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A global Core Outcome Set to optimise the evidence base for burn care (COSB-i).

Amber Elizabeth Russel Young

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Bristol Medical School,

Population Health Sciences

April 2020

Dedication

I dedicate this thesis to my amazing and wonderful husband Norman, who has supported me in health and scientific matters throughout.

I also dedicate this to my brilliant and kind oncologist, Dr Jeremy Braybrooke, who kept me alive, happy and able to work on this thesis.

I have undertaken this PhD to leave a collection of work behind after my death, that will hopefully improve healthcare for patients with burns.

My father would have been proud.

Scientific Abstract

Please see, in addition, a lay summary and pictorial abstract below.

Gold-standard medical care requires collated evidence from systematic reviews, to support clinicians in identifying the treatment that results in optimal patient outcomes. In burn care, this evidence is required to improve survival, optimise function and cosmesis, and minimise the pain and psychological impact of the injury. Although burns are common (11 million annual global incidence), management and outcomes vary within and between countries. This is likely to be due to a lack of guidelines based on synthesised evidence. One reason that data from trials cannot be synthesised, is because of a variation in outcome reporting across trials. Establishing how to improve this is challenging. The development of a Core Outcome Set (COS), a scientifically agreed minimum set of the most important outcomes to be reported in all studies of a medical condition, is likely to provide the answer.

The aim of this thesis is to explore variation in outcome reporting in burn care research and to develop a COS as a novel solution to this problem.

Four systematic reviews and a mixed-methods study, including Delphi surveys and a consensus meeting were undertaken. The reviews highlighted the extent of outcome heterogeneity across burn trials, problems with outcome definition and timing of assessment and a focus on short-term clinical, not patient-important, outcomes.

Development of the COS has used shared decision-making, with 668 health professionals from 77 countries of varying income, and 126 UK patients, ensuring relevance to both stakeholder groups. Seven core outcomes have been agreed: death, specified complications, ability to do daily tasks, wound healing, neuropathic pain and itch, patient psychology and time to return to school or previous occupation.

It is hoped that this COS will improve data synthesis, to support evidence-based clinical decision-making. This will ultimately resolve uncertainty over clinical decisions to ensure optimal care for burn patients globally.

Lay Summary and Pictorial Abstract

In healthcare, treatments need to be based on scientific research, so that patients receive the highest quality care, with the best possible information. Each year, almost 11 million people around the world require medical treatment for burns. Deciding how to treat these patients is difficult and varies considerably. Recovery outcomes, which include infection, pain, and scarring also vary. One reason for this, is that not all researchers use the same outcomes to measure recovery. This makes it very difficult to bring together and make sense of global research evidence in order to agree the best treatments.

The aim of my thesis is to understand why researchers find it difficult to use the evidence that is published, to find the best treatment for patients.

My findings have shown that researchers have difficulty in agreeing which outcomes are most important. There are also challenges in knowing which outcomes are the same and which are different (is *burn pain* the same as *the need for pain relief after a burn*?). Researchers measure outcomes at different times and most often shortly after the burn rather than years later. The latter are likely to be more important to patients. It is now possible to understand why the evidence in burn care is difficult to compare.

I have developed a practical solution to this problem through the work in this thesis, a Core Outcome Set. This is a scientifically agreed set of the most important outcomes which can be used by all researchers. This will allow researchers to compare like-with-like, when summing up evidence in burn research.

In creating the Core Outcome Set, I included the views of 668 health professionals in 77 countries and 126 patients and carers in the UK. Seven core outcomes were agreed. These were: death, serious complications, ability to do daily tasks, time to wound healing, long-term nerve pain and itch, patient psychology and time to return to school or previous occupation.

It is hoped that the COS will be widely used in research studies in burn care. It will improve patient care by making research comparable, and therefore improving the amount of evidence available to patients and professionals. This evidence will ultimately inform decision making, with the aim to improve outcomes for burn patients worldwide.

Outcome Reporting in Global Burn Care

A Problem

Burn Injuries
11 million annually globally

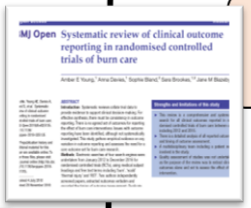
Higher in low income countries.

Varying care

Lack of evidence base

Varying outcomes

The Research



SR Clinical outcomes reported across RCTs
N=993 in 147 trials

What is a Unique Outcome?

Quantitative outcome reporting heterogeneity

Variation in outcome choice across trials

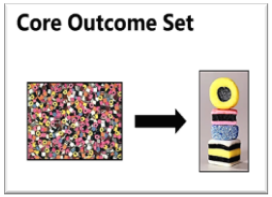
Variation in timing of assessment of one outcome

Variation in definition of one outcome

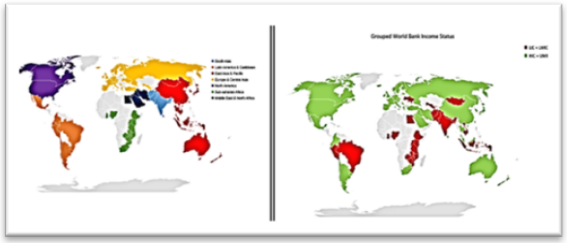
Outputs:
- 5 published papers.
- 1 accepted for publication.
- 1 ready for submission.
- 1 external grant of £139k.
- Global burn outcome research network developed.

Future work:
- COSB implementation
- Outcome lexicon for burn care

A solution



Core Outcome Set (COSB-i)
7 core outcomes
668 health care participants from 77 countries and 126 UK patients



Effective evidence synthesis

Evidence base increased to support clinical decision making

1. James, Spencer L., et al. "Epidemiology of injuries from fire, heat and hot substances: global, regional and national morbidity and mortality estimates from the Global Burden of Disease 2017 study." *Injury prevention* (2019).

Acknowledgements

I am indebted to the National Institute for Health Research (NIHR) for funding an *older* clinician to undertake a PhD. This decision has made an incredibly positive impact on my life and I hope, produced work that will benefit patients with burns internationally. I received a diagnosis of metastatic breast cancer shortly after starting the Doctoral Fellowship. I made the decision to continue, with the support of the NIHR and Professor Jane Blazeby. Continuing the research through necessary treatments, was only possible with the support of Jane, my husband Norman, Dr Jeremy Braybrooke and University Hospitals Bristol Staff, the NIHR, clinical and academic colleagues, and my very dear friends. I hope they know the difference they have made.

This project, which I am, always have and always will be passionate about, would not have been possible without the participation of patients across the UK and colleagues internationally, who have participated with excitement, wisdom and honesty. My supervisors, Professor Jane Blazeby, Professor Nichola Rumsey, Dr Sara Brookes and Professor Chris Metcalfe have supported me with knowledge and kindness. My internal assessor, Dr Shelley Potter, needs a special thank you. I would like to acknowledge the chair and multi-disciplinary steering group members. Dr Jamie Kirkham led us brilliantly through complex discussions. The group included patients and a parent. Thank you, Helen, Sophie, Livvie and Nur. Thank you to Dr Carmen Tsang who supported the statistical work and decision-making regarding methodology, and Ms Alison Horne, our REDCap expert. Thank you also to the research nursing staff led by Ms. Karen Coy who supported me in governance issues and helped with patient recruitment. Finally, I would like to acknowledge the help given to me by my colleague Dr Anna Davies. Anna supported the project from start to end. She listened to my, sometimes unorthodox, ideas and plans. She double-checked much of the data. She also helped with co-authoring papers, helping to set-up the consensus meeting and reading written work.

Disclosure

The following details describe my input into the five studies described in this thesis.

Study 1, Chapter Two: **An exploration of the variation in clinical outcome reporting across burn care RCTs.**

Published paper: Young AE, Davies A, Bland S, Brookes S, Blazeby JM. Systematic review of clinical outcome reporting in randomised controlled trials of burn care. *BMJ Open.* 2019 Feb 1;9(2):e025135.

Study roles and responsibilities:

- Dr Amber Young: I was responsible for the concept of the project with JMB. I undertook the systematic review. I was responsible for the data collected. I wrote the published paper.
- Dr Anna Davies double-checked 10% of all the data and contributed to paper-writing through editing.
- Professor Jane Blazeby was responsible for over-seeing the project and editing the published paper as senior author. Dr Sara Brookes edited the published paper.
- Ms. Sophie Bland (patient) read the paper for ease of understanding and patient relevance.

Study 2, Chapter Three: **The development of an understanding of what makes an outcome unique.**

Published paper: Young AE, Brookes ST, Avery KN, Davies A, Metcalfe C, Blazeby JM. A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. *Journal of Clinical Epidemiology*. 2019 Nov 1;115:14-24

Study roles and responsibilities:

- Dr Amber Young: I conceived the project alone. I undertook the systematic review. I was responsible for all the data. I wrote the published paper.
- Dr Anna Davies assisted with data double-checking and editing the paper.
- Professor Sara Brookes, Dr Kerry Avery, Professor Chris Metcalfe and Professor Jane Blazeby assessed the methodology and edited the paper. JMB was the senior author. All

the authors and other members of the Bristol Centre for Surgical Research (https://www.bristol.ac.uk/population-health-sciences/centres/surgical-research/) contributed to discussions on the definition of a unique outcome.

Study 3, Chapter Four: **An analysis of how variation in the definition of a specific outcome (burn wound infection) across burn care trials impacts evidence synthesis.**

Published papers: Davies A, Teare L, Falder S, Coy K, Dumville JC, Collins D, Moore L, Dheansa B, Jenkins AT, Booth S, Agha R, Shah M, Marlow K, Young AE. Protocol for the development of a core indicator set for reporting burn wound infection in trials: ICon-B study. *BMJ Open.* 2019 May 1;9(5):e026056.

Davies A, Spickett-Jones F, Jenkins T, Young AE. A systematic review of intervention studies demonstrates the need to develop a minimum set of indicators to report the presence of burn wound infection. Accepted March 2020 and in press *Burns* journal.

Study roles and responsibilities:

- Amber Young: I conceived the project, wrote the protocol and devised the methodology, undertook the systematic review with AD, double-checked 10% of the data with FS-J, co-wrote the papers with AD and acted as senior author in terms of responsibility for data and the final papers. I am chair of the national infection consensus in burns (ICon-B) project.
- Dr Anna Davies co-wrote the papers as first author and undertook data collection for the systematic review with myself.
- Ms Spickett-Jones, research nurse, double-checked 10% of the data and edited the paper.
- Professor T Jenkins (professor of Chemistry) edited the papers as a wound infection detection expert.

Study 4, Chapter Five: **An analysis of how variation in the timing of the assessment of unique outcomes across trials impacts relevance to patients.**

Paper for re-submission: Amber E. Young, Fatima Yaqub, Chris Metcalfe, Sarvnaz Sepehripour, Jane M Blazeby. Clinical trials in burns care primarily focus on short-term outcomes of uncertain longer-term patient benefit: a systematic review. Submitted to the *Journal of Clinical Epidemiology,* who returned it prior to peer-review, for submission to a burn specialist journal.

Roles and responsibilities:

- Dr Amber Young: I conceived the project, led on the systematic review, paper screening and data extraction with the support a medical student (Fatima Yaqub) and plastic surgery registrar (Sarvnaz Sepehripour) who undertook data cleaning and double-checking, and I wrote the paper.
- Professor Chris Metcalfe and Professor Jane Blazeby acted as senior authors and edited the paper.

Study 5, Chapter Six: **A consensus on which burn care outcomes are most important to patients, carers, researchers and international multi-disciplinary burn care professionals.**

Roles and responsibilities:

- Dr Amber Young: I conceived the project with JMB, wrote the published protocol as first author and have written the final paper as first author (ready for submission). I achieved all research permissions and maintained project governance with the support of the research nursing team leader (Ms Karen Coy). I undertook all patient and staff interviews. Ms Nancy Horlick transcribed all the interviews. I analysed all the interviews. I led on the final outcome long-list and achieved agreed domains with the support of AD, Ms Karen Coy and a patient representative. I led on the Delphi survey design and contenct. Ms Alison Horne set up the survey on REDCap, with the support of myself and AD. I personally e-mailed more than 500 international professional survey participants. I

extracted data with the support of AD. I attended all steering group meetings. I chaired the final consensus meeting.

- Dr Anna Davies: supported the Delphi study set-up and worked with myself and Ms Horne on REDCap. AD supported data extraction and analysis. She edited and helped prepare the final paper. She helped set up and run the final consensus meeting.
- Dr Carmen Tsang supported methodology decisions and gave statistical advice.
- Professor Chris Metcalfe supported statistical decisions and edited the final paper.
- Professor Jane Blazeby was the senior author for the final paper and supervised the project.

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- **NIHR:** This thesis presents independent research funded by the National Institute for Health Research (NIHR) Doctoral Research Fellowship DRF-2016-09-031. The views expressed are those of the author of this thesis and not necessarily those of the NHS, the NIHR or the Department of Health.
- JMB is an NIHR Senior Investigator and leads the Bristol Centre for Surgical Research.

- **The Scar Free Foundation** (https://scarfree.org.uk/) have funded part of a senior research associate to support a parallel project. This is to specifically explore the issues of short-term outcome reporting in burn care research. This work is not part of the studies reported in this thesis.

Conflicts of interest: I declare no conflicts of interest.

Prof Jane Blazeby Date: 31st March 2020

Dr Anna Davies
Date: 7th April 2020.

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:

Amber Elizabeth Russel Young

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Glossary of abbreviations

ABA	American Burn Association
BBA	British Burn Association
BWI	Burn Wound Infection
CDC	Centre for disease classification (USA)
CIS	Core Indicator Set
CMS	Core Measurement Set
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COS	Core Outcome Set
COSMIN	Consensus-based standards for the selection of health measurement instruments
COS-STAD	COS Standards for development
COS-STAR	COS Standards for reporting
EBM	Evidence-Based Medicine
FDA	USA Food and Drug Administration
HCP	Healthcare Professional
IQR	Inter-Quartile Range
ICon-B	Infection Consensus in Burns project
MeSH	Medical subject headings
NHS	National Health Service
NIHR	National Institute for Health Research
ORB	Outcome Reporting Bias
ORH	Outcome Reporting Heterogeneity
PICOS	Patient, Intervention, Comparator, Outcome, Setting
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient Reported Outcome
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trial
SD	Standard Deviation
SR	Systematic Review
WHO	World Health Organisation

Chapter 1 Evidence to support decision-making in burn care; what is quality?

1.1 Introduction

Clinical decision-making for patients with burn injuries impacts more than 11 million people globally each year, according to the most recent published data (1). Clinical choice of management strategy for these patients requires evidence synthesised from high quality, well designed and conducted studies. These studies include randomised and non-randomised studies. Non-randomised studies are defined by the Cochrane Collaboration as "any quantitative study estimating the effectiveness of an intervention (harm or benefit) that does not use randomization to allocate units to comparison groups"(2). These include cohort studies, case-control studies, controlled before-and-after studies, interrupted-time-series studies and controlled trials that use ineffective randomization strategies. However, the highest quality evidence is gained from randomised controlled trials (RCTs) and from systematic reviews (SRs) that analyse data from RCTs(3). RCTs are the preferred trial design for investigating harms and benefits of healthcare interventions because they are the least likely to be biased. In burn care, numbers of RCTs are increasing(4). However, SRs of these RCTs have not provided conclusive data to support many commonly used treatment strategies. This is most likely to be associated with poor methodological quality and inconsistency in outcome reporting (5-10). The failure to synthesise outcome data results in a lack of reliable evidence, research waste and variation in clinical practice and patient outcomes(11-13).

This thesis will explore the reasons that limit researchers' ability to synthesis data that answers clinical questions in burn care and assess any potential solutions. It will focus on challenges in aggregating data from RCTs relating to outcome choice and reporting.

1.2 Thesis aim and research questions

Thesis research question:

Is it possible to increase the provision of data from burn care RCTs that can be synthesised into evidence that answers clinical questions, through the development of a Core Outcome Set?

Objectives and chapters:

The following objectives will be used to answer the research question:

1. An exploration of the variation in clinical outcome reporting across burn care RCTs. (Chapter Two).
2. The development of an understanding of what makes an outcome unique. (Chapter Three).
3. An analysis of how variation in the definition of a specific outcome (burn wound infection) across burn care trials, impacts evidence synthesis (Chapter Four).
4. An analysis of how variation in the timing of the assessment of unique outcomes across trials, impacts relevance to patients (Chapter Five).
5. A consensus on which burn care outcomes are most important to patients, carers, researchers and international multi-disciplinary burn care professionals (Chapter Six).

In this introductory chapter, the need and requirements for developing research data of high enough quality, to be collated into reliable and truthful evidence to answer clinical questions in burn care, will be explored. This will be placed within the context of a large, global, burn-injured population, with many diverse treatments and little synthesised evidence to prevent variation in clinical decision-making.

In the Discussion chapter, the thesis research question will be answered. The methodological challenges impacting evidence synthesis in burn care research (Figure 1) will be explored. Their relative importance, will be justified, through a comprehensive assessment of the work described in Chapters Two to Five. The utility of a burn care Core Outcome Set to solve some, or all of these issues, will be debated. Future work, originating from the work undertaken for this thesis, will be presented at the end of Chapter Seven.

Figure 1: Challenges to evidence synthesis.

1.3 Burns: aetiology, epidemiology and principles of care

Ten percent of all deaths worldwide are from injury(1). In terms of global injury type, the incidence of burns is fourth. Burns are injuries caused by heat, freezing, electricity, chemicals, radiation or friction. Thermal burns from dry sources (fire or flame) and wet sources (scalds) account for approximately 80% of all reported burns(14). This thesis will focus on research relating to patients with cutaneous burns caused by thermal sources(15-17).

Burn injuries are common, with numbers particularly high in lower income countries (1, 18, 19). Globally, burn injuries increase as economic wealth decreases(20). In India, with a population of over 1 billion, there are 700,000 to 800,000 burn admissions annually(21). In Bangladesh, in 2003, a survey of 350,000 children and 470,000 adults reported an overall incidence of 166 burns per 100,000 people (22). In higher income countries, such as the USA, 410,149 non-fatal burns were reported in 2008. In England and Wales, approximately 130,000 patients attend emergency departments with burns annually (http://www.ibidb.org/ accessed December 2019). From 1st January 2003 to 31st December 2011, 81,181 patients were referred to NHS specialist burn services, of which 57,801 required hospital admission(23). Children account for almost half of the population with severe burn injuries in Europe, and children younger than five years, account for 50% to 80% of all childhood burns (24).

Of deaths from burns, more than 95% of fatal fire-related burns occur in low- and middle-income countries (25). When burn rates are compared between countries of varying economic wealth at global level, there is a negative correlation between Gross Domestic Product ($r = -0.69$, $p < 0.01$) and burn mortality rates, and a positive correlation with income inequality ($r = 0.44$, $p < 0.001$)(20). Worldwide, the incidence of deaths from burns in children is 2.5 per 100,000 people and is highest in Sub-Saharan Africa (4.5 per 100,000 people)(20). It has not been possible to identify published evidence on current numbers of deaths in adults from burn injuries worldwide. The World Health Organisation (WHO) report "an estimated 265,000 deaths occur each year from fires alone, with more deaths from scalds, electrical burns, and other forms of burns, for which global data are not available" (https://www.who.int/en/news-room/fact-sheets/detail/burns). The majority of burns, however, are non-fatal and mortality is continuing to decrease in higher income countries (1).

In the USA, the age-adjusted death rate from fire and burns has dropped from 2.99 per 100,000 in 1981, to 1.2 per 100,000 in 2006(1). Similar trends in mortality are seen in Europe and the UK(24). If death occurs, it is most commonly due to sepsis and/or multi-organ failure(26, 27).

Burn wounds range from small area burns (usually due to hot drinks or contact with hot surfaces), to a severe flame or bath water injury (23, 28). Wounds vary in severity, in terms of the tissues affected (depth) and surface area (size)(29).The severity of the injury can be quantified, which allows some ability to provide a prognosis, in terms of mortality and morbidity(30). Independent of severity, all injuries have the potential to affect patients from a cosmetic, functional or psychological viewpoint, for many years after the primary injury (31-33).

The primary aim of burn care is to achieve survival and then to restore function and cosmesis, while minimising pain and psychological impact. Management is primarily surgical, with supportive systemic care. Surgical care depends upon early excision of damaged tissue, while leaving as much undamaged dermis as possible, early wound coverage, and prevention and early treatment of infection(15, 34). Improved patient outcomes result from advances in fluid resuscitation, improved coverage of wounds, early treatment of infections, better management of the burn-induced hypermetabolic response and early functional and psychological rehabilitation (15, 35). New surgical techniques continue to be introduced, and advances are regularly made in understanding the wound environment, critical care and dressing technology(14). The frequent surgical episodes, dressing costs, short- and long-term wound and scar treatment, long lengths of stay in hospital and a need for rehabilitation, result in burn care being costly (36-38).

For clinicians to make choices regarding the management strategy that will deliver the most clinical- and cost-effective care for patients with burns, requires SRs and meta-analyses that collate evidence from high quality trials(39). This chapter will explore what is meant by high quality research. It will debate why RCTs, and SRs of RCTs, are maximally influential. Issues with RCT methodology that challenge evidence synthesis, including risks of bias and outcome choice, definition and timing of reporting will also be discussed. The chapter will propose a

possible solution to issues that limit collation of trial results in burn care, and prevent the use of evidence in clinical treatment choice globally.

1.4 What quality of evidence is required to support clinical decision-making in burn care?

In 1996, Sackett stated that the most effective way to ensure that clinical decision-making will result in improved patient outcomes is "the conscientious and judicious use of current best evidence in conjunction with clinical expertise and patient values ....." (40). The principles of using *current best evidence* to support clinical management choices, known as *evidence-based medicine* (EBM), are that evidence varies in quality, and that clinical decisions should be based on the highest quality evidence available (3, 41-44). SRs of well-designed and conducted RCTs provide the most reliable evidence regarding the effects of healthcare interventions(45, 46). If there is a lack of evidence, or evidence that cannot be synthesised, it is likely that clinical practice will remain based on historical strategies and will vary between healthcare services(47-49). Accumulated data suggests that this is true in burn care, with treatment strategies and patient outcomes inconsistent between services, within and between countries(11-13, 50, 51).

Recognition of the importance of using evidence to standardise care, has resulted in the development of the *Cochrane Collaboration*. Cochrane has developed standards for research methodology including RCT design and conduct, SR techniques and trial reporting through the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network (http://www.equator-network.org/). It has also developed processes to translate new knowledge into evidence-based clinical guidelines (*knowledge translation*) (52-55). Despite advances in EBM, it has drawn recent criticism(56). The practice has been described as relatively inflexible, not sufficiently patient-centred, and that it is difficult to draw clinical inference from studies with statistical significance alone. There are also concerns that RCT designs, and other studies, lack the sophistication to account for and provide evidence to treat patients with multiple co-morbidities(57). Despite this, there is agreement in the literature,

that EBM (perhaps with some modifications) should continue in order to provide the basis for safer, more consistent, and more cost- and clinically-effective care(41).

1.5 What makes evidence high quality?

A principle of EBM described by Sackett as *current best evidence*, requires an understanding of methodological quality. Guyatt defines quality in this context as: "reflecting the extent to which confidence in an estimate of the effect is adequate to support a particular recommendation"(58). The *hierarchy classification of evidence quality* ranks trial design for reliability of evidence of causal effects of interventions(59, 60). This prescribes the superiority of well-conducted RCTs for determining the trustworthiness or quality of evidence for the clinical benefit of an intervention(41, 61-63). An RCT can be defined as a methodological design, that includes random assignment of subjects to two or more subject groups, in which one or more clinical interventions are applied to one of the groups and not to the other(64). In burn care, RCTs are increasing in number, as new surgical techniques and care pathways are introduced. However, trial quality is uncertain(4, 65-67). Understanding quality in research, requires an understanding that any flaws in design, conduct, analysis and reporting, can bias results of RCTs and prevent the reported conclusions from reflecting the truth (68-70). This thesis will focus on one aspect of methodological quality, that can challenge the utility of RCT conclusions and make collating the data from the RCTS challenging. This relates to outcome reporting, in terms of choice, definition and timepoint of assessment(71). These issues will be explored in Chapters Two to Five, with Chapter Six suggesting a possible solution. However, understanding and resolving issues with outcome reporting still requires that reporting a truthful effect of an intervention, needs an RCT to be internally and externally valid(72, 73).

To assess the quality of RCTs, the truthfulness of the results (*internal validity*), the relevance of the study (*external validity*), the extent to which study results are free from random error (precision) and adherence of the study to standards of reporting, are all requirements for confidence in using the evidence as current best evidence (74-77). External validity can be defined, as whether research findings can be generalised to different persons, settings, and times, and is important if the research is to be clinically relevant. External validity determines the relevance of trial results(74, 78). The internal validity of a study is the extent to which it is

free from bias. Bias is a systematic error that leads to a deviation of the results from the truth(62, 79, 80). It determines if a fair comparison of intervention and comparator has been made. Bias is distinguished from random error, the latter being error due to chance, and is accommodated and quantified by statistical methods (e.g. confidence intervals)(81, 82). Precision depends upon the number of participants and events in a study (sample size) and the degree of variation in the outcome measure (83, 84).

This thesis is focused on the ability to synthesise evidence from burn care RCTs that are at low risk of bias and are internally and externally valid (of high quality).

