparin upon visual analogue scores, overall quality of life on the CFQ, or any of the three quality-of-life modules. Heparin was associated with negative effects upon both the body image (−5.56; p=0.04) and social/marginalisation dimensions (−6.67; p=0.07); however, these were not significant after incorporating a multiple comparisons adjustment for the 15 quality-of-life measures of the CFQ	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
New approaches to the treatment of chronic pain	Birmingham City University	Allied Health Orifessions, Dentistry, Nursing and Pharmacy	Randomised double blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic nonmalignant pain	2013	Randomised, double-blind controlled, parallel group trial	UK	Not specified	Visual analogue scale (VAS) pain score change and withdrawal from the study due to lack of efficacy during a 10-week follow-up
Assessing Quality of Life and Other Patient-Reported Outcomes in Diabetes and Other Chronic Medical Conditions	University of Sheffield	Allied Health Professions, Dentistry, Nursing and Pharmacy	Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment For Normal Eating (DAFNE) randomised controlled trial	2002	Randomised controlled trial	UK	Not specified	Glycated haemoglobin (HbA1c) and quality of life among patients receiving dose adjustment for normal eating (DAFNE) training or usual care
Major Advance in Identification and Treatment of HIV-1 Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS): A Common and Serious Complication of Antiretroviral Therapy	Imperial College London	Clinical Medicine	Randomized placebo-controlled trial of prednisone for paradoxical TB-associated immune reconstitution inflammatory syndrome	2010	Randomised, double-blind, placebo-controlled trial	International	Not specified	Cumulative days of hospital admission during the 12 week study period, combined with outpatient therapeutic procedures (including aspiration of lymph nodes, cold abscesses and serous effusions) which were assigned a value of one hospital day

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
New approaches to the treatment of chronic pain	Functional and psychological measures based on the Oswestry Disability Index (ODI), Hospital Anxiety and Depression (HAD) scale and Coping Strategies Questionnaire (CSQ)	VAS, Oswestry Disability Index (ODI), Hospital Anxiety, Depression (HAD) and Coping Strategies Questionnaire (CSQ)	The VAS change between baseline and the last observation was lower in the control group (Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant, Z=−1.839, p=0.070; r=−0.47. The calculation of clinical changes based on the VAS scores indicated non-significant clinical changes in 10% of the patients in the dose-reduction group (intervention); minimally clinically important changes (≥10% and and <30%) were observed in 20% of the participants randomised to this group, moderately important increase in pain (≥30% and <50%) in 40% of the participants and substantially important increase in pain (≥50%) in 30% of the patients	There were no statistically significant differences between the randomised groups in the changes detected for ODI, HAD scale anxiety and depression and all items of CSQ between the baseline score and the final observation.	Direct PRO impact
Assessing Quality of Life and Other Patient-Reported Outcomes in Diabetes and Other Chronic Medical Conditions	Satisfaction with treatment, psychological wellbeing, weight, blood pressure, cholesterol, triglycerides, and high density lipoprotein cholesterol. The number of insulin injections, total insulin dose, and blood glucose monitoring	Diabetes-dependent quality of life (ADDQoL) questionnaire, diabetes treatment satisfaction questionnaire (DTSQ), 12-item well-being questionnaire (W-BQ12)	At 6 months, HbA1c was significantly better in immediate DAFNE patients (mean 8.4%) than in delayed DAFNE patients (9.4%) (t=6.1, P < 0.0001). The impact of diabetes on dietary freedom was significantly improved in immediate DAFNE patients compared with delayed DAFNE patients (t= − 5.4, P < 0.0001), as was the impact of diabetes on overall quality of life (t=2.9, P < 0.01).	General wellbeing and treatment satisfaction were also significantly improved, but severe hypoglycaemia, weight, and lipids remained unchanged. Improvements in "present quality of life" did not reach significance at 6 months but were significant by 1 year	No Evidence of PRO Impact
Major Advance in Identification and Treatment of HIV-1 Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS): A Common and Serious Complication of Antiretroviral Therapy	TB-IRIS symptoms at week 2 and 4 visits in relation to the symptoms described at study entry	MOS-HIV	he primary combined endpoint was more frequent in the placebo than the prednisone arm (median hospital days 3 (IQR 0-9) and 0 (IQR 0-3) respectively; p=0.04).	There were significantly greater improvements in symptoms, Karnofsky score, and quality of life (MOS-HIV) in the prednisone versus the placebo arm at 2 and 4 weeks, but not at later timepoints. Chest radiographs improved significantly more in the prednisone arm at weeks 2 (p=0.002) and 4 (p=0.02). Infections on study medication occurred in more participants in prednisone than placebo arm (27 vs 17 respectively; p=0.05), but there was no difference in severe infections (2 vs 4 respectively; p=0.40). Isolates from 10 participants were found to be resistant to rifampicin after enrollment.	No Evidence of PRO Impact