1.5.1 Risk of Bias

For a clinical question to be answered truthfully and reliably, evidence synthesised from data included in SRs, must be derived from RCTs at low risk of bias(85). Bias in RCTs may lead to an over or underestimation of the true effectiveness of an intervention. The risk of bias can be assessed, and the possible effect on study results explored, through sensitivity analyses for example. It can be assessed to see how it can influence the conclusions drawn from the trial(76, 86). In burn care, few studies have assessed the risk of bias across trials, and these studies have been limited by their lack of comprehensiveness and methods of quality assessment (65, 66, 87, 88). The issues with poor quality have been noted by authors of Cochrane SRs of burn care interventions. Conclusions can commonly not be drawn, due to the high risk of bias in included studies(8, 9, 89).

Common types of bias include those listed below.

- For trials:
    - *Selection bias*: is defined as "systematic differences between baseline characteristics of the groups that are compared" (2). The aim of randomisation, is to ensure that factors that might influence outcome, whether known or unknown, are equally distributed in the trial groups (90-94).
    - *Measurement bias*: is the biased assessment of outcomes, and refers to systematic differences between groups in how outcomes are determined (95).

- *Attrition bias:* occurs if there are systematic differences in the characteristics of participants dropping out of the trial between study groups(96).
- *Outcome reporting bias* (ORB): refers to the selective reporting of some results but not others depending on the nature of the results (97).

- For systematic reviews:
  Bias is related to the systematic review process, and is also inherent within the included trials as discussed above(98). Systematic reviews need an accessible and registered protocol. Reviews also need to access literature from as many sources as possible and to clarify the extent of publication bias.
    - *Publication bias*: exists when trials with statistically significant results are more likely to be published than those with non-significant results (99).

Several other types of bias exist, which will not be covered in detail here, as they lie outside of the scope of this work.

1.5.1.1 Assessment of type and magnitude of bias in RCTs

Since the introduction of the EBM-defined hierarchy of evidence, more sophisticated judgements on assessment of bias and reporting quality have been developed(58, 100, 101). In 2005, the Cochrane Collaboration developed a strategy for assessing the quality of research, currently the most commonly used tool for assessing the risk of bias in RCTs(45). A revised version of the tool (Risk of Bias (RoB 2)) has now been developed(102).

Assessment of bias in RCTs is required to understand if the study findings represent the truth and can, therefore, be synthesised to provide more precise and truthful findings. The second group of challenges that affect RCT quality and which are further potential blocks to the ability to synthesis evidence across trials, include issues of outcome choice and reporting (71). This forms the main topic for the work covered in this thesis.

1.6 Outcome selection and reporting; what is quality?

1.6.1 Outcome selection in RCTs

The rest of this chapter will describe what is meant by an outcome and describe the different types of outcome assessed in RCTs. Methodological challenges with outcome reporting will be explored.

Clinical trials aim to assess whether a healthcare intervention is effective, by comparing outcomes chosen to reflect benefit or harm(103). A 2014 on-line Delphi survey of 48 UK Clinical Research Collaboration registered Clinical Trials Unit directors, found that "choosing appropriate outcomes to measure" was one of the top three priorities for research into study methodology(104). The World Health Organisation (WHO) stated that: "choosing the most important outcome is critical to producing a useful healthcare guideline", reflecting the impact of outcome choice on the provision of evidence for clinical decision-making(105). Outcomes selected for use in RCTs must be clearly defined and reported(106). This ensures trial relevance and ability to answer the research question. Factors affecting outcome selection relate to trial logistics(107). The choice of outcome(s) will determine the study sample size and length of follow-up (study duration)(108). Outcomes also need to be important to patients if the trial results are to be relevant(71, 106, 109, 110). This is particularly important in effectiveness trials, as discussed in Chapter Five. Disagreement by researchers on which outcomes are the most important to measure and report in any healthcare area, results in inconsistent reporting across trials and limits the ability to compare and collate evidence(111).

1.6.2 What is an outcome?

Before discussing types of outcome and issues with outcome choice and reporting, it is important to consider what is meant by a healthcare outcome and the context in which the definitions are used. The New South Wales Health Department defines an outcome as a "change in the health of an individual, group of people or population, which is attributable to an intervention or series of interventions" (112) (113). Within the context of clinical trials, with which this thesis is concerned, Ferreira states: "outcomes (also called events or endpoints) are

variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population"(114). The term *trial outcome* has been defined by Williamson et al in the Core Outcome Measures in Effectiveness Trials (COMET) handbook, as "a measurement or observation used to capture and assess the effect of treatment such as assessment of side effects (risk) or effectiveness (benefits)"(115). Chan takes the definition further by adding a temporal element. He describes a research outcome as "a variable measured at a specific time point to assess the efficacy or harm of an intervention" (116). For the purposes of this thesis, a healthcare outcome will be initially defined using Chan's definition, as the timing of outcome assessment in burn care research is important. For example, the impact of scarring is likely to be different for patients at six months in comparison to five years after injury(117). The definition of a unique (single) outcome and the impact of a variation in outcome definition and timing of assessment will be discussed in Chapters Three, Four and Five.

The above discussion relates to generic definitions of healthcare outcomes in different contexts. It is also important to consider the definition and importance of the different types of outcomes chosen, measured and reported in RCTs.

1.6.3 Types of outcomes

1.6.3.1 Primary and secondary outcomes

The USA Food and Drug Administration (FDA https://www.fda.gov/home) discusses the *hierarchy of families of endpoints*(118). These include primary, secondary and exploratory endpoint families.

The FDA defines the *primary outcome* as "the endpoint(s) that will be the basis for concluding that the study met its objective". Calvert describes the primary outcome as "the most important outcome in a trial, providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial"(119, 120). The choice of primary outcome will determine study sample size, (121). *Sample size* is the number of observations to be

included in a sample that will achieve sufficient statistical power to determine differences between groups(122). The most appropriate primary outcome, is the one for which there is the most reliable evidence associated with the intervention of interest(123). However, relevance to patients must also be considered and which will be discussed further in Chapter Five(124).

Secondary outcomes can be defined as "outcomes pre-specified in the protocol that assess additional effects of the intervention"(119). The FDA describe secondary endpoints as "not sufficient to establish efficacy in the absence of an effect on the primary endpoints; not required for establishing efficacy". Secondary outcomes are most useful if they add supporting evidence to the primary outcome(114). They are outcomes of interest which the study is not specifically powered to assess. Calculations can be made for secondary outcomes. However, this may increase the sample size required(114).

Exploratory outcomes are those used to evaluate and/or form hypotheses about the intervention outcome(s) (NCI Thesaurus: https://ncithesaurus.nci.nih.gov/ncitbrowser/). The FDA discuss exploratory endpoints as *hypothesis-generating endpoints* (clinical utility unknown) or variations on primary or secondary endpoints. There is still a lack of clarity about pre-specified secondary and exploratory outcomes(125).

1.6.3.2 Composite primary outcomes

A primary outcome may be a combination of outcomes instead of a single outcome. A composite outcome may be chosen because:

- no single outcome fully describes the overall outcome of interest.
- individual outcomes are rare and therefore statistical power would require an impractically large sample size to demonstrate a significant effect.
- when it makes biological or clinical sense to group outcomes together (126).

It is important to understand that a positive result for a composite outcome, applies only to the outcome group and not the individual components. Whilst they are valuable in overcoming the issues listed above, they also have drawbacks; for example, a composite of several event outcomes will often be dominated by the more frequently occurring early and less serious event types. Composite outcomes can also overstate the results of the individual

outcomes(109, 127). Composite outcomes are most commonly used in cardiovascular research, with this and other issues reported(127-130) In burn care research, composite outcomes are uncommon, except within trials assessing outcomes relating to critical illness and when longer-term scoring systems are used to assess scarring and function(131-133)

There are many ways to define the different types of outcome assessed in RCTs. The definitions chosen below have been selected for clarity.

Figure 2: Outcome types in RCTs.

1.6.3.3 Clinical outcomes

Clinical outcomes are the most widely chosen and reported outcomes in RCTs in healthcare. They can be defined as: "variables that reflect how a patient functions, or how long a patient survives"(134). Examples include measurable changes in clinical condition, survival status, functional or physical status, and health-related quality of life, when assessed by a clinician. In burn care, short-term clinical outcomes commonly relate to the healing process or complications related to it, such as wound infection, time to complete wound healing and survival. Longer-term clinical outcomes include scarring and physical function. Most clinical outcomes involve an assessment made by a clinician. Examples include blood pressure, core temperature, assessment of symptoms etc. Some of these are objective (e.g. blood pressure). These are not subject to individual interpretation and likely to be reliable measures(108). Others (e.g. clinician assessment of patients' symptoms; pain assessments) are subjective. In burn care, clinical outcomes include length of stay in hospital, incidence of sepsis or quantitatively or qualitatively measured scarring.

A sub-set of clinical outcomes, *surrogate outcomes*, are defined as "laboratory measurements or physical signs used as a substitute for a clinically meaningful outcome" and are usually assessed in the short-term (124, 135, 136). The number of surrogate outcomes are, therefore, likely to be more in number than longer-term outcomes and easier (cheaper) to measure(137). Surrogate outcomes can be used as proxies for longer-term patient-important clinical outcomes, but only with knowledge that the surrogate will serve as a direct substitute for the longer-term outcome (134, 137). Such validation is likely to require RCTs assessing the surrogate and clinical outcome, to demonstrate that both are changed by the intervention in a comparable manner(138). Surrogate outcomes that have not been validated as proxies for longer-term outcomes, should be described as exploratory outcomes (as described above), until validation has been proven and agreed. The relationship between surrogate and longer-term outcomes will be explored further in Chapter Five.

Another group of short-term outcomes relate to intervention complications or *adverse events*(139-142). Adverse events can be defined as "injuries or complications which occur as a

result of health care management and not as a result of the patient's pathology, and which cause prolonged hospital stay, morbidity, or mortality"(143, 144). A specific group of adverse events relate to surgery and known as *post-operative complications*(140). The definition of a surgical complication is "any deviation from the expected steady recovery after a surgical operation"(145). Postoperative complications, such as blood loss, wound infection, skin graft loss in burn patients, will necessarily impact, but cannot be substituted for other more patient-important, longer-term clinical outcomes(146).

1.6.3.4 Patient-important outcomes

A patient-important outcome has been defined as: "a characteristic or variable that reflect how a patient feels, functions or survives"(147). Patient-important outcomes are directly relevant to clinical practice(148). They may be assessed short-term (e.g. acute pain) but are more commonly assessed at a longer-term timepoint. Examples in burn care include scar quality, physical function or quality of life(149-152). Gandhi and colleagues showed that trials that are of longer duration, are more likely to report patient-important primary outcomes(124). In 2010, the US Congress set up the *Patient-Centred Outcome Research Institute*, a research funding body for comparative effectiveness research(153). It recommends "measuring outcomes that people in the population of interest notice and care about"(154). This issue will be discussed in more detail in Chapter Five.

1.6.3.5 Patient-reported outcomes.

It is important, as discussed above, that outcomes selected for use in RCTs should be relevant, and as a result of engagement with stakeholders including patients (155, 156). Researchers and research funders are increasingly assessing patient-reported outcomes (PROs), using standardised health-related questionnaires. These are outcomes assessed directly from the patient's perspective(157, 158). Not all PROs are patient-important; patients are asked, but may not have chosen the questions(159). PROs are often used to assess symptoms, such as pain or fatigue, interference with activities of daily living, treatment satisfaction or quality of life(160, 161). They may also assess emotional, psychological and physical function. Many generic, disease- and domain-specific instruments for assessing PROs have now been

developed and validated, each containing multiple scales and items(162). Condition-specific PROs are likely to have greater relevance and sensitivity to change(163, 164). PROs in burn care include scar quality, quality of life and anxiety(162).Recent work by Griffiths and team on burn care-specific PROs has produced the CARe (https://www.careburnscales.org.uk/) burn scales (159, 161, 162, 165, 166). For PRO data from RCTs to provide value, the PROs need to be reported consistently across trials, to allow comparison of data between trials(167). This is limited by the multiplicity and heterogeneity of tools available(168). In burn care, a 2010 literature review described a number of clinical and patient reported tools to quantify scars, of which five are different patient-reported versions(169).

1.6.4 Outcome classification

Classifying outcomes allows an increased ability to search for, and compare trials assessing the effect of an intervention on the same outcome. There is currently no agreement on how clinical outcomes should be classified. Wilson and Cleary suggested a taxonomy dividing clinical outcomes into biological and physiological, symptoms, functioning, general health perceptions, and overall quality of life(170). Other authors proposed the *ECHO (Economic, Clinical, Humanistic Outcomes) Model*, which also includes costs and the inter-relationships with clinical and quality of life outcomes (171). *The International Classification of Functioning, Disability and Health* is the World Health Organisation's (WHO) framework for measuring health and disability at individual and population levels(172).

A further way to understand trial outcomes relates to their use in different types of trial. Randomized trials can provide evidence related to the efficacy or effectiveness of an intervention (173, 174). RCTs using an *efficacy (explanatory) design*, aim to provide evidence of whether the treatment will work in optimal settings(175). These trials generally compare the effects of a treatment to a placebo, or usual treatment, and commonly use short-term clinical outcomes such as symptom scores or biomarkers(141). An efficacy trial can overestimate an intervention's potential effect in clinical practice (176). *Effectiveness (pragmatic) trials* assess the intervention effect under real-world clinical conditions(177). Effectiveness is a measure of the extent to which a specific intervention, when used in routine care, does what it is intended to do for a specific population. The term pragmatic was first introduced by Schwartz for trials

that combine the real-world nature of an observational study with the scientific methodology of an RCT. These trials are designed to give better answers to questions of relevance in day-to-day clinical practice (132). Pragmatic studies examine more heterogeneous patient populations, have less-standardised treatment protocols, are delivered in routine clinical settings, compare the intervention to another intervention or standard care and use longer-term outcomes such as physical function or quality of life(178). They are likely to have increased external validity (generalisability)(179). As a result, there may therefore be an increased risk of bias, which must be balanced against an understanding of the relative benefits and risks of treatments in the true clinical scenario (66, 81, 131).

1.6.5 Reporting of RCTs

1.6.5.1 Outcome reporting standards:

The *Consolidated Standards of Reporting Trials (CONSORT) statement* have been developed to standardise the reporting of RCTs (70, 77, 180). In the section below, I will focus specifically on outcome reporting.

1.6.5.2 Outcome reporting bias within RCTs

If completeness of outcome reporting, as *per* the CONSORT statement, is not achieved, trials are at risk of outcome reporting bias (ORB); defined as the publication of a subset of the original outcomes, on the basis of the results, for inclusion in publication (181). It can include:

- The omission of all data for an outcome.
- The reporting of data for a subset of time points.
- Partially reporting outcomes (sub-group analyses).

Statistically significant results have higher odds of being reported compared to non-significant results, for both benefit and harm outcomes(97, 116, 182). ORB can therefore lead to the over- or underestimation of treatment effects, with overestimation most likely (125, 183-185). ORB occurs, because researchers either do not pre-specify outcomes, or do not report all the pre-specified outcomes(186). In 2005, the International Committee of Medical Journal Editors

(ICMJE) introduced mandatory trial registration guidelines. Member journals require trial registration prior to patient enrolment, as a condition of publication (122). Registering trials requires researchers to pre-specify both primary and secondary outcomes. Despite this, the continued existence of ORB has been identified from several reviews (Table 1).

Table 1: Selection of studies providing evidence for existence of ORB in RCTs.

Note: text extracted verbatim from cited studies.

Author	Year	Methodology	Main findings	Reference
Chan et al	2004	Analysis of protocols for RCTs approved by the Canadian Institutes of Health Research with journal publications.	Of 48 trials with 1,402 outcomes, a median of 31% assessing the efficacy and 59% assessing the harm of the intervention per trial were incompletely reported.	(116)
Chan at al	2004	Analysis of 122 protocols and published reports of RCTs approved by Danish Scientific-Ethical Committees 1994-1995.	3,736 outcomes reported: 50% efficacy and 65% harm outcomes per trial incompletely reported. Statistically significant outcomes had more than a two-fold greater odds ratio of being fully reported versus non-significant results.	(187)
Chan et al	2005	Assessment of all published RCTs in PubMed whose primary publication appeared in December 2000.	519 trials, 553 publications and 10,557 outcomes identified. The median proportion of incompletely reported efficacy outcomes per trial was 42% (n=505). For harm outcomes, the median proportion per trial was 50% (n=308). Within any trial, incompletely reported outcomes had a higher odds ratio of being statistically non-significant versus fully reported outcomes.	(97)
Dwan et al	2008	Assessment of study publication bias and ORB in RCTs.	Three of 16 studies found that statistically significant outcomes had a higher odds ratio of being fully reported versus nonsignificant outcomes.	(182)
Mathieu et al	2009	Comparison of primary outcomes specified in RCTs with those reported in articles in 2008 in 10 journals with the highest impact factors to determine whether primary ORB favoured significant outcomes.	Among articles with trials adequately registered, 31% (46 of 147) showed some evidence of discrepancies between the outcomes registered and the outcomes published. The influence of these discrepancies could be assessed in only half and in these statistically significant results were favoured in 82.6%.	(188)
Dwan et al	2010	Assessment of RCTs for ORB in a SR of intravenous and nebulised magnesium for treatment of asthma.	Of 24 studies, two were excluded for not reporting either of the two outcomes of interest and there was high suspicion of outcome reporting bias in four studies.	(189)
Smyth et al	2011	Trial protocols were compared with subsequent publication(s) to identify any discrepancies in the outcomes reported. Telephone interviews were conducted with the respective trialists to investigate more extensively the reporting of the research and the issue of unreported outcomes.	268 trials were identified. Interviews were conducted with 59 (37%) of the 161 trialists. Sixteen trial investigators failed to report analysed outcomes at the time of the primary publication, 17 trialists collected outcome data that were subsequently not analysed, and five trialists did not measure a pre-specified outcome over the course of the trial. In almost all trials in which pre-specified outcomes had been analysed but not reported (15/16, 94%) of this under-reporting resulted in bias. Of trials in which pre-specified outcomes had been measured but not analysed, in (4/17, 24%) the direction of the main findings influenced the investigators' decision not to analyse the remaining collected data.	(190)
Kirkham et al	2010	Assessment of the prevalence of ORB and its impact on Cochrane reviews. Examination of unselected cohort of new reviews from 50 of the 51 Cochrane collaboration review groups published in three issues of the Cochrane Library 2006-2007.	In 31% of 2,562 trials from 309 new Cochrane reviews in 2006/7, the review primary outcome was either partially reported or not reported. ORB was suspected in at least one RCT in 35% of the reviews. For 6% of the trials, the primary outcome was measured and analysed but partial reporting meant the	(191)

			data could not be included in a meta-analysis. The median amount of review primary outcome data missing from trials for any reason was 10%.	
Page et al	2015	A Cochrane review to summarise the characteristics of studies that have investigated the prevalence of selective inclusion or reporting in SRs of RCTs.	Meta-analysis of 4 studies (including 485 Cochrane Reviews); 38 reviews added, omitted, upgraded or downgraded at least one outcome between the protocol and published SR.	(192)
Ioannidis et al	2017	Centre for Evidence Based Medicine Outcome Monitoring Project: checked articles published in 2015/16 in the top five general medicine journals based on impact factor, against protocols and registries pre-dating trial recruitment.	13% of clinical trials reported all primary and secondary outcomes the same in the protocols, registries and articles.	(193)
Howard et al	2017	Search of PubMed between 2010 and 2015 for RCTs published in the top three impact factor neurology journals.	From 180 trials, 6% of primary outcomes were demoted, 21% primary outcomes were omitted from the publication, and 34% of unregistered primary outcomes were added to the published report. There were 10% of secondary outcomes upgraded to a primary outcome, and 29% of trials changed the timing of outcome assessment.	(194)

1.6.5.3 Variation in outcome reporting across trials

ORB is an issue that occurs *within* a single RCT. Inconsistency of outcome reporting is an issue that occurs *across* RCTs within one healthcare area. It occurs because of the reporting of many outcomes assessing the same health issue, or the use of many definitions of one outcome, in terms of meaning or timing of assessment. The impact of this variation of outcome reporting, is an inability to synthesise evidence effectively(71, 168, 191, 195). This topic will be explored further in Chapters Three, Four and Five.

In burn care research, there are many outcomes used to test the effect of interventions(31). Reasons for this include a variation in patient age, mechanism of burn injury, depth, site and size of burn and a high level of different co-morbidities in adults with burns(1). Short-term outcomes, specific to burn care, include healing time, skin-graft loss, infection rates and NHS costs. Longer-term outcomes include functional, cosmetic and psychological issues, and are likely to be more important to patients (176). This issue will be explored further in Chapter Five. It is not known how extensive outcome reporting inconsistency is in published trials relating to burn care interventions and what impact this has on evidence synthesis. This will be explored in Chapter Two.

The last section of this chapter looks at the impact that the issues with outcome choice, reporting and assessment have on evidence synthesis and knowledge translation, along with a possible solution.

1.7 Synthesising evidence from RCTs

Outcome reporting variation across trials will make the synthesis of evidence from RCTs difficult and the findings unreliable. This is important because evidence from single RCTs will not usually provide an answer that is trustworthy enough to support clinical decision-making(196, 197). Synthesising evidence from multiple RCTs, into a SR is the new apex of the evidence quality hierarchy, and provides more reliable evidence to support clinical decision-making(85, 198, 199). SRs can allow the synthesis of large amounts of information and provide estimated effect sizes that have greater generalisability and reliability than individual studies (2, 200).

Systematic reviews can use a narrative or a quantitative analysis to synthesise individual study results(201). A quantitative synthesis, or *meta-analysis* can be defined as the use of statistical techniques to combine and summarise the results of multiple studies to provide new, more reliable and more precise, estimates of the effects of health care than those derived from the individual studies(202, 203). Meta-analysis can therefore be used to provide a more accurate estimate of intervention effects and analysis of whether effects are consistent across sub-groups(204). Formally assessing variability or heterogeneity between studies is important when undertaking meta-analyses. Unless the consistency of the included studies is understood, the validity of the meta-analysis findings will not be clear(205). The presence of significant and substantial heterogeneity may make a meta-analysis inappropriate altogether(206). This will be discussed further in Chapter Three.

1.7.1 Using systematic reviews to inform healthcare policy

Translating the synthesis of evidence from multiple, high quality RCTs into clinical care is necessary to improve outcomes for patients. Commonly, however, there is a gap between evidence-based practice and clinical knowledge. This has been illustrated by researchers in the USA, who assessed medical records of adults living in 12 metropolitan areas and evaluated performance on 439 indicators of quality of care for 30 acute and chronic conditions (207). Participants were found to have received 55% of evidence-based recommended care. Quality varied according to the medical condition, ranging from 79% of recommended care for senile cataract to 11% of recommended care for alcohol dependence. This is also fund to be the case in burn care, with a lack of standardisation of care across services and a resultant variation in patient outcomes(11-13, 208).

Knowledge translation describes any activity or process that enables the transfer of high-quality evidence into effective changes in health policy or clinical practice(209). Woolf defined knowledge translation as "the translation of results from clinical studies into everyday clinical practice and health decision making"(210). The Canadian Institutes of Health Research defines knowledge translation as "the exchange, synthesis and ethically sound application of knowledge to accelerate the capture of the benefits of research for patients through improved health, more effective services and products, and a strengthened health care system"(209). Knowledge translation has improved certain aspects of burn care, including fluid resuscitation, first aid, wound depth and management of the hypermetabolic response(211-214). Many other clinical strategies remain uninformed by evidence(213).

To achieve the full cycle of translating evidence from RCTs though well-conducted SRs into improvements into clinical care, improved patient outcomes and reduced research waste, it is necessary to remove any blocks, or challenges, to this cycle (Figure 1). The potential methodological blocks are:

- The risk of bias *within* RCTs.
- Reporting completeness *within* RCTs.
- The heterogeneity of outcome choice, definition and reporting *across* RCTs.

This thesis is focused on the latter two methodological issues.

1.7.2 Core Outcome Sets

A potential solution to the multiplicity of outcomes reported within and between trials, is to achieve consistency and completeness of pre-specified RCT outcome choice. This can be achieved by *standardising* outcome choice, definition and reporting. Standardised outcome reporting can be achieved through the development of a Core Outcome Set (COS). This is a minimum set of the most important outcomes that are relevant to stakeholders, as well as being scientifically agreed, defined, measured and reported in all studies of any particular condition(71). Importantly this would not prevent researchers from reporting other outcomes, but provides a subset that are standardised, and which can then be compared and collated. The effect of this, in terms of impact on aggregating data to support clinical decision-making internationally, will be discussed in more detail in Chapter Six.

1.8 Conclusion

In this chapter, the need and requirements for developing an evidence base for burn care that is of high enough quality to reduce research waste and translate into clinical knowledge, has been discussed. This need has been placed within the context of a large, global burn-injured population with diverse treatments and little evidence synthesised from high quality RCTs. The lack of evidence to support clinical decisions, results in a variation in care and patient outcomes. The term quality of research has been explored. Synthesised data from high quality RCTs are the building blocks of knowledge that inform clinical decision-making. The two aspects of quality that impact this, are the risk of bias of individual RCTs and the ability to

collate outcome data across trials (215). If outcome data cannot be effectively compared across trials, evidence synthesised will be unreliable and clinical questions will remain unanswered.

The aim of this thesis is to explore outcome reporting across burn care RCTs. Consistency in outcome reporting is one of the determinants of research quality and is necessary for effective evidence synthesis. The thesis also aims to propose and develop a possible solution to this methodological challenge.

Through the work undertaken in the following six chapters, the thesis research question will be answered:

Is it possible to increase the provision of data from burn care RCTs such that it can be synthesised into evidence to answer clinical questions?

In Chapter Two, I will explore whether there is variation in the reporting of clinical outcomes across trials of burn care. I will discuss the different forms this variation can take in terms of choice, definition and timing of assessment. These aspects of outcome reporting will be further explored in Chapters Three, Four and Five. Chapter Six will suggest a potential solution to these issues, a Core Outcome Set.

Chapter 2 Is there variation in clinical outcome reporting across burn care RCTs?

This chapter is based upon the published paper:

Young AE, Davies A, Bland S, Brookes S, Blazeby JM. Systematic review of clinical outcome reporting in randomised controlled trials of burn care. *BMJ Open*. 2019 Feb 1;9(2):e025135.

I conceived the study and wrote the paper as detailed in the *Disclosure* on page vii. Excerpts from the paper are incorporated into this chapter.

2.1 Introduction

The previous chapter set the scene for understanding the need for quality of methodology and consistency in outcome reporting across trials in burn care research.

This chapter will answer:

Thesis Objective 1: **An exploration of the variation in clinical outcome reporting across burn care RCTs.**

This will be achieved by undertaking a systematic review (SR), extracting clinical outcomes reported over a five year period across RCTs in burn care. The extraction of patient-reported outcomes are part of a separate study which is reported in Chapter Six.

2.2 Background

Systematic reviews (SR) of randomised controlled trials (RCT) are regarded as the highest quality in terms of evidence, as discussed in Chapter One (85, 216, 217). An SR identifies, appraises and synthesises all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question(218). In burn care, systematic reviews of RCTs have not provided evidence to support many commonly used interventions or management strategies, despite increasing numbers of published trials (219-221). As discussed in the last chapter, a

potential reason for the lack of synthesised outputs from burn care SRs, is that trial outcomes are reported inconsistently across trials (222). The term *trial outcome* has been defined by Williamson *et al*. in the Core Outcome Measures in Effectiveness Trials (COMET) handbook, as "a measurement or observation used to capture and assess the effect of treatment such as assessment of side effects (risk) or effectiveness (benefits)" (115). This definition will be explored further in Chapter Three. If there are differences in outcome choice, definition or timepoint of assessment across RCTs, evidence synthesis will be challenging. SRs may fail to produce reliable results, as systematic reviewers will not be able to compare and collate like-with-like. Evidence for the presence and impact of variation in outcome reporting across trials exists, is illustrated in Table 2.

The aim of this study is to undertake a SR, to determine if there is variation in clinical outcome reporting across RCTs in burn care.

Table 2: Examples of variation in outcome reporting across RCTs in systematic reviews. Note: Text extracted verbatim from reviews.

Author	Year	Method	Findings	Reference
Bruce et al	2001	Systematic review of prospective studies of surgical wound infection published 1993–1999.	90 studies reported 41 different definitions of surgical wound infection.	(223)
Bruce et al	2001	Systematic review of five databases 1993 and 1999.	Of 97 studies, 56 separate definitions of anastomotic leak after gastrointestinal surgery were reported.	(224)
Tendal et al	2011	All Cochrane systematic reviews published from 2006 to 2007 were examined to assess if protocols described the outcomes reviewed.	19 eligible meta-analyses (including 83 trials). 29% trials reported data for multiple intervention groups, 36% reported data for multiple time points, and 35% reported the primary outcome measured on multiple scales.	(150)
Blencowe et al	2012	SRs published 2005 and 2009 reporting morbidity and mortality after esophagectomy. Data analysed for frequency of complication reporting and whether outcomes were defined.	122 studies (17 RCTs, 105 observational studies), reporting outcomes of 57,299 oesophagectomies. No single complication was reported in all papers. 61% did not define any measured complications. Anastomotic leak was assessed in 80% of articles, defined in 28% with 22 different descriptions used. 115 papers reported postoperative mortality rates, 25 used 10 different definitions. In-hospital mortality was the most common term, with 6 different interpretations.	(140)
Ma et al	2018	MEDLINE, EMBASE, and the Cochrane Library searched from inception to March 2017, for placebo-controlled RCTs of adult patients with ulcerative colitis.	Data from 83 RCTs. Substantial variation in definitions of clinical or composite-clinical outcomes, with more than 50 definitions of response or remission. Greater proportion of trials published after 2007 had no standardised definitions of histologic or biomarker outcomes.	(225)
Ma et al	2018	MEDLINE, EMBASE, and the Cochrane Library searched to March 2017 for placebo-controlled RCTs of adult patients with Crohn's disease.	116 RCTs enrolling 27,263 patients. 38 unique definitions of clinical response or remission and 32 definitions of loss of response.	(226)
Whitehead et al	2014	RCTs enrolling patients with cardiac arrest (2002–2012) were identified by applying a search strategy to four databases.	61 studies. Wide variation in focus, method and timing of assessment. Over 160 individual outcomes reported across the trials. 39 different survival measures reported. 20 different assessments of activity limitation reported. Many assessments poorly defined or non-reproducible. No single outcome measure was assessed across all trials.	(155)
Deckert et al	2015	Three databases searched for studies reporting on chronic pain for at least three months.	70 studies. Most studies (45/70) assessed a combination of three health areas. Variation in domains to address these. No domain measured in all studies.	(154)
Allin et al	2016	SR conducted. Studies eligible if they compared surgical treatment of Hirschsprung's disease.	35 studies. 74 unique outcomes investigated. None of the assessed studies met all criteria for transparent outcome reporting.	(227)
Fish et al	2018	Systematic literature searches for studies evaluating radiotherapy or chemoradiotherapy. Outcomes and accompanying definitions were extracted verbatim and categorized into domains.	95 eligible studies, reporting 1,192 outcomes and 533 unique terms. No outcome was reported in every publication. Over half (43/ 86) of the standardized outcome terms reported in fewer than five studies, and 21 (25%) reported in a single study. Wide variation in definitions of disease-free survival, colostomy-free survival and progression-free survival.	(228)

2.3 Methods

The systematic review adhered to a pre-specified protocol and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(229). It was registered with the PROSPERO international prospective register of systematic reviews (ID CRD42017060908).

2.3.1 Study Eligibility

Studies were included if they met the following:

Types of studies: Full text RCTs, RCT protocols and RCT pilot studies were included. Protocols and pilot studies were excluded if the full RCT had been published within the selected time period. Conference proceedings and abstracts, non-English language publications and studies not involving human subjects were also excluded.

Types of participants: We included studies recording outcomes from patients of any age with a cutaneous burn of any type or size, determined by either clinician evaluation or objective assessment, which required treatment in any health care facility. Studies where the population consisted of patients with combined thermal and mechanical injuries, were only included if it was possible to separate out the burn care outcomes. Trials studying patients with pure carbon monoxide poisoning, chemical ocular or caustic oesophageal burns were excluded, as the former does not involve a burn and the latter have different aetiology and management to cutaneous burns.

Type of interventions: Any surgical or non-surgical burn care intervention with any appropriate comparator were included. The variety of outcomes reported across RCTs was studied, rather than the choice or effectiveness of an intervention.

Types of outcomes: These were defined as the exact terms used in a published trial abstract, methods or result sections, including tables and figures, for any observer-reported clinical endpoint. These included physiological, metabolic or adverse or mortality events, measured by researchers and relevant to patients' recovery and long-term well-being after burn care (230). Trials assessing quality of life were only included if the data were observer-reported.

2.3.2 Identification of studies

Electronic searches of Ovid MEDLINE, Ovid EMBASE, Web of Science and The Cochrane Library were searched from 1st January 2012 to 31st December 2016, for RCTs related to burn care. Medical subject heading (MESH) and free text terms including the terms *burn*, *scald*, *thermal injury* and *RCT* were used. This time period was chosen, so that the outcomes extracted, reflected use in trials relating to recent burn care. Limiting the review to five years allowed us to balance workload against the likelihood of selecting enough trials fulfilling inclusion criteria, to demonstrate whether heterogeneity of outcome reporting was present in burn care research. The thesaurus vocabulary of each database was used to adapt the search terms. The search strategy for Ovid MEDLINE is given in Table 3 (229).

Table 3: Search strategy using Ovid MEDLINE.

	Search term
1	exp Burns/
2	burn*.tw.
3	scald*.tw.
4	(thermal* adj injur*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5	(smoke adj inhalation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	1 or 2 or 3 or 4 or 5
7	heartburn.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	burnout.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9	(burn* adj out).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	burning.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11	burnish*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12	burnet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13	7 or 8 or 9 or 10 or 11 or 12
14	6 not 14
15	(randomi?ed adj control* adj trial*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16	RCT.tw.
17	trial.tw.
18	16 or 17 or 18
19	15 and 19
20	limit 20 to (english language and humans and year="2012 - 2016")
21	limit to randomized controlled trial

2.3.3 Study selection process

The reference management software EndNote (version 8, Clarivate Analytics) was used to compile all titles derived from the initial searches, with duplicates removed to allow screening of titles and abstracts against the eligibility criteria. Screening of titles and abstracts was completed independently, then in duplicate by the thesis author and another researcher (AD). All screening disagreements were discussed, with any outstanding disagreements resolved by a senior reviewer (JMB). Any studies appearing to meet the inclusion criteria based on the abstract were retrieved as full-text articles. The two reviewers then read the full-text articles in their entirety to assess for eligibility, with decisions on exclusion recorded. Reasons for exclusion were ordered hierarchically (Table 4) and applied to each full text. The highest reason for exclusion met by a paper was recorded as its reason for exclusion. Any disagreements were discussed with another author (JMB).

Table 4: Hierarchy of exclusion of trials for systematic review.

Reasons for exclusion.
Duplicate.
Not published between Jan 1st 2012 and Dec 31st 2016.
Not written in English.
Not relating to burn care alone.
Population is non-human.
Abstract with no full text available.
Study not an RCT testing an intervention on burn care.
Laboratory based and not carried out in clinical setting.
Reports only patient-reported outcomes.
Volunteer study.
Study relating to caustic oesophageal burns only.
Study relating to chemical ocular burns only.
Anaesthetic / sedation technique only.
Diagnostic test trial.
Article unavailable.
Follow-up study.

2.3.4 Quality assessment

The aim of this study was to comprehensively document any variation in clinical outcomes selected, defined, measured and reported in burn care RCTs and not to synthesise data about the effect of interventions. Inclusion of all trials, regardless of quality of methodology of the trial, was necessary to demonstrate if a variation in outcome reporting was present across trials. A quality assessment of studies was therefore not undertaken.

2.3.5 Data Extraction

Data were extracted into a standardised data extraction sheet (Microsoft Excel). This included study author, country or countries recruiting (categorised into the United Nations six regions (231)), publication year, number of sites and number of participants recruited per trial, design (full RCT, pilot, protocol) and intervention tested. For protocols, the planned participant inclusion criteria and sample size were extracted.

No distinction was made between primary or secondary outcomes. All outcomes were extracted verbatim, with 20% of the extracted data verified by a second reviewer (AD). True duplicates, spelled and worded the same, were included once. As a second process, two reviewers discussed all verbatim outcomes to assess duplicates in meaning but worded in a slightly different manner. Examples are: length of time in hospital and number of days in hospital, platelet level and levels, and serum IL-10 and IL-10 in blood. Outcomes with the same meaning were named as one outcome with the chosen wording, and the others deleted as duplicates. The remaining outcomes were therefore all different in meaning. Any discrepancies were discussed with a senior researcher (JMB). The number of outcomes per trial and the variation in outcomes reported across trials was recorded.

The timepoints after injury that outcomes were measured were noted separately, in order to assess the heterogeneity in outcome measurement timing and to understand at what stage after injury the effects of the intervention were being assessed. If a single outcome was assessed at different timepoints, all assessment timings were recorded. Data extraction for the timing of outcome reporting from 10% of trials was undertaken independently by another

researcher (AD). Timings of outcome assessment were categorised into time periods after injury:

- Less than or equal to 1 month.
- More than 1 month and less than or equal to three months.
- More than 3 months and less than or equal to six months.
- More than six months and less than or equal to one year.
- More than one year and less than or equal to three years.
- More than three years.

We reported two other outcome time periods; those assessed during *acute hospitalisation* and during *burn wound healing*, as these were commonly reported in the literature with no associated timepoint. It was clear, however, from the reported length of stay and healing data, that all these outcomes were assessed within six months of injury. The frequency of outcomes reported within each time period was recorded.

The data were tabulated so that each study was listed with study and population details along with outcomes measured. Outcomes were extracted from this spreadsheet into another, with duplicates removed, as described above. Outcomes measuring the same healthcare issue but at different timepoints were noted as one outcome for the final set. These final unique outcomes were then grouped into domains.

2.3.6 Classification of outcomes into outcome domains

In this thesis, outcome domains will be defined as groups of similar outcomes, in terms of the health issue. This is described in more detail in work undertaken by the Nephrology–Hemodialysis (SONG-HD) Core Outcome Set group and will be discussed further in Chapters Three and Six(232). Organisation of outcomes into domains is necessary, as maintaining a large set of outcomes when a significant number are similar, would make any future classification of the outcomes in terms of importance, extremely challenging.

In this study, outcomes were classified into domains in a three-stage iterative approach.

- *Stage One*: four researchers (the thesis author, AD and two senior research nurses experienced in burn care) independently reviewed the list of outcomes and attributed a potential domain to each one, using their own terms.

- *Stage Two*: the researchers met to review the domains and agreed:
    - Appropriate groupings of outcomes into domains.
    - An appropriate name for each domain.

Rules for attribution of outcomes to domains were recorded in a coding log to ensure consistency.

- *Stage Three*: a patient representative reviewed the outcomes and their attributed domains to check:
    - The clarity of the domain name.
    - That the outcomes under each domain were appropriately attributed.

A final meeting with an experienced outcome researcher (JMB) was held to finalise outcomes and domains. The use of a published classification system was not undertaken, as none appeared to allow the flexibility or fit to the types of outcomes reported in burn care trials(233, 234). This will be discussed further in Chapter Six, within the context of international outcome research.

The results described below indicate the characteristics of the reported studies and provide detail on variation of outcome reporting between studies, outcome definitions, timepoints of assessment and outcome domains.

2.4 Results

2.4.1 Included studies

The initial search strategy identified 3,110 studies. Following de-duplication, a total of 2,070 studies remained. Independent scrutiny of the titles and abstracts identified 306 potentially relevant articles for full text review. Of these, 158 studies did not meet the inclusion criteria and were excluded. Therefore, a total of 147 studies formed the basis of this study (Appendix B). Of the 147 studies (Table 5), 127 (86.4%) were reports of full RCTs, 13 (8.8%) were pilot studies and 7 (4.8%) were study protocols. The number of studies published increased between 2012 and 2016, with 26 RCTs published in 2012 and 40 in 2016.

Figure 3: PRISMA flow diagram.

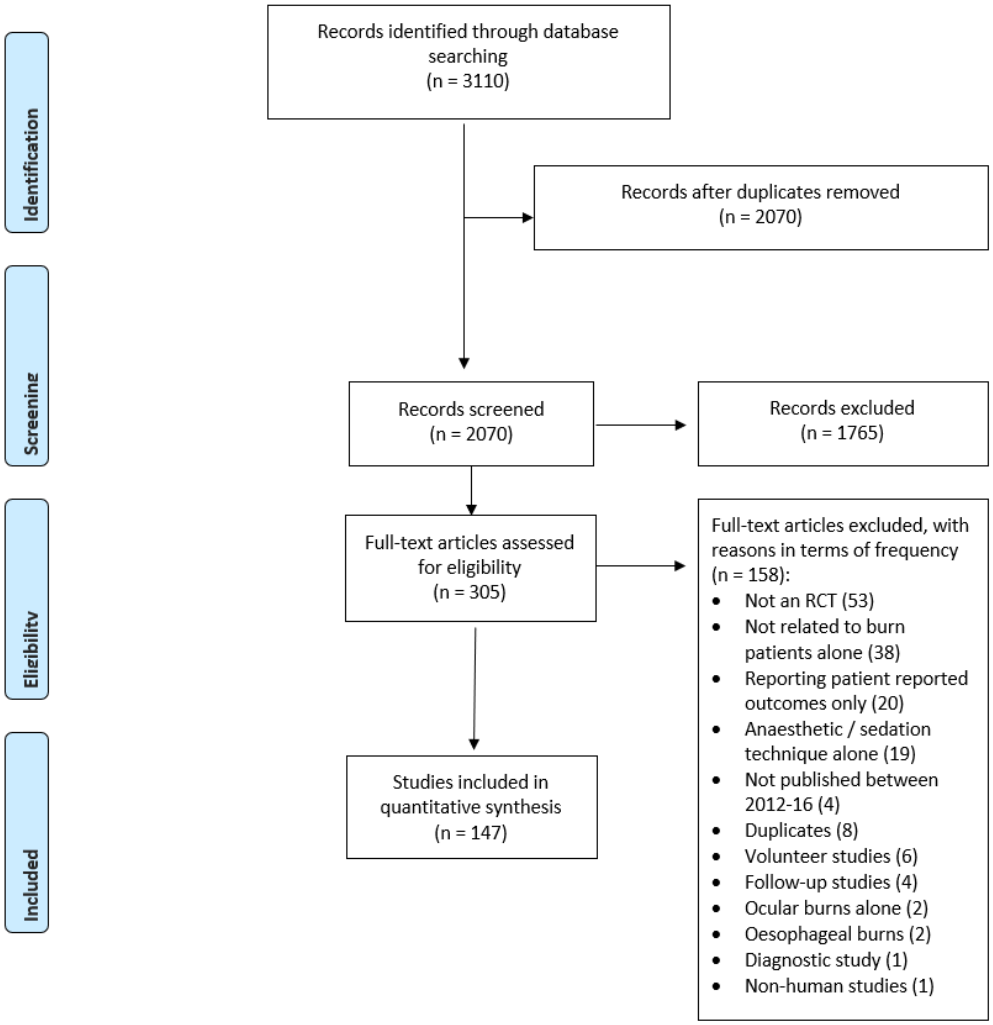


Table 5: Details of included studies.

	Studies n=147 (%)
Number of RCTs	127 (86%)
Number of Pilot studies	13 (9%)
Number of RCT protocols	7 (5%)
World region for recruitment (n=147):	
- Asia	54 (37%)
- North America	36 (25%)
- Europe	26 (18%)
- Africa	15 (9%)
- Latin America	1 (1%)
- Australasia	15 (9%)
Year published (n=147):	
- 2012	26 (18%)
- 2013	24 (16%)
- 2014	24 (16%)
- 2015	33 (22%)
- 2016	40 (27%)
Number of sites (n=147):	
- 1	132 (90%)
- 2-3	9 (6%)
- 4-5	2 (1%)
- > 5	4 (3%)
Number of participants in full RCTs (n=127):	
- ≤ 10	4 (3%)
- 11-50	62 (49%)
- 51-100	39 (31%)
- 101-150	11 (9%)
- >150	11 (9%)
Participants (to be) recruited (n=147):	
- ≤ 18 years	24 (16%)
- > 18 years	59 (40%)
- Mixed age range	25 (17%)
- Not stated	34 (23%)
- N/A (protocol)[c]	5 (3%)
Type of intervention (n=147):	
- Dressings and wound care	38 (26%)
- Surgical technique	19 (13%)
- Treatment of pain or itch[a]	16 (11%)
- Impact of exercise and rehabilitation	13 (9%)
- Intensive care management	10 (7%)
- Treatment of hypermetabolism	8 (5%)
- Nutrition	8 (5%)
- Scar management	7 (5%)
- Treatment of inhalational injury	3 (2%)
- Use of topical rHGM	3 (2%)
- Use of rHGH	3 (2%)
- Sugar management	2 (1%)
- Treatment of infection	2 (1%)
- Treatment of DVT	2 (1%)
- Blood management	2 (1%)
- Extracorporeal shock wave therapy	2 (1%)
- Platelet rich plasma use	2 (1%)
- Others[b]	7 (5%)

[a]Including: distraction for dressing changes.

[b]Including: levamisole, hyperbaric oxygen, fibroblast growth factor, oral calcium use, ketoconazole, low intensity laser.

Details of the studies are shown in Table 5. Across the 140 studies (protocols not included n=7), 9,022 participants were recruited. The number of patients recruited per trial ranged from 3 to 612 (median 50; IQR 30-88) for full RCTs, and from 10 to 52 (median 21; IQR 16-28) for pilot studies. Of the full RCTs, 50% recruited fewer than 50 participants. The large majority (90%) of studies recruited (or planned to recruit) participants on one site alone. Of the 15 (10%) studies that were multi-centre, nine (60%) undertook research at two or three sites only. Thirty-two countries, from six global regions, recruited patients into the 147 RCTs. The number of studies per continent are listed in Table 5. In terms of individual countries, the USA undertook most trials (33 (22%)), followed by Iran (19 (13%)) and China (16 (11%)). Of the 32 countries, 19 (59%) published only one trial in this time period. The most common trial interventions related to dressings and wound care 43 (29%), followed by surgical technique 17 (12%) and management of pain and itch 11%.

2.4.2 Outcome reporting

From all studies, 1,494 differently defined clinical outcomes were reported. After grouping those with the same meaning, 955 unique outcomes remained. The number of the original 1,494 outcomes reported per trial varied from one to 37 (median 9; IQR 8) (Table 6).

The data that is of interest to this thesis, however, is how many times the outcome with the same definition or meaning (unique) is reported across trials. Key outcomes should be reported in all trials. This study shows that 810 unique outcomes were each reported in *only one trial* (Table 7). No single outcome was reported across all 147 studies. This identified problem indicates the clear need for consistent reporting of a minimum set of outcomes across trials.

A Core Outcome Set (COS) would resolve this problem.

Table 6: Number of reported outcomes per study.

Number of outcomes per study:	Number of studies n=147 (%)
1	4 (27%)
2-5	34 (23%)
6-10	53 (36%)
11-20	41 (28%)
>20	15 (10%)

Table 7: Number of studies in which each outcome is reported.

Number of studies reported in.	Number (%) of unique outcomes (n=955)
1	810 (84.8)
2 - 5	108 (11.3)
6 - 10	25 (2.6)
11 - 15	5 (0.5)
16 - 30	7 (0.7)

2.4.2.1 Outcome definition variation

Outcomes assessing the same healthcare issue were commonly defined differently. An example is burn wound healing, which was defined in 166 different ways (Table 8). Examples include, healing percentage at specified timepoints, incidence of complete wound healing and length of time until 50% epithelialisation of the burn wound. There was a similar variation in the definition of burn wound infection and scarring. For wound infection, 79 unique outcome definitions were reported, including: bacterial colonisation of burn wound, days of antibiotics, incidence of local infection, incidence of positive wound cultures, peri-wound redness, rate of bacterial clearance from wound and number of inflammatory cells in the wound. This issue will be explored further in Chapter Four.

Table 8: Variation in definitions of wound healing across trials.