Case study	Submitting Institution	Clinical area	Trial name	Year of publication	Trial design	Leading study centre	Trial phase	Primary outcome
Improved treatment and quality of life for patients with overactive bladder syndrome through developing new ways of administering Botulinum Toxin–A	King's College London	Clinical Medicine	Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial	2007	Double-blind, placebo, randomised controlled trial	UK	Not specified	Change in maximum cystometric capacity
Treatment Outcomes in Epilepsy (SANAD trial)	University of Liverpool	Public Health, Health Services and Primary Care	The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial	2007	Unblinded randomised controlled trial	UK	Not specified	The time from randomisation to treatment failure (stopping the randomised drug due either to inadequate seizure control or to intolerable side-effects, or both, or the addition of other antiepileptic drugs, whichever was the earliest); and the time from randomisation to the achievement of a 1 year period of remission of seizures

Case study	Secondary outcomes	PRO instrument	Primary outcome significance	Secondary outcome significance	Type of impact
Improved treatment and quality of life for patients with overactive bladder syndrome through developing new ways of administering Botulinum Toxin–A	Changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry and reflex detrusor volume.	Incontinence Impact Questionnaire short form 7 and Urogenital Distress Inventory short form 6	Significant increases in maximum cystometric capacity were observed at 4 weeks (difference 144.69 ml, 95% CI 100.95 to 215.75, $p < 0.0001$) and 12 weeks (difference 95.71 ml, 95% CI 47.47 to 172.45, $p = 0.001$) in patients treated with botulinum toxin-A compared to placebo. Botulinum toxin-A reduced frequency ($p < 0.001$, $p = 0.003$) and urgency urinary incontinence ($p = 0.03$, $p = 0.008$) episodes at 4 and 12 weeks, respectively. Urgency was reduced at 4 weeks ($p = 0.005$) in the botulinum toxin-A group. In patients receiving botulinum toxin-A, post-void residual increased at 4 weeks ($p = 0.024$) but became insignificant by 12 weeks ($p = 0.406$). Of these patients 6 required intermittent self-catheterization	Significant improvements in quality of life were observed following botulinum toxin-A. The extension study suggests that the beneficial effects of botulinum toxin-A are maintained for at least 24 weeks.	No Evidence of PRO Impact
Treatment Outcomes in Epilepsy (SANAD trial)	The time from randomisation to a first seizure (an efficacy outcome that is to some degree dependent on choice of the initial drug dose); time to achieve a 2-year remission; the incidence of clinically important adverse events and side-effects emerging after randomisation. Quality of life outcomes and cost-effectiveness	NEWQOL (Newly Diagnosed Epilepsy Quality of Life) battery	For time to treatment failure, lamotrigine was significantly better than carbamazepine (hazard ratio [HR] 0·78 [95% CI 0·63–0·97]), gabapentin (0·65 [0·52–0·80]), and topiramate (0·64 [0·52–0·79]), and had a non-significant advantage compared with oxcarbazepine (1·15 [0·86–1·54]). For time to 12-month remission carbamazepine was significantly better than gabapentin (0·75 [0·63–0·90]), and estimates suggest a non-significant advantage for carbamazepine against lamotrigine (0·91 [0·77–1·09]), topiramate (0·86 [0·72–1·03]), and oxcarbazepine (0·92 [0·73–1·18]).	Response rates for quality of life outcomes in arm B were 80% at baseline and 67% at 2-year follow-up. There were no significant differences in response rates between treatment groups	Indirect PRO impact

Appendix 3 - The impact of patient-reported outcomes (PROs) from clinical trials: perspectives from international stakeholders

Appendix 3.1 - Topic Guide

Consent: We are conducting the research how do patient-reported outcomes (PRO) trial results impact on future patient care and healthcare decisions.