Verbatim definitions of wound healing (n=166) across RCTs (n=147) listed alphabetically (with % and < listed first).		
% burn wound healed at each assessment	Duration of treatment for complete wound healing in relation to wound depth	Skin necrosis
% burn wound reepithelialisation at 4 to 6 days	Duration of treatment for complete wound healing in relation to wound size	Start of epithelialisation
% burn wound size reduction at 3,7,10,14,21,28,35,42 days	Epithelialisation time	status of burn wound
% burn wounds fully healed at 4 weeks	Expression levels of vascular endothelial growth factor in local wound tissue	Time for formation of granulation tissue
% epithelialisation at day 10	Failure to heal burn with a need for skin grafting	Time of formation of basement membrane.
% epithelialisation at specified time points until day 21	Healing % at 14 days	Time of healing
% epithelialisation of wound at 5-7 days after grafting	Healing % at 7 days	Time to > 90% eschar removed
% improvement in burn wound at 4 weeks	Healing rate	Time to > 90% reepithelialisation
% initial wound area healed at each dressing change	Healing rate on 10th day	Time to > 95% burn wound epithelialisation
% of burn wound epithelialisation at dressing changes	Healing rate on day 14	Time to > 95% epithelialisation
% of burn wounds that are 50% healed at 4 weeks	Healing rates	Time to > 95% wound epithelialisation
% of type I and type III collagen in dermis	Healing time	Time to >95% reepithelialisation
% of wounds healed at 1 week	Healing time in relation to burn depth	Time to 100% reepithelialisation
% of wounds healed at 2 weeks	Incidence of 30% wound healing	Time to 90% confluent re-epithelisation of the donor site
% of wounds healed at 3 weeks	Incidence of 70% wound healing	Time to 95% burn wound epithelialisation
% of wounds healed at 4 weeks	Incidence of burn wound depth conversion	Time to complete epithelialisation
% of wounds healed by day 21	Incidence of complete wound healing	Time to complete epithelialisation after burn
% of wounds re-epithelialised after 14 days	Incidence of complete wound recovery at 2 months	Time to complete epithelialisation or granulation
% reepithelialisation	Incidence of healed burn wound > 95% at day 10	Time to complete healing
% reepithelialisation at each dressing change	Incidence of incomplete wound recovery at 2 months	Time to complete wound closure
% wound epithelialisation	Incidence of wound deepening from partial to full thickness	Time to complete wound healing of burn wound
% wound healing	Incomplete wound closure	Time to complete wound reepithelialisation
% wound progression	Length of time for 50% re-epithelialisation of burn wound	Time to healing
% wounds healed by day 10	Length of time for 70% reepithelialisation of burn wound	Time to healing in relation to age
> 90% wound Reepithelialisation	Length of time to > 95% wound healing	Time to healing in relation to burn depth
> 95% Burn reepithelialisation time	Length of time until complete healing	Time to healing in relation to burn size
Amount of granulation tissue present inside the ulcer/wound;	Mean time to wound closure	Time to healing of grafted wounds to > 90%
Amount of necrotic tissue present inside the ulcer/wound	Median wound healing time	Time to healing of un-grafted wounds
Amount of wound healing by means of epithelization of the ulcer/wound	Need for wound debridement	Time to wound healing
Basement membrane structure	Number of apoptotic cells in dermis at 48 hours after burn	Time until epithelialisation
Blinded assessment of time to complete reepithelialisation	Number of blood vessels in wound	Total time of wound healing

Burn wound area every 4 days	Number of burn wounds epithelialised within 10 days	Type of granulation tissue present inside the ulcer/wound;
Burn wound condition	Number of burn wounds epithelialised within 20 days	Vascular density in wound bed at specified time points up to 21 days
Burn wound healing time	Number of burn wounds epithelialised within 30 days	Wound closure > 95%
Cellular and molecular regenerative effects in burn wounds	Number of burn wounds epithelialised within 40 days	Wound epithelialisation
Change in burn depth after treatment	Number of burn wounds requiring a skin graft	Wound healing
Complete wound closure	Number of burn wounds requiring debridement in relation to burn size	Wound healing duration
Complete wound healing time	Number of cases completely healed at 4 weeks	Wound healing rate
Condition of edge of wound	Number of days to 95% epithelialisation for donor site	Wound healing rate at 14 days
Condition of surrounding skin	Number of days until > 95% reepithelialisation of burn wound	Wound healing rate at 20 days
Condition of surrounding unburned tissues	Number of debridement surgeries	Wound healing rate at 28 days
Days to re-epithelialisation adjusted for deepest part of wound	Number of fibroblasts in wound	Wound healing rate at 3 days
Days to re-epithelialisation adjusted for wound depth	Number of keratinocyte cell layers in wound bed at specified time points during healing	Wound healing rate at 5 days
Days until 95% epithelialisation of burn wound	Number of wounds healed by day 24	Wound healing rate in relation to burn depth
Days until wound closure	Numbers achieving complete healing before 18 weeks	Wound healing time
Density of angiogenesis in wound bed at specified time points during healing	Numbers of wounds not re-epithelialising > 95% before discharge	Wound reepithelialisation to > 95%
Density of arterioles, meta-arterioles and venules in wound bed at specified time points during healing	Numbers of wounds reepithelialised in 14 days or more	Wound secretion
Density of endothelial cells in wound bed at specified time points during healing	Optical density of the fibroblast growth factor in burn wound	Wound size at 10 days
Density of fibroblasts at specified time points during healing	Optical density of the vascular endothelial factor in burn wound	Wound size at 2 days
Density of inflammatory cells in wound bed at specified time points during healing	Progression of burn to full thickness	Wound size at 21 days
Density of keratinocytes at specified time points during healing	Proportion of wounds healed at day 21	Wound surface area at 14 days
Density of myofibroblasts in wound bed at specified time points during healing	Rate of re-epithelialisation	Wound surface area at 7
Difference in healing time based on anatomical location	Reepithelialisation rate after skin grafting on day 21	Wound surface area at 7 and 14 days
Difference in healing time related to cause of burn	Reepithelialisation rates	Wound surface healing time
Duration of healing	Size of remaining wound at specific time points until day 21	
Duration of healing time	Size of wound	

2.4.2.2 Outcome timing variation

There were 2,743 outcomes reported, if the same outcome, measured at different timepoints across all the 147 RCTs, are included. For example, the size of burn wound measured at one week and again at two weeks, were recorded as two different outcomes for this exercise.

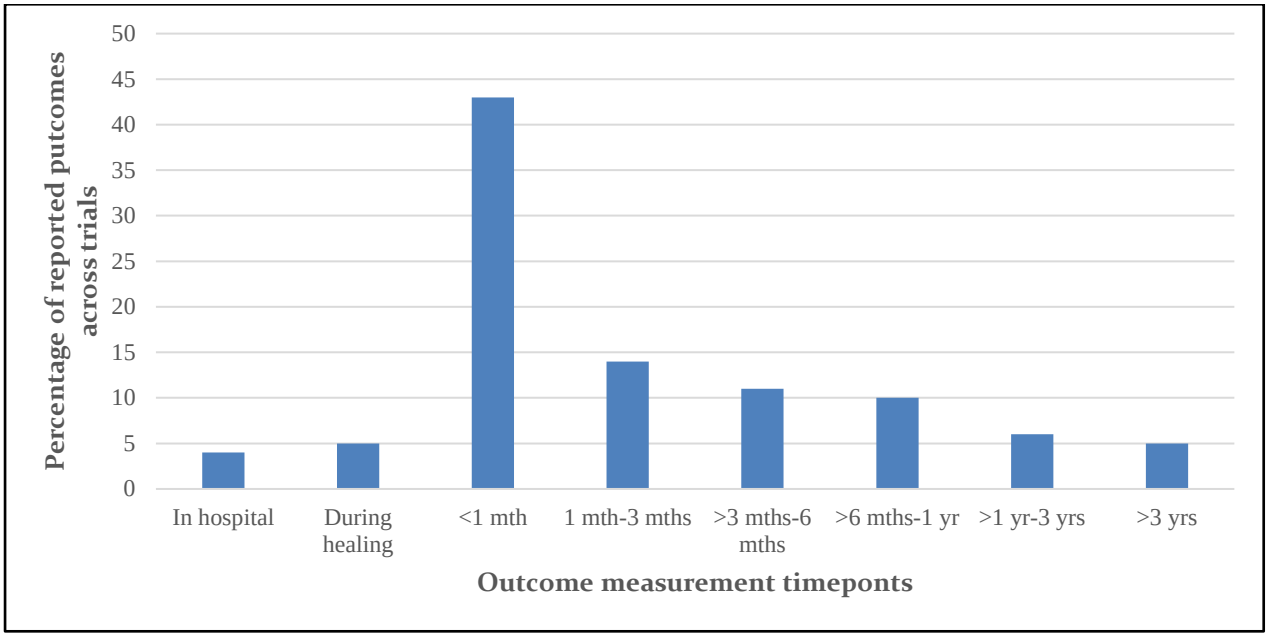
In terms of timing after injury (Figure 4):

- 77% (2,109) were assessed before, or at, six months after injury.
- 17% (456) were measured after six months and before, or at, three years after injury.
- 5% (140) were measured at more than three years after injury.

The timing of outcome measurement was not reported for 38 outcomes. This issue will be explored further in Chapter Five.

Figure 4: Timing of outcome assessment.

Note: This is the percentage of all outcomes reported across all included trials with their associated timepoints. Mths = months; Yrs=years.



2.4.3 Outcome domains

The 955 different clinical outcomes were initially organised into 54 domains (groups of similar outcomes). Table 9 groups the domains into over-arching categories and gives examples and total numbers of outcomes within each domain

Table 9: Outcome category, domains with outcome examples and numbers of outcomes per domain.

Outcome Category	Outcome Domain	Outcome Examples	Nos. of unique outcomes per domain
Patient-reported	Ability to carry out daily tasks	Functional level of independence	3
	Anxiety about medical procedures and appointments	Pain anxiety Anxiety before dressing changes	4
	Generalised anxiety	General anxiety	1
	Appearance	Facial symmetry Overall scar appearance	3
	Blister fluid	Amount of exudate	3
	Burden of care	Frequency of dressing changes Time taken for daily wound cleaning	8
	Comfort of dressings	Dressing comfort	2
	Psychological wellbeing	Improvement in well-being	1
	Mental ability	Cognitive performance	2
	Sleep	Quantity of sleep Incidence of sleep disturbance	16
	Effect of scar on movement (contractures)	Ability to walk	3
	Return to work/school or previous function	Return to work or previous function	1
	Burn wound pain	Wound pain intensity at baseline Pain tolerance	48
	Donor site pain	Donor site pain at rest Donor site pain while walking	10
	Pain during procedures	Wound pain at dressing changes Pain during hydrotherapy	7
	Scar pain	Functional scar pain Incidence of neuropathic pain	4
	Itch	Baseline pruritus Itch severity reduction	22
Pathophysiological	Ability to fight infection	Change in IgA IL-1beta in blood Serum interferon gamma levels	40
	Body weight maintenance	Incidence of weight loss Body weight decrease from baseline	14

	Bone strength	Bone mineral density Incidence of osteoporosis	21
	Breathing and lungs	Forced expiratory volume in 1 second Functional residual capacity	36
	Donor site problems after healing	Donor site pigmentation Sensation of donor site	23
	Effect of burn on genes	Gene expression patterns	5
	Effect of burn on how the body uses energy	Change in percentage of predicted resting energy expenditure	1
	Effect on heart and blood circulation	Incidence of cardiomegaly Number of patients requiring noradrenaline	36
	Fitness	Max. aerobic capacity Exercise max. minute ventilation	5
	Growth in children	Duration of growth arrest Percentage change in height	12
	How well muscles work	Facial mimic function Change in muscle function	19
	Mobility	Stride length Knee range of motion	11
	Kidney function	Incidence of acute kidney injury Requirement for renal replacement therapy	18
	Liver function	Hepatic function Ammonia levels	15
	Medical tests to indicate how unwell a patient is	Albumin level Change in Ph	40
	More than one organ failing (multi-organ failure)	Incidence of multi organ failure Percentage of patients with organ dysfunction	6
	Muscle strength	Knee extensor strength Hamstring strength adjusted for body weight	41
	Stomach and bowel function	Days of diarrhoea Incidence of abdominal distension	14
	Burn wound healing	Burn wound area at timepoints Days until wound closure	160
	Donor site healing	Donor site healing to 90% Time to donor site re-epithelialisation	17
Complications	Complications of drug treatment	Adverse drug reactions Allergic dermatitis	36
	Blood product transfusion	Blood transfused per kg during hospitalisation Total volume FFP transfused	14

	Burn wound infection	Wound bacterial colonisation Wound contamination post-operatively	86
	Death from burn injury	Mortality related to burn size	1
	Death from any cause	Overall mortality In-hospital mortality	13
	Effects of fluid from a drip	Incidence of fluid creep Net fluid balance at specified times	22
	Infections other than burn wound infection	Incidence of central catheter related infections Pulmonary infection	11
	Sepsis	Days of sepsis Incidence of positive blood cultures	10
Scar-related	Scar colour	Erythema index Scar melanin levels	16
	Scar texture	Scar height Change in scar distensibility	40
	Scar size	Scar surface area	2
	Treatment for scars	Numbers of patients assessed for scar management Numbers of patients needing scar management	2
Healthcare-related	Costs of treatment for NHS/Hospital	Costs of analgesics for dressing changes Pressure garment costs	14
	Length of hospital stay	Length of stay adjusted for burn size Days in hospital	6
	Length of stay in intensive care unit	Length of ICU stay	3
	Length of time on life support machine	Duration of mechanical ventilation	3
	Use of medicines to treat symptoms	Pain relief required during dressing changes Opioid consumption	4
Total	**54**		**955**

2.5 Discussion

2.5.1 Outcome reporting variation across trials

In this chapter, I have reported an SR showing variation in clinical outcome choice and reporting across burn care RCTs. This is one type of outcome reporting variation *across* studies and is illustrated in Figure 5. Of the 147 studies included in the SR, 1,494 outcomes were identified. Only 15% of the outcomes reported were included in more than one study. Outcomes that were more commonly reported, included: length of hospital stay (n=30 studies, 20% of 147 studies), incidence of wound infection (n=28, 19%), scar pliability (n=21, 14%), scar vascularity (n=20, 14%), adverse events (n=18, 12%) and mortality (n=18, 12%). There was no single outcome reported across all 147 trials and 810 outcomes were reported in only one study.

Commonly reported outcomes were defined differently between trials. Burn wound healing was defined in 166 different ways across the 147 studies. These variations in definition, included a variation in timing of outcome assessment. Such heterogeneity of outcome reporting across trials will limit evidence synthesis and result in research wastage. Variation in outcome definition will be explored in more detail in Chapters Four and Five. Chapter Three will explore how to define a unique outcome. Chapter Four will concentrate on the variation in definition of one specific outcome; burn wound infection. Chapter Five will explore variation in timing of outcome assessment and impact on outcome relevance.

Figure 5: Versions of outcome reporting variation across trials.

Note: this diagram will be developed further in later chapters.

2.5.2 Outcome grouping into domains

In this systematic review, I identified and agreed the grouping of the 955 unique outcomes into 54 outcome domains. There is no agreement on how to best classify outcomes with similar meaning, into groups, known as domains. Dodd and colleagues published a taxonomy of categorised outcome domains (235). Other authors have suggested various additional categorisation methods, all addressing different needs(111, 233, 234)). In the Williamson taxonomy, the authors state that of 99 systematic reviews grouping outcomes into domains, only 21 applied their own approach to outcome classification and only six used an existing system. It is unclear how the remaining authors classified the extracted outcomes. As many different clinical burn outcomes have been identified in this review, and as the outcomes extracted did not clearly fall within the Dodd taxonomy, a classification system determined by the author of this thesis was used instead. There is a plan for a re-look at the use of the Dodd taxonomy with burn outcomes in the future. This was achieved with input from five multi-disciplinary colleagues and a patient, as described in section 2.2.6. The team worked independently, and subsequently together, to bring different views and as little bias as possible to the process. This process was challenging and involved much learning from each other, with the final domain names and associated outcomes agreed by all. Classification of outcomes into domains will be discussed in more detail in Chapter Six.

2.5.3 A potential solution

The findings in this review, in terms of the variation in outcome reporting, have been observed elsewhere in the burns-specific literature. A Cochrane review of 30 RCTs concluded that it was impossible to draw conclusions about burn dressing effectiveness, as the trials evaluated a variety of clinical outcomes(8, 236). Since 2000, 12 Cochrane reviews have had direct relevance to the management of patients with cutaneous burns(8, 10, 89, 237-245). None could draw firm conclusions, due to methodological issues including heterogeneity of outcome reporting. This is discussed further in Chapter Six.

One way to resolve variation in outcome reporting across trials is to pre-specify a minimum set of outcomes through the development of a Core Outcome Set (COS) (246). The development of a COS for burn care research will be presented in Chapter Six.

In burn care research, there is no agreed set of clearly defined outcomes, despite problems with outcome reporting being increasingly reported(8, 33, 150). Pre-specifying outcomes requires research to determine and agree the most important outcomes for a clinical condition. If this is not undertaken, the outcomes reported may not reflect patients', carers' or other stakeholders' needs, and outcomes will vary between studies (71, 186). Choosing the most important outcomes to measure in burn care is complex, as patients are a heterogeneous population, with variations in age, mechanism of injury, depth, site and size of burn (247, 248). The time frame at which outcomes are measured, may also determine the types of outcomes assessed. Outcomes reported in clinical trials during the acute treatment phase include healing time, skin-graft loss, infection rates and NHS costs (38, 249-251). Longer-term reported outcomes relate to functional, cosmetic and psychological issues (152).

2.5.4 Strengths and limitations

The strengths of this review are that the protocol and data extraction proforma were pre-specified and the literature search was systematic and comprehensive, including four major healthcare trial databases. This review was undertaken to a pre-specified protocol which has been published(252). To account for multi-disciplinary perspectives, two researchers, two clinicians and a patient were involved in the process of defining the outcome domains. All screening of abstracts and full texts and all data extraction was double-checked in completeness or partially, to assess agreement. The review is novel, as it is the first to demonstrate, in detail and using systematic methodology, the scale of the heterogeneity of outcome reporting in burn care research. Limitations include the exclusion of publications in languages other than English. However, international publications were included to reduce the risk of selection bias. The search was also time-limited, which may have excluded outcomes from older studies. The time limitation was applied, to identify research relevant to recent burn care. The search was also limited to trials reporting clinical outcomes. Other work has been undertaken to assess patient-reported outcomes in burn care research. This will be

reported in Chapter Six. A formal quality assessment of studies was not undertaken, as we were researching the reporting of outcomes and not attempting to analyse the effects of interventions.

2.6 Conclusion

This study has demonstrated that multiple, different, apparently individual, outcomes are reported across RCTs of burn care interventions. Various definitions are used to report the same outcome and outcomes are measured at different time points after injury. This inconsistency in outcome reporting prevents effective evidence collation, as researchers cannot compare like-with-like. Until there is greater consistency of outcome reporting, it is unlikely that clinicians will be able to synthesise data across studies. This will limit understanding of the effectiveness of surgical and non-surgical treatments for burn injury. One potential solution to this, is a COS for burn care research (Figure 5).

In the following chapter, I will explore in more detail the methodological challenges demonstrated by this systematic review. This will relate to an exploration of the definition of an individual (unique) outcome in research reporting. The work will explore how difficulties in determining what makes one outcome different to another, affects the magnitude of the variation in outcome reporting across trials in one healthcare area.

Chapter 3 What is the definition of a unique trial outcome?

This chapter is based upon the published paper:

Young AE, Brookes ST, Avery KN, Davies A, Metcalfe C, Blazeby JM. A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. *Journal of Clinical Epidemiology* 2019 Nov 1;115:14-24.

I conceived the study alone and wrote the paper, with input, in terms of editing and readability, by the senior authors. The *Bristol Centre for Surgical Research* assisted with the development of a proposal for a unique outcome. All collaboration is presented in the *Disclosure* section. The paper was peer-reviewed. Excerpts from the paper are incorporated into this chapter.

3.1 Introduction

This chapter will answer:

Thesis Objective 2: The development of an understanding of what makes an outcome unique.

The chapter will focus on the methodological challenges relating to the definition of an individual (defined here as unique) outcome in research reporting and in COS development. The chapter will also explore the requirement to provide transparent methodology for the basis of any quoted magnitude of variation in outcome reporting in COS literature reviews. This concept will be defined as outcome reporting heterogeneity (ORH). The implications of ORH in COS development, and on the need for a COS in any healthcare area, will be discussed. The impact of a lack of definition of a unique outcome on the development of a COS long-list and on subsequent evidence synthesis in general, will be explored.

The chapter will report a systematic review using the Core Outcome Measures in Effectiveness Trials (COMET) database, which will identify how individual outcomes are extracted and grouped into unique outcomes by researchers undertaking COS systematic reviews. The chapter will conclude with a suggested definition of a unique outcome, and a proposed strategy for refining verbatim outcomes into unique outcomes, to allow quantitative reporting of ORH. The work will link ORH, to variation in definition of the same outcome, as discussed in Chapter Four and variation in outcome measurement timing, as discussed in Chapter Five.

3.2 Background

Well designed and conducted randomised controlled trials (RCTs) determine effectiveness, through an un-biased comparison of outcomes (events or endpoints) by intervention group (103). The choice and selection of outcomes is critical in RCT design and trials may be regarded to be "only as credible as their outcomes"(253, 254). Trial outcomes, however, may be defined in various ways(112, 113, 115, 195, 255-257). These include: "as variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population"(114) and as "a variable measured at a specific time point to assess the efficacy or harm of an intervention"(116). Whilst these definitions explain the role of an outcome in a trial, they do not define what an outcome is *per se*. Other authors have defined outcome reporting using four or five levels. These include outcome, measurement, metric, aggregation of outcomes and timing of measurement (258, 259). None of these publications describe how to determine what makes an outcome unique (116, 192). Without a definition for an individual or *unique* outcome, difficulties arise in differentiating one outcome from another. As illustrated in the previous chapter, the lack of a definition for a unique outcome, results in the reporting of multiple, apparently different, outcomes across studies and impacts negatively on evidence synthesis. This contributes to research waste. The lack of definition of a unique outcome, may also complicate the development of Core Outcome Sets (COS).

A COS is a minimum set of outcomes that are selected, measured and reported in trials of a specific healthcare condition(71). COSs will be discussed in more detail in Chapter Six. They are typically developed by identifying all outcomes in the literature and discussion with stakeholders, and combining these into groups or domains for stakeholders to prioritise using a consensus process. The first part of this process requires that researchers scrutinise the

literature and extract outcomes verbatim, for reasons of transparency(115). Outcomes are then de-duplicated and grouped into unique outcomes for the prioritisation process. The process may identify between 20 to more than 1,000 outcomes(260-263). This wide variation is likely to reflect the lack of application of a uniform definition of a unique outcome, in addition to real differences in numbers of different outcomes. Guidance as to when the use of different wording defines the same outcome, and when it does not is lacking; for example, 30 day mortality and in-hospital mortality(264, 265). There is no advice as to how to group similar outcome terms into a single unique outcome. Some researchers may choose to include all the definitions of a specific outcome under one term, with others seeking more granularity and reporting several different definitions as unique (227, 261). There is no clarity as to which process is correct for demonstrating variation in outcome reporting in a quantitative manner, and for outcome long-list generation for COS development. It is also unclear whether the timing of outcome measurement affects the singularity of an outcome. For example, the incidence of wound healing at two specified timepoints. Some researchers will count these as two outcomes and others as one(266, 267).

The reporting of methods for extracting and grouping outcomes in COS development studies is often poor. The impact of identifying unique outcomes is that that different researchers may extract a different number of outcomes from the same dataset, and the scale or presence of true variation in outcome reporting, will therefore be difficult to establish. Inconsistency in methods for extracting outcomes, means that the scale of ORH is difficult to establish. ORH is a quantitative measure of the variation in outcomes reported across trials in one healthcare area and has been defined through the work in this thesis. It is commonly reported in COS development as a number: n=x different outcomes were reported across n=x trials in a specific healthcare area. ORH will impact on the validity of the long-list of outcomes used to inform the consensus processes in the development of COSs.

In this chapter, I will suggest a first working definition for a unique outcome, through work undertaken for this thesis and on discussion with the senior co-authors of this paper and other senior members of the Bristol Centre for Surgical Research (https://www.bristol.ac.uk/population-health-sciences/centres/surgical-research/). A final agreed definition will ensure that COS researchers can accurately and consistently identify a quantitative assessment of the inconsistency of outcome reporting (defined here as ORH). This work is a starting point for a debate between international COS researchers, with further validation required prior to use of the definitions and methodology.

The aim of this chapter is to examine methods used to extract and combine outcomes with the same meaning, from published research papers. Standardisation of this process would inform how to establish a reproducible and quantifiable long-list of unique outcomes.

3.3 Methods

This study consisted of two phases:

- *Phase 1*: an in-depth literature review was undertaken to analyse and summarise methods for outcome extraction, grouping, defining and counting, from SRs used to inform COS development.
- *Phase 2:* combined the findings from Phase 1, with the input of multidisciplinary expert opinions. This informed the development of a first working definition of a unique outcome, and methodology for the conversion of outcomes extracted verbatim from trials into unique outcomes. A first definition of ORH was developed, based on the definition of a unique outcome.

3.3.1 Phase One Literature Review

3.3.1.1 Data source and search strategy

A structured search of the COMET database (a repository of COS studies http://www.comet-initiative.org/Studies) was undertaken. As optimal COS development methodology is still evolving, it was hypothesised that the most current advances in methodology are likely to be found in recent studies registered with the COMET database. This database allows the use of filters to identify the nature of the COS work (e.g. protocol, full paper, population studies etc.).

3.3.1.2 Study selection criteria and identification

Searches of the COMET database were used to identify COS development papers. The filters applied in this study are described in Table 10. Hand-searching the reference lists of these papers, and the use of two other search engines (Ovid MEDLINE and PubMed), were used to identify related articles using key words from the COMET database articles (268). Papers were included if they met the inclusion criteria below. Articles needed to report any details of

outcome extraction, grouping and counting from literature reviews, to inform the presence of ORH, as well as reporting the development of a COS outcome long-list. The study flow chart is illustrated in Figure 6.

Inclusion criteria:

- A primary COS development study published between January 1st 2015 and August 20th 2018.
- A COS protocol (without an associated final COS published within the above time period).
- A previously published literature review that was referenced in, informed or directly related to a primary COS study published within the above time period.

There was no restriction on the type of studies in terms of patient characteristics or disease area.

3.3.1.3 Identification of studies

Full-text articles were retrieved and reviewed to determine eligibility, independently and in duplicate by myself and another researcher (AD). Reasons for exclusion were ordered hierarchically in order of importance (Figure 6) and applied to each full text. Discrepancies were resolved by discussion and consulting with co-authors. Reference lists of full texts were hand-searched to identify a comprehensive list of all literature reviews to support COS development.

Table 10: Filters for the COMET database.

COMET Filters
• COS for clinical trials or clinical research • COS for practice • COS for registry • Defining clinical improvement using the core outcome set • Overview of literature • Recommendations made for systematic reviews • Recommended outcome measures (measurement) • Systematic review of core outcome sets • Systematic review of outcome measures/measurement instruments • Systematic review of outcomes measured in trials

Figure 6: Study methodology.

Data extraction and synthesis:

Two authors extracted data using a form developed and piloted by the author of this thesis. Data extracted were:

1. *Type of study*: primary COS study, COS protocol, literature review to support a COS.
2. *Methodology for extraction and grouping*: whether outcomes were extracted verbatim. Methodology for grouping similar outcomes into unique outcomes.
3. *Outcome details*: total number of unique outcomes reported (quantitative measure of ORH), presence of different wording for the same outcome and impact of timing of outcome measurement on numbers of unique outcomes.

Results were compared between researchers, with any disagreements resolved by a senior COS researcher (JMB). Primary COS development studies and their respective literature review(s) that directly informed the development of that COS were paired for data extraction, so that data was not duplicated.

Data analysis:

Numerical data are presented as summary statistics. A narrative synthesis was applied to methods for extracting and grouping outcomes from trials and for managing the timing of outcome assessment(269-271). Heterogeneity and/or similarity of outcome extraction methodology was noted, exploring relationships between studies.

3.3.2 Phase 2: Development of a definition of a unique outcome and methodology for grouping verbatim outcomes into unique outcomes.

A summary of the findings from Phase 1 of the study were presented to, and discussed by, a single-centre multidisciplinary group of senior researchers experienced in COS research (Bristol Centre for Surgical Research https://www.bristol.ac.uk/population-health-sciences/centres/surgical-research/). A first working definition of a unique trial outcome, and methods for conversion of outcomes extracted verbatim into unique outcomes, were developed. These were iteratively refined through further discussion and a detailed review of the data from Phase 1. A first definition for ORH was subsequently proposed, based on the

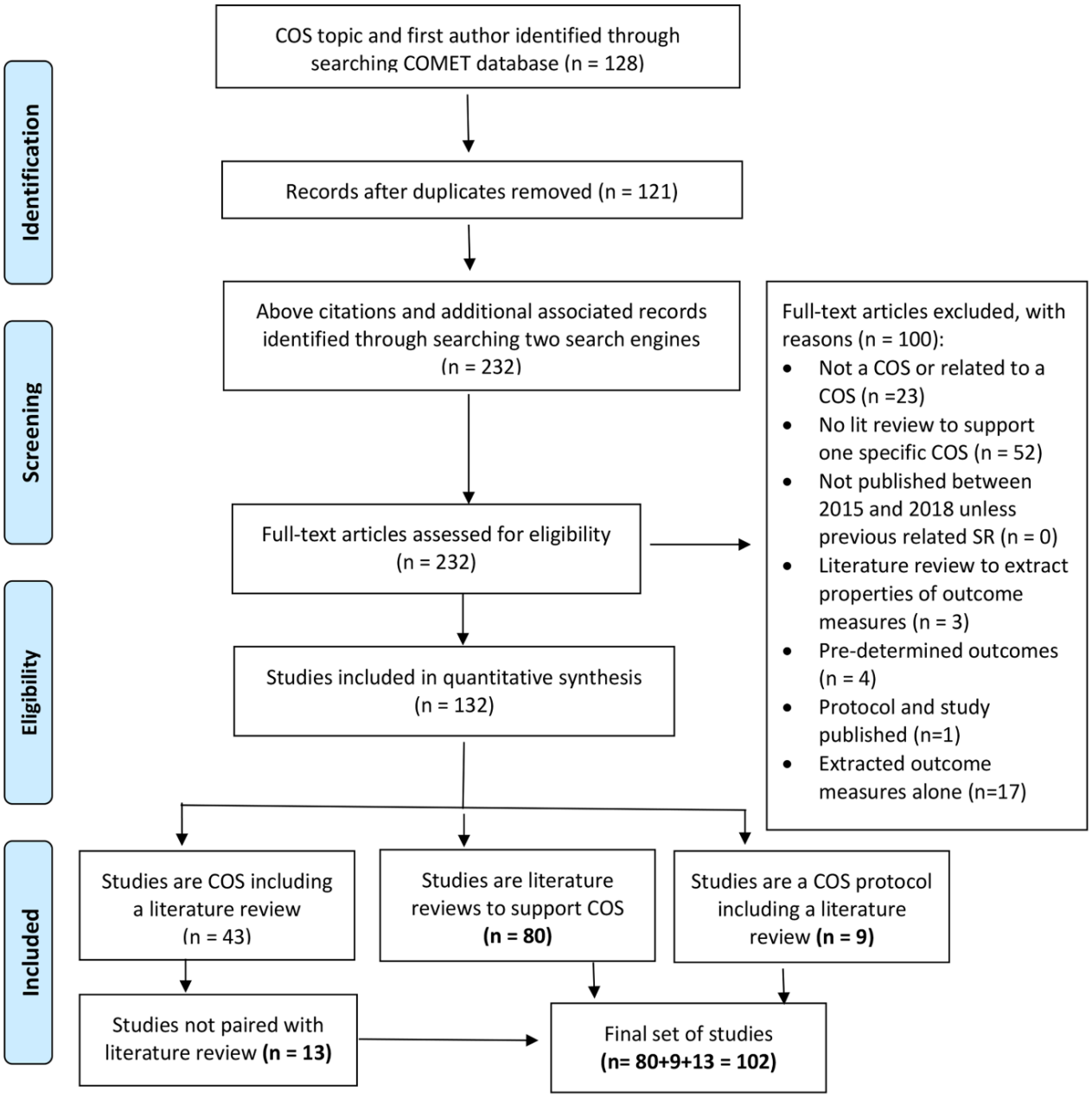
ability to define a unique outcome. These definitions are a first attempt to describe a unique outcome and to use this to understand ORH. The definitions will be finalised after formal collaboration with COS developers and COMET, prior to validation.

3.4 Results

3.4.1 Phase 1: Literature review

The COMET database search yielded 121 titles (seven duplicates removed) for COS studies. These 121 articles were identified in OVID Medline and PubMed and full texts were extracted. Hand-searching identified a further 111 related literature reviews. This led to a total of 232 studies (Figure 7). Of these, 100 articles did not reach the inclusion criteria, leaving 132 studies for data extraction.

Figure 7: PRISMA flow diagram.



Type of study: Of the 132 included studies (listed in Appendix C), 43 (33%) were a final COS, 80 (61%) were a literature review undertaken to support a COS, and nine (7%) were COS protocols with details of a literature review, where the final COS was not yet published. Of the final COSs, 30 (70%) paired directly with a previously published literature review, leaving 13 COS studies that were analysed alone. The results described below are therefore taken from 102 (132-30) different COS studies. Final numbers of unique outcomes are taken from 93 studies. The 9 protocols were excluded as they did not report extracted outcome numbers, as detailed in Figure 7.

Outcome Details (Table 11): Thirty-two studies (31%) discussed the issue of the timing of outcome assessment. In 17 (53%) these were counted as unique outcomes (e.g. wound infection at 30-days was reported as a different outcome to wound infection at 90-days) based on time alone, whereas the remainder of studies counted these as just one outcome. Of the 102 studies (with the nine protocol studies excluded i.e. n=93), 82 (88%) reported a quantitative assessment of the number of outcomes reported across the included trials (a quantitative assessment of ORH). The total number of unique outcomes reported, varied from 12 to 5,776 per review (median: 82 IQR: 261). Varying definitions for the same outcome across included trials were reported in 53 studies (52%).

Methodology for extraction and grouping: 18 studies (18%) reported that extraction of outcomes was verbatim. Of these 18, 44% (8% of all 102 studies) included some text description of the authors' methodology for grouping these into unique outcomes (Table 12).

Table 11: Outcome details.

Note: paired study data were collated.

Numbers of studies reporting:	**Number of studies (%)**
Final numbers of unique outcomes reported across trials within systematic review (excluding protocols n=9)	82/93 (88)
Researchers state that outcomes were extracted verbatim from trials within systematic review	18/102 (18)
Researchers report different definitions for the same outcome across trials within systematic review	53/102 (52)
Researchers report the timing of outcome assessment	32/102 (31)
Researchers report that the timing of assessment impacts on number of outcomes reported	17/32 (53)
Methodology reported for grouping outcomes into unique outcomes	8/18 (44)

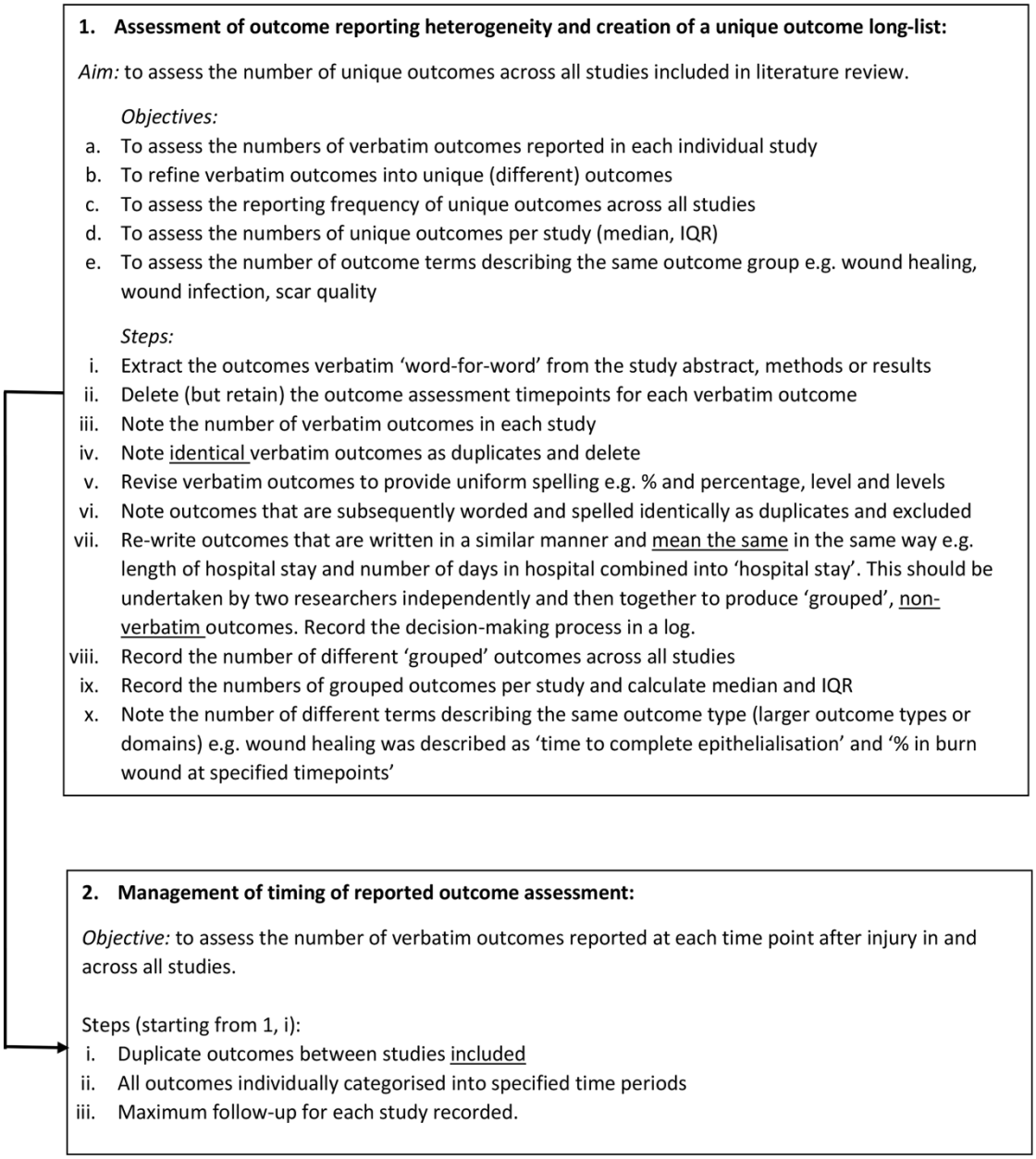
Table 12: Methodology for identifying outcomes as unique.

COS review title	**Conversion of verbatim outcomes into unique outcomes (text extracted)**
A systematic review of outcomes in postoperative pain studies in paediatric and adolescent patients: towards development of a core outcome set(272).	"Outcomes were abstracted based on group consensus. We defined an outcome as the exact word-for-word terms ..... for any clinical end-point, or physiological, metabolic or mortality event measured by clinicians or researchers." "Final outcomes were then standardised to improve the consistency of naming. For example, 'objective pain score' was changed to 'pain measurement'. After the outcomes had been standardised, we placed them in broader domains."
Evaluating physical activity in dementia: a systematic review of outcomes to inform the development of a core outcome set(273).	"From verbatim outcomes to outcome domains: One author, ..., grouped verbatim outcomes with the same semantic meaning, into outcome domains. For instance, the verbatim outcomes 'Functional independence', 'Ability to develop basic activities of daily living' and 'Functional performance' were grouped into the outcome domain 'Functional abilities and independence'."
Outcomes mapping study for childhood vaccination communication: too few concepts were measured in too many ways(274).	"For each outcome mentioned in an included trial, we extracted into a spreadsheet all information defining the outcome, such as type..., outcome variables ..., age of the subjects, and any other related details. We used the exact words of the trial authors. We did not extract data related to the timing and scale or tool used to measure the outcomes, as examination of how specific outcome variables were measured was not the subject of the research." "Two researchers reviewed the extracted data. One author coded the individual outcomes according to what these measured, using the language of the trialists. These codes were discussed and confirmed." "This first round of codes became the most specific level of the taxonomy. We retained a relatively large number of different groups, rather than aggregating the information and potentially losing important details."
Variability of outcome reporting in Hirschsprung's Disease and gastroschisis: a systematic review(227).	"In the 35 included studies, 95 outcomes were investigated a total of 337 times." "35 outcomes were considered to be too similar to at least one other outcome to be meaningfully differentiated, and these outcomes were therefore mapped to one common term (e.g. continence/ incontinence, or frequency of stool/bowel movement frequency). Following this exercise, 74 unique outcomes were identified as having been reported." "Within the included studies, 102 outcomes were investigated a total of 247 times. Within these 102 outcomes there were 63 that were felt to be too similar to at least one other outcome to be meaningfully differentiated, and these were therefore mapped to one common term. Following this mapping process, there remained 62 unique outcomes."
No common denominator: a review	"We also did not record outcomes multiple times where these corresponded to repeated measurements at several time points." "For each reported outcome, we extracted the numerator and denominator." "Where pregnancy or live birth were reported, we extracted

of outcome measures in IVF RCTs(275).	the corresponding definition used by the study authors." "Data were extracted into two databases, one containing study-level information and another containing reported-outcome-level information. Due to the large number of outcomes identified, we reported only those appearing in more than one study. We simplified the results by combining similar numerators and denominators. For example, we combined live birth with take home baby rate, and combined the denominators 'per patient with sufficient embryos' and 'per patient with sufficient blastocysts', where 'sufficiency' could be defined on the basis of quantity or quality of embryos (or both)." "For this primary analysis, we did not distinguish between subtly different definitions of outcomes (e.g. clinical pregnancy may have been defined as foetal heartbeat on ultrasound at different time points in different studies). However, at the suggestion of an anonymous peer reviewer, we also present the definitions used by trial authors for pregnancy and live birth outcomes."
Systematic review of outcome measures following chemoradiotherapy for the treatment of anal cancer (CORMAC)(228).	"Verbatim outcomes were initially reviewed by a single researcher and assigned a standardized name ('standardized outcome term') to overcome variations in wording used for the same outcome. The standardized outcome term and domain assigned to each verbatim outcome were reviewed and agreed at a meeting of the CORMAC Study Advisory Group (SAG). There were 533 unique terms collapsed into 86 'standardized outcome terms', representing outcomes with the same meaning but with differing wording, and assigned to the appropriate outcome domain."
Outcome reporting in randomized controlled trials and systematic reviews of gastroschisis treatment: a systematic review(276).	"We anticipated some diversity in terminology used to report outcomes and therefore grouped similar outcomes. We identified outcomes that seemed similar or of a similar theme despite differing definitions used across studies and assigned an appropriate term to them. For instance, the outcomes 'proven catheter-related sepsis (line positive blood cultures necessitating antibiotic treatment or catheter removal)' and 'central line infections' were included in the term 'central venous catheter sepsis'."
Developing a core outcome set for fistulising perianal Crohn's disease(277).	"Reported outcomes were extracted verbatim and listed in preparation for categorisation into domains."

3.4.2 Phase 2: Agreement on methodology for grouping verbatim outcomes into unique outcomes

Figure 8: Unique outcome methodology proposal.



Detailed discussions undertaken with a single centre, multidisciplinary, expert panel of senior COS researchers explored how a unique outcome should be defined and how this would impact the quantitative measure of ORH. After iterative refinement, the following definition of a unique outcome was suggested:

"A unique trial outcome is one that has original meaning and context".

Outcomes with different words, phrasing or spelling, addressing the same concept and context should be categorised as a single outcome. In other words, researchers should group together outcome synonyms into one unique outcome term. By the term *original meaning*, individual clinicians and patients would need to clearly understand what a particular outcome meant and how it was different to any other outcome. For example, number of days in hospital has the same meaning as hospital length of stay. The term *original context* should be taken to mean that researchers must be clear when defining the context of the outcome. For example, post-operative pain and neuropathic pain would be two different outcomes as they are different in context.

The timing of outcome measurement should be clearly stated, but an outcome differing only in this aspect is not considered to be unique. Supporting evidence for this is in the fact that outcomes measured at different time-points can be pooled in a meta-analysis(278).

The definition of ORH, relates to the quantitative variation in outcome choice and reporting across trials in one healthcare area and is dependent on the ability to define a unique outcome. The definition of ORH is proposed as:

"the reporting of multiple unique outcomes across trials within one healthcare condition".

The definitions suggested here are proposals for further discussion and validation. Other types of ORH will be explored in Chapters Four and Five.

3.5 Discussion

The work in this chapter has explored, through examination of COS literature reviews, what makes one outcome different to any other outcome. Of all 102 COS studies included in this review, only eight reported any methodological detail about how verbatim outcomes were grouped into final unique outcomes. Despite this inability to report how the final long-list of

different outcomes were determined, authors of 88% of studies, still reported the final unique outcomes as a number i.e. they reported variation in outcome reporting across studies of one healthcare area quantitatively.

3.5.1 Quantitative measure of ORH across trials

The number of reported outcomes across studies in this review varied from 12 to 5,776 (median: 82 IQR: 261). It is unclear why there was such a wide variation in the numbers of different outcomes extracted between reviews. The answer is likely to lie in the authors' decisions regarding the granularity of outcomes extracted and the use of timing of measurement to define unique outcomes. Chong *et al.* in a systematic review on pediatric chronic kidney disease, reported 5,776 different outcomes from 213 studies(279). In one group of outcomes, 19 relate to glomerular filtration rate and were measured at several time points. Each of these was counted as a unique outcome. This resulted in 148, apparently unique, outcomes in this one group. Another review used in the development of a COS, on the variability in the reporting of renal function endpoints in immunosuppression trials in renal transplantation, reported only 345 outcomes in total (compared to 5,776 in the previously quoted review) from 213 studies(280). This review did not include outcomes measured at different times as unique. It is otherwise not possible to clarify this disparity, as neither paper reports how the number of unique outcomes were calculated.

The timing of outcome assessment was reported in just under one third of studies. Of these, more than half reported outcomes with different times of assessment as unique. *Definitions of outcomes with similar meanings* varied across 52% of included reviews. For example, different definitions of wound healing (as also illustrated in the review in Chapter Two) such as length of time to heal to 50% or to 70% healed and time to 90% re-epithelialisation, suggests that further grouping of outcomes was necessary and that these outcomes were not unique.

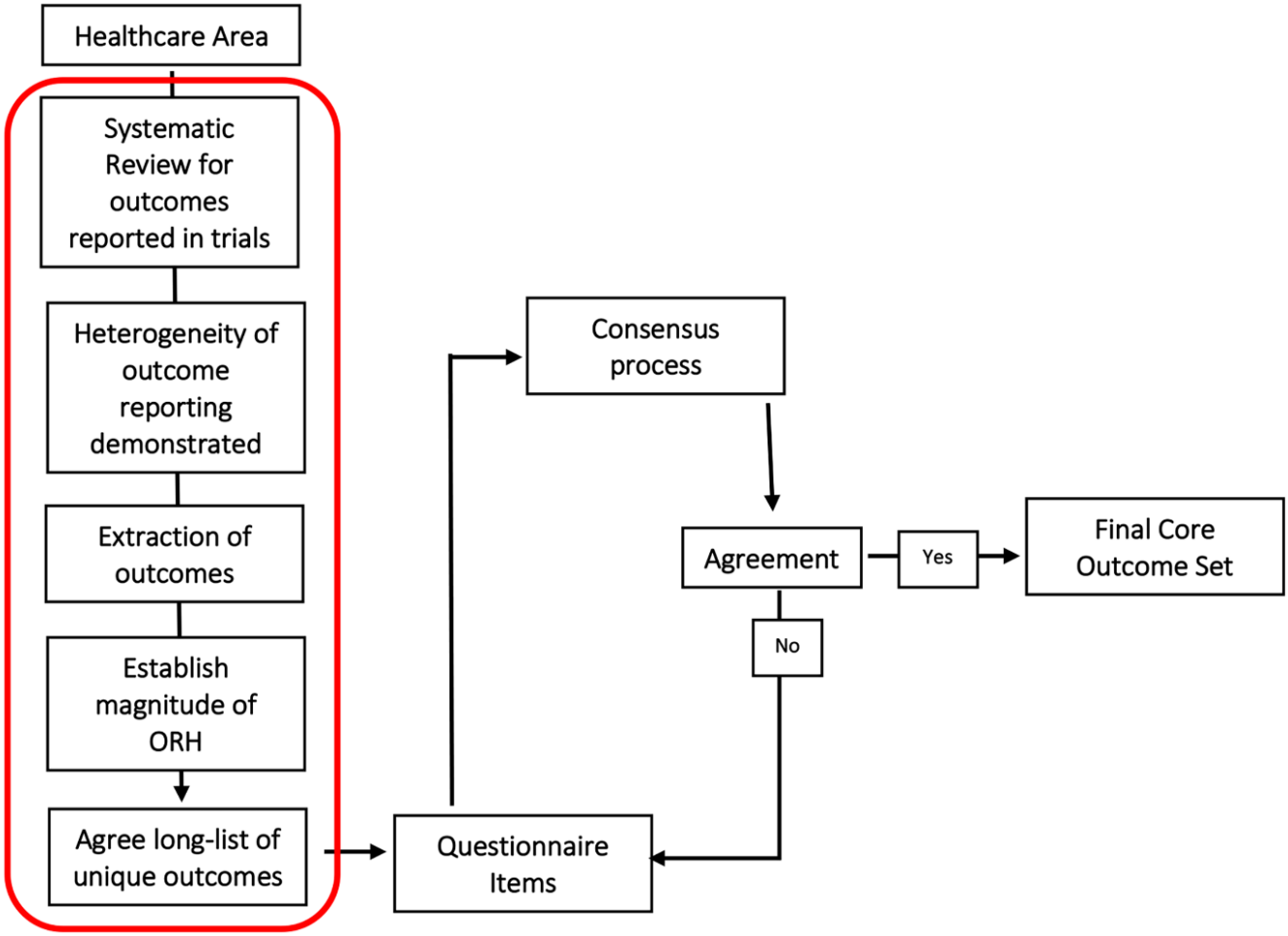
The lack of methodological detail and significant variation in numbers of outcomes reported across studies suggests a non-systematic approach to outcome extraction and counting. This approach, therefore, will not allow any true variation in numbers of outcomes reported across studies to be accurately assessed (quantitative measure of ORH). The following chapter will look in more detail into the issue of the timing of outcome assessment.

3.5.2 Defining ORH

Other authors have previously described, but not defined, the variation in outcome reporting or ORH (226, 227, 281). They have, however, demonstrated that it leads to problems in evidence synthesis (227, 282, 283). One reason for the existence of ORH, is a lack of clarity regarding what constitutes a unique outcome; what makes one outcome different to another. Although COSs have been developed to resolve ORH, they require the extraction of outcomes verbatim from trials, and the subsequent grouping of the same or similar outcomes into individual, unique outcomes. This process requires an understanding of what constitutes a unique outcome and which outcomes are so similar they can be combined into one term. It is important to agree the level of granularity required in outcome reporting and this may be partially responsible for the wide variation in the numbers of unique outcomes reported across trials.

The presence of variability in aspects of COS development, has been noted by the COMET Initiative (284-287). Their analyses have identified variations in the scope, stakeholder involvement and consensus process (284, 285, 288, 289). COMET has undertaken work to provide methodological guidance regarding these aspects of COS development (115, 286-291). This is useful, although there is little focus on the early part of COS development. These early stages include extraction of comprehensive lists of outcomes and identifying the magnitude of ORH. They are undertaken, not only to justify the need for a COS, but to directly feed into the COSs themselves (Figure 9).

Figure 9: Early stages of outcome extraction and long-list formation for a COS.