If you agree, I would like to ask you some questions about this topic. The interview should take up to **45 minutes**. Your responses are **confidential and anonymized**. You are able to **withdraw** at any moment during and after the interview, up to 10 working days, without giving a reason.

- Have you received and read the participant's information sheet?
- Do you have any questions about the study or the interview process?
- Are you willing to proceed with the interview and allow me to use your anonymized data to inform the study and any future publications?
- Would you like have access to any publications that will arise from this research project?
    - **If YES to above**
- Are you happy for me to contact you using the email address you have provided?

Aim of the study: i) to explore in depth the impact of patient-reported outcome (PRO) trial results on clinical practice, clinical guidelines and health policy development, drug approval, pricing and reimbursement decisions, clinical decision-making and consent for treatment. ii) To explore perceived barriers and facilitators of effective dissemination and impact on healthcare decisions and patient care. iii) Ultimately the results of this qualitative study will help inform the development of a PRO impact metrics framework.

By impact, we mean a positive change or benefit on the economy, society, health, policy and academia.

May I proceed with the first question?

Background:

1. Could you tell me about your background and area of research expertise?
2. Do you think PROs trial findings have influenced your own practice?

    ***If yes**, can you describe any examples?*

    a. *How did PRO trial findings influence your practice?*

b. *Why do you think it was important to incorporate PRO trial findings in your practice?*
c. *Who benefited from the incorporation of PROs?*
d. *What were the benefits of incorporating PRO trial findings in your practice?*
e. *When was the trial conducted?*

***If not**, why do you think PRO trial findings do not influence your practice?*

3. Can you think of a specific PRO trial that has led to impact? This could be a trial you have been directly involved or you are aware of.
    a. *Were you involved in this trial?*
    b. *When was the trial conducted?*
    c. *What was the clinical area?*
    d. *Tell me about the impact, why do you think this PRO trial led to impact? (pricing decisions, clinical practice, health policy, clinical guidelines or reimbursement decisions)*
    e. *How did PROs were incorporated?*
    f. *How did PROs facilitate the impact?*

4. In your experience, what is the most effective way to identify an impactful PRO clinical trial that could influence practice? *If necessary*, *use as further explanation for the participant. Presentation of trial results at conferences, publications or clinical practice guidelines.*
    a. *Why do you think this is the most effective way?*
    b. *What are the advantages of this method?*
    c. *What are the disadvantages of this method?*
5. Can you think of any other effective ways to identify impactful PRO clinical trials?

Barriers and facilitators:

We are interested in identifying what barriers and facilitators influence the use of PRO trial findings in healthcare decisions and patient care.

6. Thinking about the same impactful PRO trial, what were the **main key things or facilitators** that helped its dissemination and uptake in practice?

    If necessary, rephrase. Assuming we have a well conducted study. How can we maximise the benefit of PRO data and inform patient care and healthcare practice?

7. Can you think of a clinical trial collecting PROs that **has not** led to PRO research impact? This can be a clinical trial you have been involved with or you are aware of.

    ***If yes,** can you describe it?*
    a. *Why did not it lead to impact?*

   b. *What were the consequences of conducting a PRO trial that does not lead to impact?*
   c. *What were the main limitations of those PRO trial findings?*

8. In your experience, what are the potential **barriers** that prevented the impact of the previous PRO trial results? *If necessary, use as further explanation for the participant. These can be related to trial design, conduct and analysis, reporting, uptake in practice and other factors.*

9. Do you have any suggestions on how best to address barriers to realising PRO impact, or any ideas on how to proactively facilitate such impact? *If necessary, use as further explanation for the participant. Clinicians training, use of SPIRIT and SPIRIT-PRO, CONSORT and CONSORT-PRO*

Impact metrics:

We are interested in identifying ways that determine the impact of PRO trial findings have on healthcare decisions and patient care.

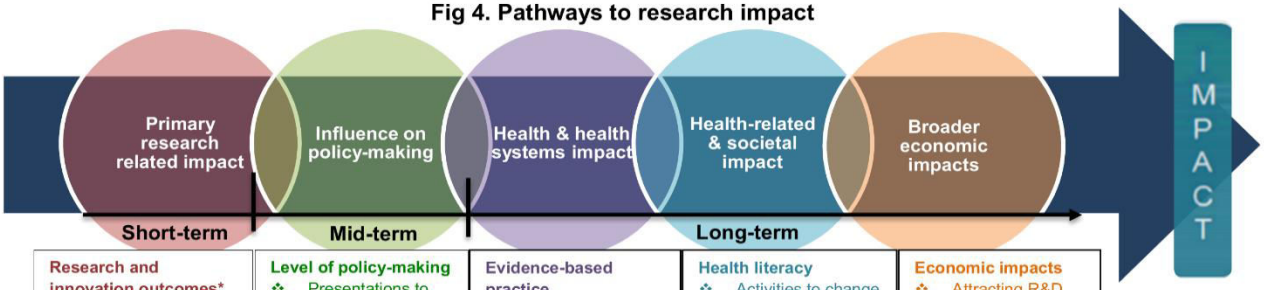
6. How could we measure the impact of PRO trial findings on healthcare decisions and patient care in future?
   If necessary, example of metric: FDA – number of labelling claims approved
7. What ways to measure impact would be the most representative?
8. Do you think it would be useful to have a framework compiling the different measures mentioned?
   a. *Why do you think it would be useful?*
   b. *What are the benefits of having this framework?*
   c. *Who do you think will benefit from this framework?*
   d. *How would it benefit you or other stakeholders involved in PRO trial research?*
   e. *When would it be useful for PRO trial research to use this framework? (Before or after conducting a trial)*
9. Are you aware that this sort of information is being captured?
   a. *If yes, can you give me some examples?*

Conclusion:

- I have no more questions, but I would like to give you the opportunity to add anything else we have not discussed.
- Thank you for taking part in this interview. If you have any further questions or comments, please don't hesitate to contact me.

Appendix 3.2 - Pathways to research impact

Fig 4. Pathways to research impact



Research and innovation outcomes*
- Publications
- Peer-reviewed articles (journal impact factor)
- Citation rates

Dissemination and knowledge transfer*
- Conferences, seminars, workshops and presentations
- Teaching
- Mass media

Capacity building, training and leadership*
- PhD and post-doc studentships
- Academic careers advancement
- Subsequent grants received

Academic collaborations, research networks and data sharing

Level of policy-making
- Presentations to decision-makers
- Influence on public policy debate
- Information base for political and executive decision-making

Type and nature of policy impact
- Changes to legislations, regulations and government policy
- Influence and involvement in the decision-making process
- Changes to clinical or healthcare training, practice or guidelines

Policy networks
- Collaborative research with industry
- Staff movement between academia and industry

Evidence-based practice
- Improving diagnostics and response prediction
- Fulfilling previously unmet clinical needs

Quality of care and service delivery
- Improved health outcomes (QALYs)
- Patient satisfaction (PROMS)
- Making services more accessible for local communities
- Reduction in waiting times

Cost containment and effectiveness
- Cost savings
- Increased service effectiveness

Resource allocation
- Better targeting and accessibility while allocating resources

Health workforce
- Reduction in the number of work loss days

Health literacy
- Activities to change health-risk behaviours such as strategies and campaigns

Health knowledge, attitudes and behaviours
- Increased levels of public engagement with science and research
- Outcomes from focus groups to assess changes in attitudes, behaviours and attitudes

Improved social equity, inclusion or cohesion
- United Nations Millennium Development Goals
- Human rights

Economic impacts
- Attracting R&D investment from NHS, medical charities and overseas
- Income from intellectual property
- Spill over effects
- Patents granted/licenses awarded and brought to the market
- Spin-out companies
- Research contracts and income from industry

Key: [Bold, [impact categories]; Diamond, [impact subgroups]; *top three metrics]