3.5.3 Strengths and limitations

The strengths of this review are that 132 COS development studies, including 90 systematic reviews used to inform COSs, have been critically and systematically analysed. A limitation of the study is that a full systematic review was not undertaken, but attention was focussed on studies identified through the COMET database, with related articles identified through two other search engines, as *per* the published advice on methodological systematic reviews(289, 292). To support this approach, Gargon *et al*. noted the comprehensive nature of the COMET database, in that 720 studies relevant to the development of COS had been included in the database by the end of December 2015 (286). Moreover, COSs registered on the COMET database are likely to be of high quality due to the publication of the COMET standards for COS development and reporting (115, 286). The search was extended by including directly related studies identified though two search engines and hand searching references. It is unlikely that COS development studies reported before 2015 will have described methodology for the extraction of unique outcomes, if later studies do not. The work for this chapter, is not aimed to be comprehensive in exploring all COS development papers. The focus of the study is to demonstrate, that in a recent group of high-quality COS research collected in a pre-specified manner, no-one has determined objectively and with repeatability, how to extract and count unique outcomes to determine a quantitative measure of ORH across papers in one healthcare area.

3.6 Conclusion

This review has shown that the process of extracting outcomes from trials included in COS literature reviews and grouping the verbatim outcomes into a list of outcomes that are individual and different (*unique*) from each other, is complex and poorly reported. Verbatim outcome extraction is recommended by COMET, for reasons of transparency(71, 115). “The first step is to group these different definitions together (extracting the wording description verbatim) under the same outcome name”(115). Issues with this, include determining when outcomes are the same, even when they are differently worded; for example, serum albumin and albumin levels in plasma. Another issue is how to incorporate the timing of outcome assessment into this process; for example, percentage wound healed at two weeks and

percentage wound healed at six weeks. If authors could agree and transparently report how they extracted, grouped and counted the outcomes reported, a true quantitative assessment of ORH would be possible. A lack of understanding of what constitutes a unique outcome will impact on the validity of the reported presence and magnitude of ORH, as demonstrated by the widely varying numbers of unique outcomes reported in the COS literature reviews included in this study. Furthermore, when outcomes presented in the later stages of COS development are not unique, it makes prioritisation difficult and can hinder the consensus process.

A final agreed definition for a unique outcome, and methods for objectively grouping outcomes extracted verbatim into unique outcomes, will provide a methodological basis for COS researchers to develop a reproducible long-list and to determine an quantitative measure of ORH. The aim of this work is to start formal discussions between international COS researchers and COMET for the purpose of raising awareness of this methodological issue and to undertake collaborative work to refine and validate a definition for a unique outcome.

The next two chapters will describe two other versions of ORH. Chapter Four will explore how agreeing unique outcomes is further complicated by variations in the definition of any specific unique outcome. The chapter will use burn wound infection (BWI) as the unique outcome example. A systematic review will explore the variation in the definition of BWI across studies assessing burn care interventions and reporting BWI. Chapter Five will explore, through another SR, how the management of the timing of outcome assessment also impacts negatively on evidence synthesis and affects relevance to patients.

Chapter 4 Defining Burn Wound Infection; a systematic review

This chapter is based upon two papers:

1. Davies A, Teare L, Falder S, Coy K, Dumville JC, Collins D, Moore L, Dheansa B, Jenkins AT, Booth S, Agha R et al Young A.E. Protocol for the development of a core indicator set for reporting burn wound infection in trials: ICon-B study. *BMJ Open*. 2019 May 1;9(5):e026056.
2. A systematic review of intervention studies demonstrates the need to develop a minimum set of indicators to report the presence of burn wound infection. In Press *Burns* journal.

As senior author and lead for the national infection consensus in burns (ICon-B) project, I conceived the study, developed and defined the term, Core Indicator Set (CIS), for burn wound infection. I co-wrote the paper with AD who I supervise. Data production was by AD. I double-checked all data and oversaw the final dataset. The other members of the group inputted ideas, edited, assessed readability and data sign-off for the project. The papers were peer-reviewed. Excerpts from the paper are incorporated into this chapter.

4.1 Introduction

This chapter will answer:

Thesis Objective 3: An analysis of how variation in the definition of a specific outcome (burn wound infection) across burn care trials impacts evidence synthesis.

The work undertaken in Chapter Three, explored what makes one healthcare outcome different to another and how it might be possible to define a unique outcome(293). In this chapter, I will debate how challenges with the definition of a unique outcome impacts evidence synthesis. In this study, the example used is acute (before healing) burn wound infection (BWI). If varying definitions of this outcome are used across trials, difficulties will arise in collating trial data on interventions to detect and treat BWI (223, 294-296). This has been shown to be true for other outcomes across healthcare; wound healing, mortality and

acute renal failure(4, 297, 298). Variation in definition of the same outcome across trials is another example of outcome reporting heterogeneity (ORH). In Chapter Three, ORH was defined as "the reporting of multiple unique outcomes across trials within one healthcare condition". The issue discussed in this chapter is different. The same outcome is reported across trials, but the definition varies(293). See Figure 10 below.

Figure 10: Version 2 of definitions of the variation of outcome reporting across trials.

4.1.1 Nomenclature

Studies use varying terms for describing the reporting of outcomes. In this chapter, the following terms have been listed here and defined for clarity. In the study, we use these to define one specific outcome (BWI), but they could equally apply to any other outcome.

Unique outcome: this was defined in Chapter Three and a working description proposed:

"a trial outcome is one that has original meaning and context".

Outcome reporting heterogeneity (ORH): this was defined in Chapter Three as:

"the reporting of multiple unique outcomes across trials within one healthcare condition"(293).

There are three types of ORH:

- Variation in outcome choice and reporting across trials.
- Variation in the definition of one unique outcome across trials.
- Variation in the timing of outcome assessment within and between trials.

Outcome measurement tool: An outcome measurement tool refers to how an outcome is assessed. It is the magnitude of the quality or quantity of an outcome. The tool can be a single question (pain score tool) or series of questions (quality of life tool), a score obtained through physical examination (scar assessment tool) or a laboratory measurement (C-reactive protein) for example(299-302). (https://www.cosmin.nl/tools/guideline-selecting-proms-cos/).

The difference between a unique outcome and an outcome measure is explained by COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN; https://www.cosmin.nl/): "When selecting an outcome measurement instrument for research or clinical practice, first the outcome to be measured should be clearly defined. That is, one should define what to measure" (303). There are, in some instances, multiple definitions for an outcome, such as disability. The World Health Organization (WHO) defines disability as: "problems an individual may experience in functioning, namely impairments, activity limitations and participation restrictions"(304). The 2010 Equality Act defines disability as: "a physical or mental impairment that has a 'substantial' and 'long-term' negative effect on your ability to do normal daily activities" (https://www.gov.uk/definition-of-disability-under-

equality-act-2010). Variation in the definitions for one unique outcome across trials is another version of ORH and impacts evidence synthesis.

Clinical indicator: The definition of an outcome may require the reporting of a collection of clinical indicators. We have defined a clinical indicator, in the absence of any other descriptor, as one of the following:

- A wound-related indicator (presence of pus).
- A clinical observer reported sign (pyrexia).
- A patient-reported symptom (increased local pain).
- A laboratory test (white blood cell count or presence of bacteria in the wound). These are non-specific and report inflammation rather than clinical infection.
- Wound microscopy to assess bacterial colonisation; the quantity and type of microbes in the wound.

A minimum set of these indicators is required by health care professionals (HCPs), to diagnose and report BWI consistently across trials.

Clinical consensus diagnostic tools: can be defined as a collection of indicators used to define the outcome, used as one criterion. Consensus on a small number of diagnostic tools for BWI has been achieved, but most are considered impractical in everyday clinical care(305).

Composite measure: can be defined as the measurement of an unobservable variable or construct by means of aggregating scores on several observable variables into an overall score. This is different to the diagnostic tool, as it uses a score(306, 307).

4.2 Background

Infection is a common complication after burn injury. The loss of the protective epidermis which is a natural barrier to bacterial invasion, allows a direct entry route of bacteria into the wound. Burn wounds produce exudate (a liquid produced in response to tissue injury), which creates a moist, nutrient-rich environment for bacterial growth(308, 309). BWI results in pain, delayed healing, an associated increase in scar presence and quality, a risk of sepsis if untreated, and increased healthcare costs related to increased lengths of hospital stay and interventions (308, 310-312). Data from France indicates that 19% of inpatients with burns will develop a wound infection(313). Infection is still the leading cause of death in patients with

burns(314). In those with burns of more than 40% of the total body surface area, it is estimated that 75% of mortality is related to infectious causes(305, 315).

It is important to identify the effects of interventions to detect and treat BWI to prevent the increased morbidity and mortality in burn patients. This requires evidence from systematic reviews which summarise well-designed and conducted RCTs. One challenge with evidence synthesis is a variation in the definition of the same outcome across trials (Figure 1)(230, 316, 317). If definitions of an outcome vary between studies, or are not stated, the validity of the aggregated data may be compromised(4, 318). There will be an associated risk of over or underestimating the true treatment effects. In the systematic review in Chapter Two, 166 ways of defining burn wound healing were reported across 147 studies. It is unclear if a similar heterogeneity in the definition of BWI exists across burn care research.

One reason for hypothesising that a variation in the clinical indicators used to define BWI may exist across studies, is that there is no agreed objective method for the clinical diagnosis of BWI. Early accurate diagnosis is difficult, as this is based on clinician judgement, supported by data from non-specific clinical indicators (12, 14, 312, 319). There is no reference standard(320). The clinical indicators used, include those described in the nomenclature section above, including patient- and clinical-observer reported symptoms and signs, non-specific laboratory tests for inflammation and wound microscopy.

Quantitative bacterial counts from swab cultures are acknowledged as providing only supportive information, as wounds will be colonised with bacteria within 24-48 hours of injury(319, 321). This does not imply that there is clinical wound infection requiring treatment. Clinically important BWI requires critical colonisation of the bacterial bioburden or virulence. This is known as the *tipping point of toxin release* at which low-level colonisation progresses to invasive infection requiring urgent treatment(322). Acute wound infection has also been defined as the presence of a wound environment with microbes in sufficiently large numbers, or of sufficient virulence to provoke an immune response locally, systemically or both(323). Diagnosis of this state, is further complicated by the fact that many of the signs used in the diagnosis of BWI, such as pyrexia and tachycardia, are non-specific and may exist or co-exist as part of the normal systemic inflammatory response to a burn(305). Clinicians currently do not have access to a point of care tool to diagnose BWI(324, 325).

To support a consistent diagnosis of BWI, *clinical consensus diagnostic tools* have been developed by the American Burns Association (ABA(305)) and Center for Disease Control

(CDC(326)). These are formal collections of indicators used for the diagnosis of BWI. There are, however, accepted practical limitations that preclude the routine use of these in clinical care. For example, the ABA and CDC criteria require the use of a wound biopsy. Evidence for the use of wound biopsy in burn care in the diagnosis of BWI is inconsistent and not commonly undertaken in Europe and low-income countries(319).

These inherent difficulties with the diagnosis of BWI are likely to lead to the use of varying definitions to report BWI across trials in burn care. This issue is supported by three recent systematic reviews of the effect of antibiotic prophylaxis to prevent BWI and treatment for facial burns. These reviews found variation in the indicators used to define BWI across trials(220, 238, 239). In the Cochrane review of 36 RCTs evaluating the effectiveness of antibiotic prophylaxis in burn patients, 15 studies did not describe BWI diagnostic indicators, 14 studies diagnosed BWI using swab culture or biopsy with or without clinical signs, four studies used wound signs or clinical observation, two studies used systemic signs and one study used chondritis to diagnose BWI(238). In the Cochrane review assessing topical therapy for facial burns, of three studies reporting BWI, three different indicators were used for diagnosis(239). One study used swab cultures, the second study used qualitative assessment of exudate and cellulitis, and the third study used the presence of chondritis. If the reporting of BWI is based on varying diagnostic indicators across trials, or if the diagnostic indicators used are not reported, the validity of a systematic review and the collation of evidence across trials, will be more challenging. Subjective decisions would need to be made regarding the similarity of definitions for BWI. For example, is *redness around the wound* the same as *spreading erythema*? Judgement will be required as to whether the outcome definitions are comparable enough across studies for the data to be brought together in a meta-analysis. The Cochrane Handbook states: "if there are differences between studies in the way the outcomes are defined and measured, this may be expected to lead to differences in the observed intervention effects"(327).

The aim of this study is to assess the consistency of definitions for acute (defined here, as before healing) BWI across studies of interventions in burn care. This is undertaken through a systematic review of the literature.

4.3 Method

Methods for this review were pre-specified through publication, and the protocol registered on the PROSPERO database: REF CRD4201809664(328). It is reported in accordance with the PRISMA statement for systematic reviews(329).

4.3.1 Study identification and selection

4.3.1.1 Inclusion and exclusion criteria

Peer reviewed journal articles published between 1st January 2010 and 30th November 2016, in English, and meeting the following Population, Intervention, Control, Outcome, Study design (PICOS) criteria were identified:

1. *Participants*: studies reporting data from patients with acute burn wounds (acute defined here as: before healing). Studies with mixed populations, where patients had both burn and other traumatic injuries, were excluded, unless data relating to patients with burns were presented separately.

2. *Intervention and control groups*: Studies reporting any intervention (surgical, non-surgical, psychological, homeopathic etc.) to treat patients of any age with burn injury and any comparator intervention or standard care were included.

3. *Outcomes of interest*: Studies reporting BWI as an outcome in the abstract, methods, results or discussion sections were included. We accepted any study where the authors used the terms burn wound infection or wound infection, in patients with burns.

4. *Study design*: Studies were included if they employed an RCT, controlled trial, observational study design, case control study or reported a protocol for a trial or observational study. (*Note*: observational studies were defined as a single group observed over time with impact of intervention observed; non-randomised studies were defined as a trial in which people are allocated to different interventions using methods that are not random). Exclusion criteria are detailed in Table 13.

4.3.1.2 Electronic search

An electronic search of four databases was undertaken to identify relevant studies: Cinahl, Ovid Embase, Ovid MEDLINE and the Cochrane Register of Controlled Trials (CENTRAL). To identify studies that met the inclusion criteria, three groups of search terms were iteratively developed relating to burns, wound infection, interventions and trials. Medical Subject Headings (MeSH) were used where available. Synonyms for each term were combined using an *OR* term, and the groups of terms were combined using an *AND* term. Following piloting of the search strategy in two databases (Ovid Embase and Ovid MEDLINE), *NOT* terms were added to increase the specificity of the search, thus removing studies irrelevant to the topic (e.g. NOT Coxiella Burnetii, burnout). The search string used in MEDLINE is presented in Table 14. This was modified for each database. The search terms were applied to the title, abstract and keywords where possible.

Table 13: Exclusion criteria for study selection.

1. Duplicate 2. Full text not available 3. Not a full text 4. Not about acute burn injuries 5. Not written in English 6. Not reporting BWI as an outcome 7. Non-human participants (e.g. animal studies) 8. Trial is not a clinical study (i.e. laboratory testing) 9. Trial investigates bacterial surveillance or would colonisation only

Table 14: Search strategy terms in Ovid MEDLINE.

1. exp Burns/ 2. burn*.tw 3. Scald*.tw 4. thermal injur*.tw 5. exp wound infection/ 6. wound infection*.tw 7. infect*.tw 8. bacteria*.tw 9. exp clinical trial*.tw 10. clinical trial* 11. trial*.tw 12. interven*.tw 13. compar*.tw 14. random*.tw 15. observ*.tw 16. 1 or 2 or 3 or 4 17. coxiella burnetii/ 18. burnetii*.tw 19. 17 or 18 20. 16 not 19 21. 5 or 6 or 7 or 8

Selection of papers for inclusion: Search results were downloaded from each database and combined in an EndNote database (Clarivate Analytics version 8), where records were manually reviewed to remove duplicates. Citations were exported to a Microsoft Excel database for screening. Titles and abstracts were reviewed against the exclusion criteria. Full text articles of retained citations were obtained and screened using the same criteria. Twenty percent of all citations were double-checked by the author of this thesis (see the Disclosure Statement for this study). Discrepancies in agreement throughout, were resolved between the two researchers and, if necessary, a third senior reviewer.

4.3.1.3 Data extraction

A proforma to standardise data extraction was developed in Microsoft Excel by myself and piloted for comprehensiveness and clarity. Where the same dataset was reported across two or more studies, extracted data about the studies were combined as a single dataset. Data extraction from 20% of papers was checked by the author of this thesis.

Extracted data to describe each study were:

1. Study identifiers (title, authors, date and citation).
2. Study design.
3. Intervention/s evaluated.

Extracted data to describe BWI reporting were:

1. Whether a study reported that they planned to assess BWI as an outcome.
2. Whether the study reported clinical indicators or a clinical consensus diagnostic tool for reporting BWI. Where studies reported use of clinical consensus diagnostic tools (e.g. the ABA(305) or CDC(326) consensus statements), the indicators used in the tool were not reported as separate indicators.
3. A report of each clinical indicator used to define BWI was extracted verbatim. Each indicator was categorised under a label to allow summary and comparison of data (see below). The number of indicators used to define BWI were noted for each study.
4. Whether there was consistency in the use of clinical indicators used to define BWI across included studies.
5. Whether numerical values were reported for clinical indicators to report BWI.

6. Whether a method for combining data from several indicators to determine presence of BWI was specified (e.g. a count of the number of indicators present or a weighted scoring system).

Grouping of clinical indicators with similar meanings: If the terminology used to describe the same indicator varied across studies, a process was undertaken by two reviewers (the author of this thesis and AD) to group indicators with the same meaning, under a consistent label. This was a similar technique to that for collating similar outcomes into domains in COS development studies. It was undertaken to enable an accurate count of different indicators used and to prevent double-counting. As an example, indicators included *wound microscopy from swab*, *bacteria in wound identified using swab*, *swab of wound pus*. These indicators have the same meaning and were assigned the same label.

A small number of studies reported defining BWI with a clinical indicator that represented a group of signs or symptoms, for example *clinical signs*, *cellulitis*. These indicators were labelled using their verbatim terminology. While it is acknowledged that these indicators represent a group of signs and symptoms, since it is not known what signs and symptoms the authors referred to, they were counted as a single indicator.

4.3.1.4 Data synthesis

No risk of bias assessment of studies or meta-analysis of outcome data was conducted, since this review aimed to report the indicators used to assess presence of BWI across studies and did not aim to assess the effectiveness of interventions. A narrative review of the data is presented.

4.4 RESULTS

4.4.1 Results of electronic search

The electronic search identified 4,314 records, of which 2,056 were duplicates. Data from two related studies were combined into one dataset(330, 331). Following the two screening stages, 72 studies, comprising 71 unique datasets, met the inclusion criteria (Figure 11).

Figure 11: PRISMA flow diagram.

4.4.2 Characteristics of included studies

Data extracted on the included studies demonstrated the detail in Table 15.

Table 15: Characteristics of included studies.

Design of studies	**n=71 (%)**
RCT	37 (52)
Controlled trial (without randomisation)	12 (17)
Observational study	21 (30)
Case control	1 (1)

Interventions tested	
Antimicrobials/ Antifungals	3 (4)
Dressings; comparisons of dressings versus topicals	17 (24)
Enteral nutrition Faecal containment Grafting/ Skin flaps Granulocyte-macrophage colony-stimulating factor hydrogel Insulin/Metformin Analgesia Resuscitation fluid Skin Substitutes Topicals	4 (6) 2 (3) 4 (6) 2 (3) 5 (7) 2 (3) 2 (3) 3 (4) 15 (21)
Other (1 each): Glutamine supplementation, hyperbaric oxygen, maggots, olive oil, phage therapy, pressure garments, probiotics, silk dressing, Versajet™, biocide impregnated gauze, phosphate repletion protocol, structured burn care approach.	12 (17)

4.4.3 Extracted data on the reporting of BW

1. *Whether a study reported that they planned to assess BWI as an outcome*:

Fifty-nine studies (83%) described that BWI would be assessed as a study outcome in the methods. The remaining 12 studies (17%) did not report that they planned to assess this outcome in their methods (no methodological definition of BWI), despite reporting it in the results(332-343).

2. *Whether the study reported a clinical consensus diagnostic tool or individual indicators for diagnosis of BWI*:

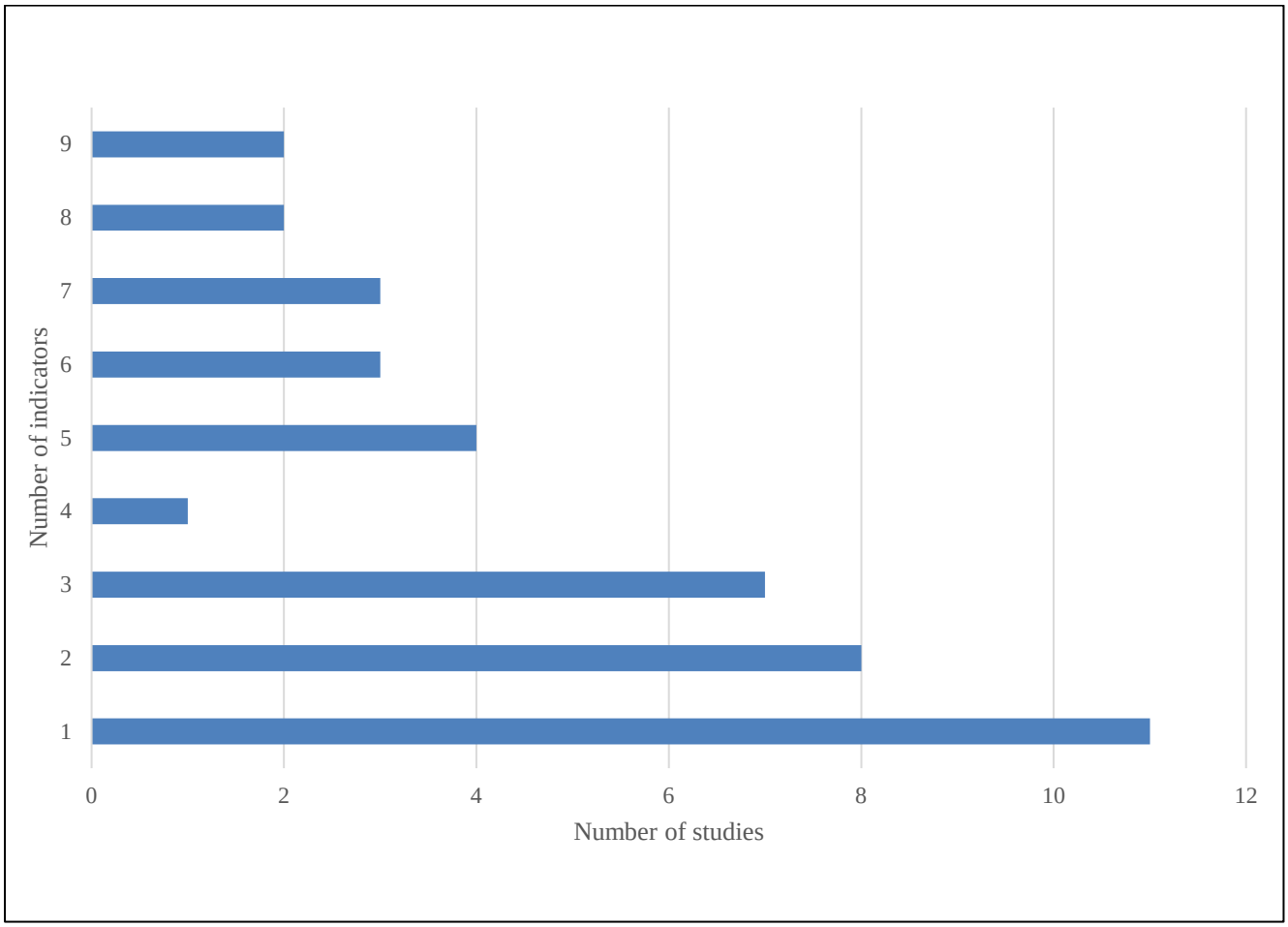
Forty-four of the 59 (75%) studies that stated that they planned to assess BWI as a study outcome, provided a definition of BWI in the study methods or results. Fifteen of these studies (25%) stated that BWI would be assessed, but did not describe the clinical indicators used to define the outcome(344-358).

Six studies (14%) reported that they had defined BWI using a clinical consensus diagnostic tool (359-364). Four studies used the ABA consensus statement(359, 362-364). Two studies reported that they had used criteria developed by Peck and colleagues(361, 365). One study combined Peck and colleagues' criteria with criteria developed by Silla and colleagues(366). Three of the studies using a clinical consensus diagnostic tool, also reported the use of additional specific indicators(361, 362, 364). Therefore, of the 59 studies that stated that they planned to assess BWI, 41 (70%) defined it using one or more indicators of BWI.

3. *Numbers of indicators used to define BWI*:

The number of indicators used to define BWI within studies, ranged between one (27% of studies) and nine (5% of studies) (Figure 12). The median number of indicators used was 3 (IQR=1-4).

Figure 12: Numbers of BWI indicators per study.



The indicators used to define BWI in the 41 studies (70% of the total studies), that reported the use of one or more clinical indicators, are presented in Table 16. Twenty-seven different indicators were used to define BWI across all included studies.

The most frequently reported clinical indicators used to define BWI, were presence of bacteria in the wound identified from swab of pus or exudate (n=25 studies, 61%), change in colour or volume of exudate (n=25 studies, 49%), spreading erythema (n=16 studies, 3%), wound oedema (n=10 studies, 24%), pyrexia and pain (n=9 studies, 22%).

Eleven of 41 studies (27%) that reported indicators of BWI, reported the use of only one indicator (330, 364, 367-375). Of these, six (55%) used wound biopsy or tissue culture(362, 364, 370, 371, 373, 376) and four (36%) used bacteria in the wound identified from swab of pus or exudate (330, 372, 374, 375). The remaining study, describing the use of a single indicator to define BWI, defined the indicator as cellulitis(369). As noted above, this represents a collection of signs and symptoms.

Table 16: Indicators for BWI per study (reported verbatim or grouped under one label).

First author	Number of indicators	Pain	Odour/ malodour	Temperature of wound	Change in colour / quantity exudate	Slough	Rapid eschar separation	Change in wound depth	Change in wound breadth	Spreading Erythema	Discolouration/ purple	Inflammation	Oedema/ swelling	Tissue necrosis	Presence of blistering	Lymphangitis	lymphadenitis	Pyrexia	Tachycardia	Bacteria in wound identified from swab of pus or exudate	Bacteria in wound or surrounding tissues from biopsy or tissue culture	Blood samples /microbiology	Leucocytosis	Raised ESR	Clinical signs	Biological markers	Administration of systemic antibiotics	Cellulitis
Abedini(377)	**2**																	✓		✓								
Adly(378)	**8**		✓		✓				✓	✓			✓					✓	✓				✓					
Ahmed (379)	**6**	✓			✓		✓	✓		✓										✓								
Aramwit(380)	**6**				✓		✓			✓				✓				✓		✓								
Bujang-Safawi(381)	**2**				✓																							✓
Chahed(382)	**9**				✓			✓		✓	✓		✓					✓		✓		✓	✓					
Chong(383)	**2**																				✓		✓					
Finnerty(370)	**1**																				✓							
Gee Kee(331, 384)	**1**																			✓								
Genuino(385)	**5**	✓			✓					✓			✓				✓											

Grippaudo(386)	**2**				✓															✓								
Hubik(387)	**2**				✓															✓								
Hyland(388)	**3**				✓															✓								✓
Jeschke(364)	**1**																				✓							
Jeschke(363)	**1**																				✓							
Kahn(369)	**1**																											✓
Kahn(389)	**2**																			✓								✓
Kement(371)	**1**																				✓							
Khorasani(390)	**3**																			✓		✓					✓	
Kibor(338)	**2**																			✓		✓						
Lau(372)	**1**																			✓								
Lu(373)	**1**																				✓							
Malik(374)	**1**																			✓								
Martirosyan (375)	**1**																			✓								
Mayes(391)	**2**																			✓							✓	
Nagoba(392)	**9**			✓	✓	✓				✓	✓			✓						✓			✓	✓				
Nasiri(393)	**7**	✓		✓	✓					✓		✓	✓					✓										
Park(361)	**5**	✓														✓		✓		✓			✓					
Rashaan(394)	**7**	✓		✓	✓					✓			✓					✓		✓								
Rose(395)	**3**																				✓				✓	✓		
Ryssel(376)	**1**																				✓							
Schiefer(396)	**5**	✓			✓					✓		✓	✓															
Scholten-Jaegers(397)	**4**									✓			✓					✓		✓								
Shahzad(266)	**6**	✓	✓		✓					✓				✓						✓								

Silverstein(398)	**5**		✓		✓					✓					✓					✓								
Soltan-Dallal(267)	**7**				✓			✓		✓	✓	✓						✓		✓								
Verbelen(249)	**8**	✓	✓		✓					✓			✓			✓				✓								✓
Weissman(399)	**3**				✓							✓	✓															
Yan(400)	**3**				✓							✓								✓								
Yang(401)	**3**	✓								✓										✓								
Yuan(402)	**3**				✓					✓			✓															
Total indicator numbers reported across studies.		**9**	**4**	**3**	**20**	**1**	**2**	**3**	**1**	**16**	**3**	**5**	**10**	**3**	**1**	**2**	**1**	**9**	**1**	**25**	**8**	**3**	**5**	**1**	**1**	**1**	**2**	**5**
% of studies reporting each indicator.		**22**	**9**	**7**	**48**	**2**	**4**	**7**	**2**	**39**	**7**	**12**	**24**	**7**	**2**	**4**	**2**	**22**	**2**	**61**	**19**	**7**	**12**	**2**	**2**	**2**	**4**	**12**

4. Whether there was consistency in the use of indicators to report BWI across studies.

Thirteen studies (32%) reported BWI in the same way as at least one other study. Six of the 11 studies (55%) that defined BWI with a single indicator, used bacterial presence (362, 364, 370, 371, 373, 376). Of the nine studies using two indicators to define BWI, two (22%) used the same indicators: presence of bacteria in the wound from swabs, and a change in colour or the quantity of exudate(386, 387). Administration of antibiotics was used to define presence of BWI in two studies (4.9%)[58, 59].

5. Whether numerical values were reported for indicators to diagnose BWI.

Of the 25 studies using presence of bacteria from wound swabs to define BWI, six (24%) described the numerical values used (more than 10^5 microbes per gram of tissue)(249, 361, 375, 392, 401, 403). For tissue cultures, five of eight studies (63%) reported numerical values (more than 10^5 colony forming units per gram of tissue)(362, 364, 370, 376). The remaining studies did not report what numerical values were used for the presence of bacteria in the wound. One of the nine studies (11%) using pyrexia as a clinical indicator, reported the numerical values used to determine fever and high fever (>37.4°c and >38°c respectively)(380).

6. Whether a method for combining data from several indicators to determine presence of BWI was specified (e.g. a count of the number of indicators present or a weighted scoring system).

Seven of the 41 studies defining BWI (17%) used indicators that represented a group of signs and symptoms. *Cellulitis* was used as an indicator to define BWI in five studies(369, 381, 388, 389, 404) (12.2%), and *clinical signs* and *biological markers* in one study (2.4% respectively)(405). Thirty-one studies (76%) used more than one indicator to define BWI. Of these, 10 (32.3%) reported a method for rating or combining data from the multiple indicators used to determine whether BWI was present. In four of these 10 studies (40%), BWI was evaluated by counting the number of signs present(249, 393, 396, 406).

4.5 DISCUSSION

The systematic review described in this chapter, was undertaken to identify whether BWI is defined consistently across studies assessing the effect of interventions in burn care and reporting BWI as an outcome. Across all included studies, 12 (17%) did not report that they planned to assess BWI in their methods, despite reporting data on BWI in the results. Of all the studies, 59 (83%) *did* describe planning to assess BWI as an outcome in the study methods. Of these, 15 (21% of all studies) did not state how they defined BWI. Of those studies that did describe the clinical indicators used to define BWI, 27 different indicators were used across the studies (range 1-9, median=3). Only 13 of 41 studies (32%) reporting the indicators that they used to define BWI, used the same indicators as at least one other study. Six studies (13.6%) reported that they had defined BWI using a clinical consensus diagnostic tool.

There are three key findings from this review.

1. BWI is commonly not defined in studies reporting it as an outcome.
2. There is considerable heterogeneity in which clinical indicators are used for BWI when it is defined across studies. Several studies also used non-specific terms, including cellulitis, wound signs, and biological markers.
3. The use of consensus tools is uncommon, possibly due to practical issues with their design.

This lack of consistency in the definition of BWI, weakens the case for collation of data describing intervention effectiveness(407). If data from studies with varying outcome definitions are synthesised, the findings may not represent the truth about the magnitude of the effect of the intervention. The lack of specificity in the definitions of BWI, and other unique outcomes across studies, replicates the findings of other systematic review work in burn care. These findings include definitions of sepsis, scarring and wound healing (4, 408-410). The impact of this problem has been highlighted in recent Cochrane Reviews for patients with burns. The authors reported that the validity of their findings was compromised, due to a variation in the indicators used to define BWI across studies:

- The use of antibiotic prophylaxis ("Outcome measures and follow-up times were heterogeneous, or not even defined, which made it difficult to interpret the results of the review and to determine their applicability")(238).
- Facial burn treatment ("Heterogeneity of interventions and outcomes prevented pooling of data")(239).
- Immuno-nutrition (".... some of the outcome measures used are subject to a high degree of variability (e.g. time to healing).")(241).

A variation in the definition of one specific outcome has been found in systematic reviews of other health areas such as surgical site infections(223) and healthcare-associated infections(411).

A further funding from this review is an over-reliance on the use of one specific indicator, with little clinical justification for its use. Six of the 11 studies used a single indicator to define BWI, the presence of bacteria in the wound. Recent studies investigating the reliability of the use of bacterial presence in wound swabs and tissue sampling as an indicator of BWI, reported difficulties(319, 321, 412, 413). More than one sample of the wound may be needed to obtain an accurate estimate of bacterial load, as correlation between swabs and biopsies is frequently poor and biopsies are invasive and costly. A further literature review supports the view that quantitative microbiology should not be used without reference to clinical signs and symptoms. It is suggestive that the 10^5 colony forming units/gram of tissue cut-off is arbitrary, since clinically relevant infection is more likely to be found at higher bacterial concentrations(319, 414). These data suggest that quantitative microbiology *alone,* may be an unreliable indicator of BWI and may overstate the incidence of BWI, since bacteria are frequently present in burn wounds without being clinically relevant (wound colonisation).

Using a formal collection of more than one indicator has been attempted when reporting BWI. Clinical consensus diagnostic tools have been developed to standardise BWI reporting. However, only six of the 71 studies (9%) reported their use. This may relate to a lack of evidence for the individual parts of the tools and practical limitations of these tools in clinical practice. These include the use of wound biopsy(305, 326), which is costly, may cause

scarring, and is infrequently used in some health care systems such as the UK NHS, as described above.

A better solution would be a composite measure or scale to answer the yes/no question to the presence of wound infection. A composite measure has been defined as: "a variable, made up of two or more variables or measures, that are highly related to one another conceptually or statistically" (415). Another definition by Barclay *et al*. is: "measurement of an unobservable variable or construct by means of aggregating scores on several observable variables into an overall score"(416). Examples include the *Hull reflex cough questionnaire* and *GHQ depression scale*(417, 418). Ultimately, a composite measure would solve the problem of varying definitions of BWI using different clinical indicators. There is, however, currently not enough evidence to develop such a measure. Data is needed to provide an explanation of the reasons underlying the development of each indicator in the composite measure, including the choice of measure, different aims of the individual measures and the relationship between included clinical indicators.

As we do not have enough evidence to produce a composite measure for BWI, the aim of this study was to identify the variation in reporting of clinical indicators for BWI across trials. The review has demonstrated the need for standardisation of reporting of this outcome. The use of a small number of the most important clinical indicators for reporting of BWI would achieve this; a Core Indicator Set (CIS).

4.5.1 Strengths and limitations

This literature review employed a systematic approach to the identification and selection of studies reporting BWI as an outcome. The use of four databases to identify RCTs, observational studies, case control studies and protocols, provided a comprehensive review of how BWI has been defined across studies. Other strengths included the double-checking of all screening and inclusion of studies and of data extracted. Limitations include the exclusion of studies published before 2010. This limit was placed to ensure that we identified reports relating to current BWI diagnostic practices. Studies that were not published in English were

excluded due to funding constraints. While unpublished literature was requested from interested parties, no additional studies or work in progress reports were put forward.

Clinical decision-making about effective treatments for BWI requires that evidence is synthesised across relevant studies. Inconsistent definitions of BWI, a form of outcome reporting heterogeneity, creates noise in the data which may obscure the true effect of interventions and interventions that are effective may not be identified. There is a need to improve the consistency of how BWI is defined, and for this to be reported in the study methods and results. However, identification of a consistent definition is difficult as there is no objective diagnostic method for determining the presence of clinically relevant BWI. Until this is available, a minimum set of the most important indicators of BWI, a CIS, needs to be agreed and reported consistently.

4.6 CONCLUSIONS

This systematic review has shown that 38% of included studies did not report how BWI was defined, that there is considerable heterogeneity in the indicators reported to define BWI when it is reported, and limited use of existing clinical consensus diagnostic tools. The lack of an agreed definition and heterogeneity of clinical indicators used when BWI is defined, will limit the validity of evidence syntheses, preventing the identification of the most effective treatments for patients with burns. Until there is an objective method to diagnose clinically relevant BWI, development of a CIS is needed, to standardise reporting in trials reporting a BWI outcome.

This chapter has described the second type of outcome reporting heterogeneity (ORH) presented in this thesis. In this example, one unique outcome (BWI), has been shown to be defined differently across trials. The following chapter will describe a third type of ORH. This is a variation in the timing of assessment of one unique outcome within and between trials. The chapter will discuss how this effects evidence synthesis and how it impacts patient relevance.

Chapter 5 Outcome definition: the effects of timing of outcome assessment

This chapter is based upon a submitted article:

Amber E. Young, Fatima Yaqub, Chris Metcalfe, Sarvnaz Sepehripour, Jane M Blazeby. Clinical trials in burns care primarily focus on short-term outcomes of uncertain longer-term patient benefit: a systematic review.

I conceived the idea for the project. I co-wrote the paper, led on data extraction and analysis, with the support of co-authors Ms. Yaqub and Ms. Sepehripour. Professors' Metcalfe and Blazeby inputted ideas, edited and assessed readability for the paper. The paper has not yet been peer-reviewed. It was returned from the Journal of Clinical Epidemiology prior to peer review, with the advice to submit the paper to a specialist burn injury journal.

Excerpts from the paper are incorporated into this chapter.

5.1 Introduction

This chapter will answer:

Thesis Objective 4: An analysis of how variation in the timing of the assessment of unique outcomes across trials, impacts relevance to patients.

In Chapter Three, I discussed the concept of a unique outcome, as one requiring differences and originality in outcome *meaning and context*(293). In Chapter Four, the focus was on the impact of a variation in the definition of one unique outcome across trials. In this chapter, another aspect of outcome variation across trials will be explored; a variation in the timepoint of outcome assessment. In Chapter Two, the impact of timing of outcome assessment on the ability to collate evidence effectively was discussed (2, 419). In this chapter, I will focus on the

impact of variation in the timing of outcome assessment on trial relevance. Any field, including healthcare, should be measured from the customer's perspective. It is now considered important in healthcare, that care should be assessed using patient-important outcomes(420-425). Porter *et al*. wrote about the *Outcome Measures Hierarchy*(426). He stated that: "outcomes should involve the health circumstances most relevant to patients". Linking outcome timing and relevance, he reported that "the set of outcomes should cover both near-term and longer-term patient health, addressing a period long enough to encompass the ultimate results of care". For chronic conditions, therefore, outcomes should be measured for periods long enough to reveal the sustainability of health, the incidence of complications and the need for additional care. In terms of patient-importance, these outcomes are likely to include quality of life, postoperative complications, and survival, among others(110). Despite the acceptance that patient-important outcomes should be prioritised, this is commonly not the case in healthcare research(148, 149, 427).

The timing of assessment of reported outcomes, impacts evidence synthesis in terms of outcome reporting heterogeneity (as defined in Chapter Three), and in terms of relevance to patients.

5.2 Background

Well designed and conducted randomised controlled trials (RCTs) determine intervention effectiveness through an un-biased comparison of outcomes (428). To optimise the value of trial data, high quality outcome reporting is required. In terms of the timing of outcome assessment, the CONsolidated Standards of Reporting Trials (CONSORT) statement highlights the importance of reporting the timepoints of outcome assessment(429). It states that "when outcomes are assessed at several time points after randomisation, authors should indicate the pre-specified time point(s) of primary interest". Selection of the time point of primary interest needs to reflect the research question(430), length of trial follow-up (and associated costs)(431, 432) and importance to patients(433). Patients often value longer-term outcomes (e.g. function, cosmesis, survival), more than short-term events (e.g. length of hospital stay, the need for re-operation)(150, 151, 434-437). However, for pragmatic and

economic reasons, RCTs frequently focus on relatively short recruitment and follow-up periods(106, 151, 248, 431). The relationship between the reporting of short- and long-term outcomes, is therefore important (438-441).

In burn care research, recent RCTs and systematic reviews, show that outcomes measured in the short-term include operative blood loss, ventilator days, wound infection, wound healing and length of hospital stay(4, 442-446). Although important at the time of treatment, it is unknown whether these short-term outcomes are important to patients. Patient-important outcomes can be defined as: "a characteristic or variable that reflects how a patient feels, functions or survives", such as quality of life or physical function(150, 437, 447). Burn injuries are chronic conditions, with patients injured as children, managing disability for the rest of their lives, including neuropathic pain and itch, functional, cosmetic and psychological issues(448, 449). Despite this, there is evidence that effects of interventions are increasingly being assessed using short-term outcomes, sometimes making the assumption that these will reflect longer-term outcomes that are more important to patients (4, 30, 151, 450, 451).

If the short-term outcomes reported in trials *are* reliable markers of longer-term outcomes, and are effected in the same manner by an intervention as a longer-term outcome outcome, then they could be legitimately used as surrogate endpoints (109, 452-456). *A surrogate outcome* is an outcome measured in the short-term (such as a laboratory measurement or physical sign) that does not measure the effect of primary interest, but is expected to reliably predict this (457). Surrogate outcomes need to be validated to test whether they are true proxies of the associated longer-term outcomes(438, 458, 459). A valid surrogate outcome has to have a strong association with the real outcome of interest (158, 460). It is known that short-term outcomes are increasingly being used as surrogates *without* evidence reliably linking them to longer-term patient-important outcomes (124, 137, 461). It is also known, that short-term outcomes used in trials in other clinical areas, frequently do not predict important longer-term outcomes, and neither do they translate well onto important longer-term outcomes (e.g. tumour response and survival, glycated haemoglobin HbA1c and co-morbidity for diabetes)(462, 463). This important issue has not been examined in burn care research.

The aim of this chapter is to explore the timing of outcome assessment in RCTs assessing interventions in burn care. It will debate whether authors that report short-term outcomes, are implicitly, or explicitly, using these as surrogates of longer-term patient-important outcomes.

5.3 Methods

Methods for this review were specified in advance and the protocol registered on the PROSPERO database: reference CRD42019150513. The review adheres to the PRISMA statement for reporting systematic reviews [37]. This review updates the review presented in Chapter Two to provide a more recent assessment of the timing of outcomes in burn RCTs.

5.3.1 Study Eligibility

Studies were included using the following Patient, Intervention, Comparison, Outcome, Setting (PICOS) characteristics:

Type of study: Full text RCTs, RCT protocols and RCT pilot studies were included. Protocols and pilot studies were deemed relevant, as this review is focused on the outcomes themselves, rather than the results of intervention effects. Pilot studies were excluded, if the full RCT was published within the time period specified in this review. Feasibility studies without an external pilot RCT, were excluded, as they generally report outcomes relating to the practicalities of a full RCT such as screening issues, recruitment etc. Conference proceedings, abstracts, non-English language publications and studies not involving humans were also excluded.

Participants: Study participants consisted of patients of any age, with cutaneous burns of any aetiology or size requiring treatment in a healthcare facility. If a study population contained patients with combined thermal and mechanical injuries, the study was only included if burns-related outcomes could be separately identified. Study populations composed of

patients with carbon monoxide poisoning alone, chemical ocular or caustic oesophageal burns were excluded, as they did not involve cutaneous burns and would be managed differently, with different outcomes reported.

Intervention: Trials were included if they reported surgical or non-surgical burn care interventions with any *comparator*.

Outcomes: All outcomes reported by clinical observers and/or patients were included. These included physiological, cosmetic, psychological, functional, metabolic or histological findings, adverse or mortality events and quality of life or long-term indicators of patient well-being. Financial outcomes were excluded. No distinction was made between primary and secondary outcomes in terms of data extraction. The timing of the last assessment of each outcome was assessed.

5.3.2 Identification of studies

Ovid MEDLINE, Ovid EMBASE, Web of Science and The Cochrane Library were searched electronically, for a time period commencing 1 January 2017 to 22 March 2019 for RCTs relating to burn care. Medical subject heading and free text terms included *burn*, *scald*, *thermal injury* and *RCT*. The search terms were adapted by the thesaurus vocabulary of each database. Details of exact terms and the search strategy can be found in Table 17. The time period was restricted to include outcomes relevant to recent burns trials, and to evaluate the degree of heterogeneity or consistency in outcome timing within a two-year timeframe, whilst still including enough studies for evaluation.

Table 17: Search strategy for Ovid MEDLINE.

Ovid MEDLINE search strategy	
1.	Burns/ (MESH) exp
2.	Burn*.tw
3.	Scald*.tw
4.	Thermal* adj injur*
5.	1 OR 2 OR 3 OR 4
6.	Heartburn
7.	Burnout
8.	Burn* adj out
9.	Burning
10.	Burnetii
11.	Burnish*
12.	Burnet*
13.	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14.	5 NOT 13
15.	Limit to RCT, clinical trial, English language, human, last five years

5.3.3 Study selection process

Reference management with Endnote (Clarivate Analytics version 8) was used for compilation of titles based on initial searches. Duplicates were removed and abstracts were screened against predetermined eligibility criteria (Figure 13). Full text articles were retrieved for all abstracts appearing to meet inclusion criteria. The full texts were read in their entirety independently by the author of this thesis and another reviewer (AD), and assessed for eligibility. This resulted in final decisions for inclusion or exclusion, with decisions recorded. Disagreements were resolved by discussion. Reasons for exclusion were ordered hierarchically from most to least important (Figure 13). The most important reason for exclusion met by a paper was recorded as the reason for exclusion.

5.3.4 Quality assessment

Quality assessment of RCTs was not undertaken, as it was not relevant to the data extracted.

5.3.5 Data extraction and analysis

A Microsoft Excel data extraction form developed specifically for this review was refined iteratively and piloted prior to formal data extraction. Data were independently extracted by the author of this thesis and another reviewer (AD). Judgements were compared. Any areas of discrepancy, were resolved by discussion amongst the two reviewers.

5.3.5.1 Study data extracted

Study design: RCT, pilot RCT or RCT protocol.

Study details:

- Authors, year of publication, citation.

- Participant numbers.
- Recruiting country.
- Number of recruiting sites.

5.3.5.2 Outcome data extracted

Outcome detail: for each study, all reported unique primary and secondary outcomes were extracted verbatim from the trials' abstracts, methods, results, tables or figures as discussed in Chapter Three(464). In terms of recording the timing of assessment, no distinction was made between primary and secondary outcomes, or if the outcomes were clinical observer or patient-reported. All outcomes were treated equally. The timings of assessment were categorised as below.

Timing of assessment for each individual outcome across studies: for each extracted outcome in each included study, the timing of the last assessment from the time of burn injury was recorded.

Outcome assessment timings were categorised into time periods:

- Less than or equal to six months after injury. This was defined as short-term.
- More than six months after injury. This was defined as longer-term.

Further classification of short-term outcomes in relation to the time of injury, was undertaken:

- Less than or equal to 24 hours.
- From 24 hours up to and including two days.
- From two days up to and including one week.
- From one week up to and including two weeks.
- From two weeks up to and including one month.
- From one month up to and including three months.
- From three months up to and including six months.

Longer-term outcomes were divided into the following time points after injury:

- More than six months up to and including one year.
- From one year up to and including three years.
- From three years.

Timepoint of assessment for each outcome: If the timing of the study outcome, in relation to injury, was not clearly stated, we used *pre-agreed decision rules* to estimate timings. Frequently, the time of outcome assessment was linked to the length of hospital stay. If this was not stated, it was calculated as two days per percent total body surface area of the burn (465-467). If a range of burn sizes were given, the last assessment was based on the largest burn size. If the article did not provide enough data to determine the timing of outcome assessment, the timing was reported as not stated (NS).

Outcome assessment timing for each whole study: Whole studies were classified as reporting short-term or longer-term outcomes, using the six-month cut-off as defined above. Studies reporting longer-term outcomes were explored in more detail.

Authors' reported views of the association between short and longer-term outcomes: Reasons for the use of short-term outcomes were extracted verbatim from each article. The use of the term surrogate outcome was extracted, if it was stated. Implications for the use of the short-term outcomes to predict longer-term outcomes, were extracted verbatim if reported. Any details of validation testing performed for an early outcome to act as a surrogate was noted.

5.3.5.3 Data analysis

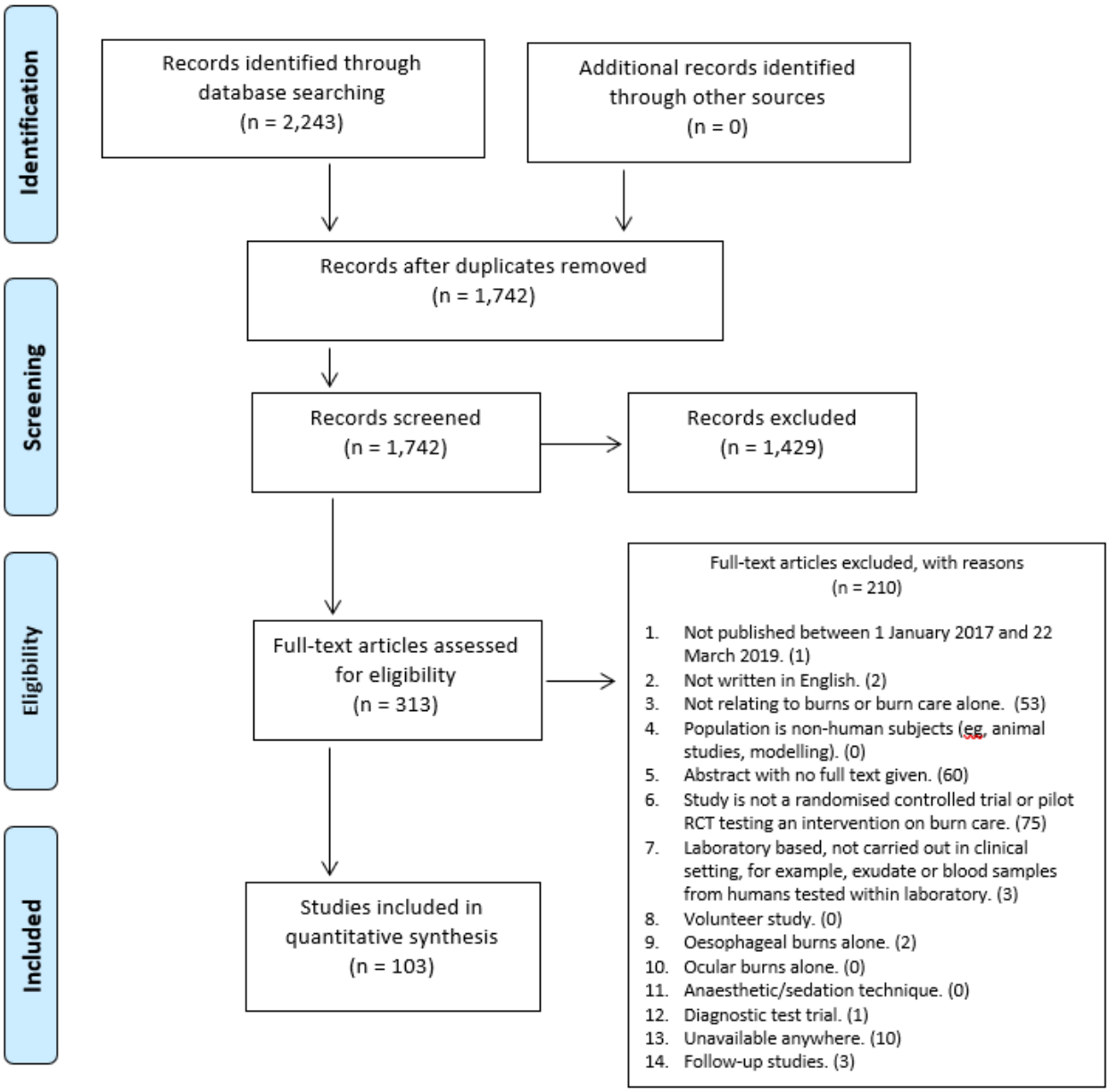
Numerical data are presented as summary statistics. A narrative synthesis was applied to the study authors' description of the use of surrogate outcomes. Any themes were developed iteratively.

5.4 Results

5.4.1 Included studies

The initial search strategy identified 2,243 records. Following de-duplication, a total of 1,742 records remained. Scrutiny of the titles and abstracts identified 313 potentially relevant articles for full text review. Of these, 210 studies did not meet the inclusion criteria and were excluded. A total of 103 studies were therefore included in the review (Figure 13).

Figure 13: PRISMA flow diagram.



5.4.2 Study and outcome detail

Of the 103 included studies, 90 (87%) were reports of full RCTs, 7 (7%) were pilot studies and six (6%) were study protocols (Table 18). The number of patients recruited per trial ranged from nine to 352 (median 50; IQR 30–73) for full and pilot RCTs. Of full and pilot RCTs, 46% recruited fewer than 50 participants. Most studies, (83 (81%)) recruited (or planned to recruit) participants on one site alone. Studies were undertaken across the five continents, with most (37%) recruiting in Asia (Table 18). In total, 1,021 outcomes were reported across the 103 studies.

Table 18: Study and outcome details.

	Studies
Study Type (n=103):	
Number of RCTs	90 (87%)
Number of Pilot studies	7 (7%)
Number of RCT protocols	6 (6%)
World region for recruitment:	
Asia	47 (37%)
North America	26 (25%)
Europe	11 (18%)
Africa	9 (9%)
Australasia	8 (9%)
Latin America	2 (1%)
Year published:	
2017	36 (35%)
2018	48 (47%)
2019 (part year)	19 (18%)

5.4.3 Timing of assessment for each individual outcome across studies

Of the 1,021 outcomes reported across all 103 included studies, 706 (69%) were last assessed at less than, or equal to, six months, 179 (18%) were last assessed at more than six months, 48 (5%) were assessed at more than a year after injury and for the other 136 (13%), outcome timings were not clearly stated (Figure 14).

5.4.4 Outcome assessment timing for each whole study

Of the total of 103 included studies, only 29 (28%) were classified as long-term, with outcomes assessed at more than six months after injury(394, 468-495) (Table 19). Of the 29 studies, 19 clearly reported that the study outcomes were assessed at more than six months after injury. Two were determined using the decision rules described above. Of these 21, four reported outcomes at between six months and one year, 13 between one and three years inclusive, and only one at more than three years after injury.

In the other eight studies that did not state the timing of outcome assessment *at all* (classified as not stated), there was sufficient evidence to demonstrate that the outcome assessment was made long-term after injury and related to scar management (468, 469, 474, 480, 482, 484, 491, 495). For these studies, time from randomisation, rather than injury, was more commonly reported. The time after injury was long-term but the time after randomisation was either short- or long-term.

Figure 14: Outcome timepoints in relation to injury time across all included studies.

Note: n=1,021.

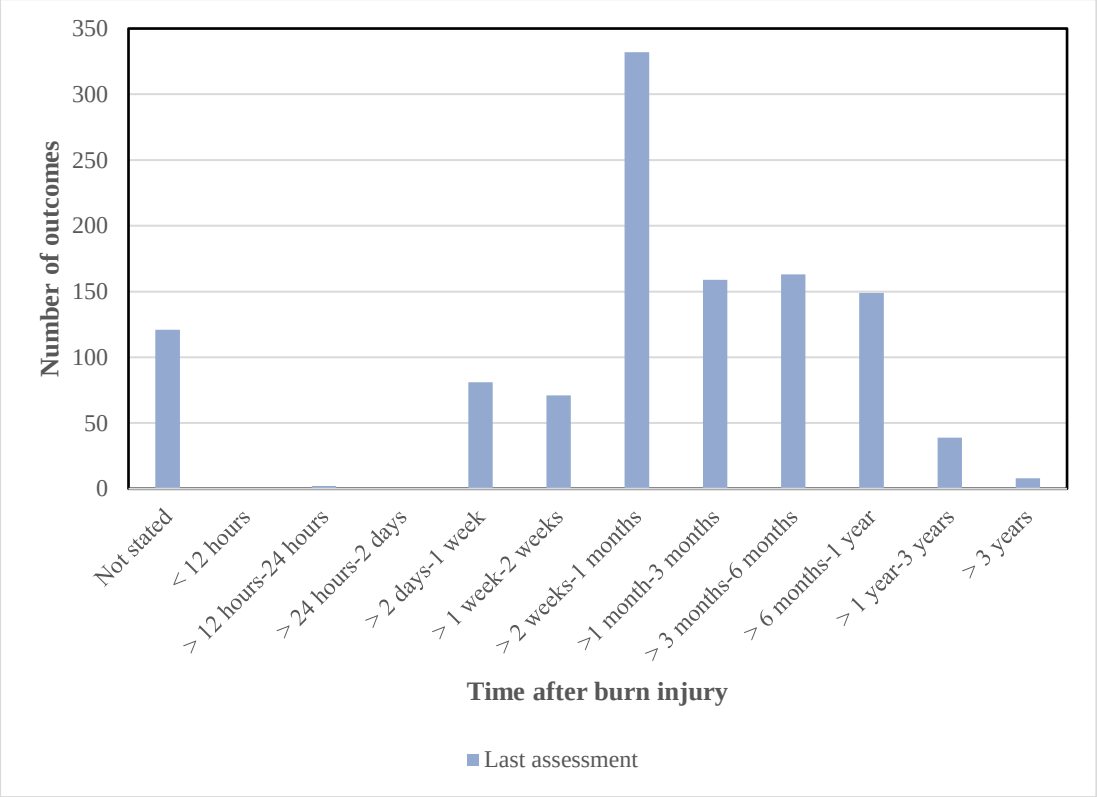


Table 19: Whole studies, with outcomes last assessed at more than six months after injury.

First Author (reference)	Studies last assessing outcomes at > 6/12 and < 1 year after injury.	Studies last assessing outcomes ≥ 1 year after injury	Studies last assessing outcomes during reconstruction / scar management, but time after injury not stated.	Studies last assessing outcomes at reconstruction in relation to randomisation.
Alsharnoubi(468)			Hypertrophic scarring treatment.	Outcomes last measured at three months *post-randomisation*.
Bashir(469)			Contracture treatment.	Outcomes measured last at 14 days *post-randomisation.*
Boyce(470)		One year		
Douglas(471)		Three years		
Elrashid(472)	Not stated. No burn size stated. Intervention more than two months after healing. Intervention for one month. Outcome assessed after intervention; likely to be more than six months approximately after injury.			
Frew(473)		One year		
Gal(474)			Participants had *mature scars.*	Outcomes measured last at 12 months post-randomisation undertaken on mature scars.
Gottschlich(496)		One year		
Herndon(497)		Two years		
Hibbard(477)		Two years		
Holmes(478)		One year		
Holmes(479)		One year		
Hosseini(480)			During reconstruction for burn contractures.	Six months *post-randomisation.*
Legemate(481)		One year		
Mohammadi(482)			During reconstruction for hypertrophic scar formation.	Six months *post-randomisation.*
Moiemen(498)		One year		
Muangman(484)		One year		
Nedelec(485)		33 months		
Pena(486)		One year		
Perera(487)		One year		
Rashaan(394)		1 year		

Rivas(488)	8.5 months.			
Ro(489)		1 year		
Samal(490)			Median time from injury to intervention 24 months.	Not stated but post-operative complications and graft take. Approximately 1 month maximum from randomisation.
Stekelenburg(499)			During reconstruction for wide scar contracture.	1 year after intervention.
Sveen(492)		1 year		
Wiseman(493)			Burn reconstruction. Type not stated.	6/12 post-intervention.
Zacharevski(494)	6 months			
Zoheiry(495)	Likely to be ≥ 6 months; intervention after discharge of patients with burns of ≥ 30% BSA and intervention lasts 3 months.			

5.4.5 Authors' views of the use of short-term outcomes as surrogate outcomes

Of the 74 studies that assessed short-term outcomes, only 19 (26%) made comments that linked the short-term outcomes reported, to longer-term outcomes that had not been measured. These comments were not supported with any surrogate outcome validation data (Table 20). The word *surrogate* (or similar) was mentioned in only 3% (n=2) of studies.

Table 20: The use of short-term outcomes to predict longer-term outcomes.

Note: verbatim extraction of data from included studies.

Comments on the use of short-term outcomes to predict long-term outcomes.
"Secondary outcomes including knee height was measured as a **surrogate** measure of the height." (500)
"Instead, we used the presence of hypertrophic scarring determined by a burn care provider, as well as the need for further interventions, as **surrogates** of quality of scar appearance." (501)
"In addition, as thermal burn is associated with scarring, so the healing process should decrease the scar and its related problems." (502)
"Changes in parameters which are seen on first few days of acute burns have a long-term effect." (503)
"One of the main limitation of our study was that our sample size was not adequately sized to comment on the long-term benefits of administering tranexamic acid like 6 months or 1 year mortality rate, graft failure rate, renal failure rate, etc." (504)
"Indeed, difficulty walking, running, feeling of weakness, and fatigue have been reported in burn patients as much as 17 years post-injury." (505)
"Pain from burns early in life has been found to have potential long-term effects on pain processing linked to the developing nervous system." (506)
"The extent of injured and unhealed wound burden is the greatest contributor to mortality in burns. Hence, any process that inhibits wound healing or results in less than optimal graft take after definitive surgery can theoretically impact overall outcomes. The study was not powered or designed to detect a difference in mortality." (507)
"The resulting morbidity inhibits patients' return to normal societal activities and reduces quality of life." (508)
"Low physical work and muscular strength are major obstacles in allowing burned children to return to school and to perform activities of daily living. interventions." (509)
"The poor control of pain is associated with physiological and psychological results, including intractable pain, depression, and post-traumatic stress, and also extensively with suicidal thoughts." (510)
"For children especially, the long-term physical and psychological con- sequences of these scars can be devastating." (511)
"Numerous retrospective studies have demonstrated the number of transfusions burns patients received was associated with infectious episodes, organ dysfunction, length of hospitalisation and mortality." (512)
"If acute pain is not adequately managed, it can lead to altered long-term pain perception and maladaptive coping strategies, which can persist into adulthood. Previous research also suggests that inadequate pain control can lead to the development of anticipatory anxiety for future medical procedures. Therefore, optimising pain management during the acute phase of a paediatric burn is critical not only for the physical and cosmetic outcome of the injury but also for the child's well-being at the time and in the long-term." (513)
"This is based on studies that show that there is a correlation with hypertrophic scarring in those children with scald burns who take more than 14 days to heal." (514)
"Clinical practice has confirmed that improper wound disposals can induce infection easily, which can delay wound healing or even deepen it and scar hyperplasia is comparatively serious even though the wound is healed." (515)
"Anticipatory anxiety can delay in wound healing and recovery process, disturb metabolic and immunologic process." (516)
"Having higher levels of anti-oxidants in plasma is realistically advisable, but this needs to be linked to absolute improvements in clinical outcome." (517)
"Failure to maintain joint flexibility can necessitate surgery in which scarred tissue is replaced with grafts of normal skin." (518)

5.5 Discussion

The systematic review presented in this chapter, explored the timing of outcome assessment reported in burn care RCTs. Included were 103 RCTs that reported a total of 1,021 unique outcomes. Most outcomes, (69%), were last assessed at less than six months after injury. Of the 103 whole studies, only 28% reported outcomes last assessed at more than six months after burn injury, and only one study followed patients for more than three years. Of the 74 studies assessing short-term outcomes, 26% mentioned implications for the longer-term impact of the observed short-term outcomes, but none used validated surrogate outcomes.

Outcomes measured shortly after injury have undoubted importance in assessing surgical technique, health care costs or adverse events, and trials with these measures are important. Most patients, however, are more interested in the impact of interventions on their life many years after injury (106, 149). Evidence shows that patients want knowledge of the impact of burn injury and its treatment, on longer-term functional ability including the capacity to work, cosmesis, psychological adaptation and quality of life overall(519-522). If short-term outcomes, shown by this review to be more commonly reported in burn care research, can be validated as useful surrogate outcomes and represent a true proxy for longer-term outcomes, then it will be possible to extrapolate data from short-term studies to understand impact on patient longer-term outcome.

Validating an outcome as a surrogate for a longer-term outcome, is challenging and time-consuming. Prentice was one of the first to define this relationship: "a surrogate endpoint is a response variable, for which a test of the null hypothesis of no relationship to the treatment groups under comparison, is also a valid test of the corresponding null hypothesis based on the true endpoint"(523). Prentice's criteria to assess the validity of a surrogate outcome requires the surrogate to be formally correlated with the true clinical outcome, but also for the treatment effect on the surrogate to predict the treatment effect on the true clinical outcome. This requires high quality trials assessing both the surrogate and the longer-term outcome, for which it is considered a potential proxy(524).

Without this undertaking, interventions that have a positive effect on a surrogate outcome, may have no effect, or a harmful effect, on the longer-term outcome or *vice versa*(525). This may lead to implementation of interventions without positive (or with potentially harmful) effects on patient survival or quality of life. This is illustrated in oncology research, where the validation of surrogate end points is increasingly being explored. In a study to determine the strength of the surrogate-survival correlation for cancer drug approvals, the authors found that the use of surrogate end points often lacked formal verification of the strength of the surrogate-survival association(526).

Certain surrogate outcomes do have supporting evidence to promote their use as true proxies for longer-term outcomes. A meta-analysis of individual-patient data for 830 patients from 11 randomized trials evaluating four intervention types was undertaken. The authors showed that, a lower risk for doubling of serum creatinine level, end-stage renal disease, or death, was associated with an early decline in proteinuria at nine months (short-term) and this was consistent across studies(440). Currently there are no validated surrogates for burn injury.

It is understandable why short-term outcomes are being used in RCTs in burn care. They are easier to measure, and trials are shorter and cheaper(124). If longer-term trials are too difficult or costly to undertake, research in burn care needs to establish the relationship between the more commonly measured short-term outcomes and the longer-term patient important outcomes, as described above. This would allow short-term outcomes to be reliably used as surrogates for patient important outcomes. Some work has started in this area; there is evidence to support the link between wound healing (surrogate outcome) and the longer-term outcome of scar presence or quality (527, 528). However, this research is at an early stage, and similar work has not been undertaken on other commonly measured outcomes, such as the impact of early pain on future psychological outcomes or fluid over-resuscitation on longer-term lung function(450, 529, 530). A future research area could determine if there is a need for trials in burns care to follow up patients for more than six months, so that the effectiveness and patient benefit for interventions can be fully appreciated.

5.5.1 Strengths and limitations

The strengths of this review are that the protocol and data extraction proforma were pre-specified, and the literature search was systematic and comprehensive, including four major healthcare trial databases. Limitations include the exclusion of publications in languages other than English. However, international publications were included to reduce the risk of selection bias. The search was also time-limited, which may have excluded outcomes from older studies. The reason for the time limitation, was to identify research relevant to recent burn care. There is also evidence from an earlier review of burn care RCTs, that a selection of trials published earlier would not change the outcome of this review(4). Another limitation was in excluding studies that followed-up RCT populations (n=3). This was undertaken to prevent the use of duplicate data. In future work however, it would be useful to look in more detail at these studies, to increase the understanding of longer-term patient follow-up after burn care RCTs. The use of assumptions to report the last timings of assessments for included outcomes was also a limitation. This calculation for length of hospital stay is likely to be too simple to account for all the factors that impact on hospital stay and on the last time-point of the outcomes assessed. The length of stay association with burn size, is also likely to vary between burn services. In the USA and Europe, some centres will achieve better outcomes such as, one day (rather than two days) hospital stay per percent burn size(11, 467). In lower-income countries, the hospital stay relating to burn size is likely to be longer, but this is difficult to ascertain from the literature(531-534). However, our assumptions, even if incorrect, would only have resulted in an error of weeks, not months or years.

Research into interventions in burn care should aim to improve patient care(158). To achieve this, trials (specifically pragmatic and clinical effectiveness studies) are required to assess outcomes that reflect importance to patients in terms of timing of assessment. If limitations to research funding, trial length or fast-changing technology precludes this, then more work will need to be undertaken to understand how surrogate outcomes reliably impact on longer-term patient important outcomes.

5.6 Conclusion

This review has shown that most trials of burn care interventions report short-term outcomes, that are not validated surrogates for longer-term patient-important outcomes. More trials are needed in which longer-term patient important outcomes are assessed, or work needs to be undertaken to validate surrogates for longer-term outcomes in burn care research.

In Chapter Six, evidence from this and the preceding four chapters, will be used to suggest a possible solution to these methodological issues relating to outcome reporting: choice of different outcomes, varying definitions of the same outcome and varying outcome assessment timepoints across trials. These issues impact evidence synthesis and patient relevance for burn care research. The work undertaken for Chapter Six, will aim to resolve these challenges through the development of an international Core Outcome Set for burn care research.

Chapter 6 An International Core Outcome Set for burn care research (COSB-i); shared decision-making in outcome choice to improve research outputs

The methodology for this chapter is based upon the published protocol.

Young A, Brookes S, Rumsey N, Blazeby J. Agreement on what to measure in randomised controlled trials in burn care: study protocol for the development of a core outcome set. *BMJ Open*. 2017 Jun 1;7(6):e017267. Changes from this protocol are highlighted in the text below.

I conceived the project with the support of JMB. I wrote the paper cited above. The other members of the group contributed ideas, editing, readability and data sign-off for the project. The full details for collaboration for the project are listed in the Disclosure section. Excerpts from the paper are incorporated into this chapter.

6.1 Introduction

This chapter will answer the following thesis objective through the development of an international Core Outcome Set (COS) for use in burn care research:

Thesis Objective 5: A consensus on which burn care outcomes are most important to patients, carers, researchers and international multi-disciplinary burn care professionals.

6.2 Background

The provision of evidence to support clinical decision-making relies upon data from randomised controlled trials (RCTs) collated in systematic reviews(535-537). One issue that challenges evidence synthesis, is a variation in outcome reporting across trials. This has, in this thesis, been termed outcome reporting heterogeneity (ORH) and has been discussed in detail in Chapter Three (71, 538). ORH makes it difficult to synthesise evidence from trials. Different outcomes are measured in different studies using different definitions and different timepoints of assessment, as discussed in Chapters Four and Five. This makes data difficult to interpret. It results in research waste (539-541). The issue of waste in burn care research is illustrated by a systematic review undertaken for this thesis in Chapter Two(4). The review identified 955 different outcomes extracted from 147 included articles. Of outcomes, 810 were reported in only one study. No single outcome was reported across all studies. Other burn care systematic reviewers have reported difficulty combining evidence due to ORH(8, 10, 89, 237, 238). As evidence collated from well conducted RCTs is required to resolve the persisting clinical uncertainty regarding the optimal management strategy of patients with burns, ORH limits effective clinical decision-making. There is, therefore, an urgent need to agree a minimum set of the most important outcomes to standardise, but not restrict, outcome reporting in burn care research. This requires the development of a COS(71).

A COS is a minimum group of outcomes to be reported in all trials of a specific condition (71, 542, 543). COS are identified scientifically by stakeholders, as being the most important outcomes in determining the effects of an intervention or treatment in one healthcare condition(115, 544). COSs should include outcomes relevant to international clinical practice and patient need. This COS project was conceived following NHS England discussions regarding Key Performance Indicators in burn care with UK health care professionals (HCP) and patients, in which the author of this thesis was involved. Participating patients and carers were vocal about the outcomes that were important to them and which they felt were overlooked by HCPs. This highlighted the need for *shared decision-making* between clinical staff and patients, to inform the development of a COS for burn care research. It was agreed that decisions regarding the study methodology and study outputs should be agreed jointly, or

shared, between both groups. Shared decision-making is "a process in which clinicians and patients work together to select tests, treatments or management based on clinical evidence and the patient's informed preferences" (https://www.nice.org.uk/Media/Default/About/what-we-do/SDM-consensus-statement.pdf). The concept was introduced in the *Institute of Medicine report: Crossing the Quality Chasm*, as a key approach to improving the quality of American health care(545). Historically, shared decision-making was regarded as the means to protect patient autonomy and to move way from paternalism in healthcare(546). More recently, there has been a shift to investigate the impact of shared decision-making on patient outcomes, which has been shown to be beneficial(547). In the view of the author of this thesis, the next step, is to use shared decision-making to agree the most important outcomes to report in healthcare research. Shared decision-making is different to incorporating patients', and carers' views into decisions already taken by HCPs. The term is used in this chapter, to express the need to put equal weight on both groups' views with respect to outcome choice in research. Without such engagement, there is a risk that trial data will be based on outcomes, that may not represent what is most important to patients and HCPs, particularly in effectiveness trials.

Once the core outcomes have been agreed, the intention is that all future studies on that condition report these outcomes, in addition to any other outcomes relevant to the research question (115). This is supported by work from Ioannidis, and a linked editorial by Koroshetz(548, 549). They argue that, agreed core outcomes should be reported in trials in a clinical area, for each medical intervention, regardless of the intervention tested. The basis of the argument is that data from one trial can be used to support data from another, if the outcomes are common to the two studies, even if the trials test different interventions. The research costs will, therefore, be used to greater benefit.

The aim of this study, is to present the development of an international COS for burn care research, using shared decision-making.

6.3 Methods

Current recommendations are that the development of a COS requires the identification of all potential outcomes in one clinical area(115). These outcomes are then prioritised in terms of importance and relevance, to determine the core set. This is undertaken through a consensus process. To achieve relevance, it is important that COS stakeholders should include patients, carers and multidisciplinary HCPs and researchers.

This COS (Core Outcomes in Burn Care Research international (COSB-i)) was registered on the Core Outcome Measures in Effectiveness Trials (COMET) database (http://www.comet-initiative.org/studies/search/). It has been developed and reported in accordance with recommendations of the Core Outcome Set-STAndards for Developing and Reporting (COS-STAD and COS-STAR) and the COMET handbook (115, 288, 550). Changes to the published protocol are highlighted and explained. The systematic review informing the COS, was registered on Prospero CRD42017060908 and has been published(4). Ethical and other research permissions were obtained from the South West-Frenchay Research Ethics Committee, reference 17/SW/0025 (Appendix D). The study sponsor was the University of Bristol (Appendix E).

The need for this study was demonstrated by the heterogeneity in outcomes reported across trials demonstrated through the systematic review in Chapter Two. On searching, the COMET database showed no evidence of an existing COS for burn care research (http://www.cometinitiative.org/studies/search/ accessed Autumn 2016).

Study objectives:

1. To determine a comprehensive list of clinical and patient-reported outcomes after burn injury.
2. To prioritise these outcomes from patient, carer and HCP viewpoints.
3. To achieve consensus on a minimum set of the most important and relevant outcomes for burn research reporting; the COS for burn care research (COSB-i).

Participant inclusion criteria:

- Patients of, or over the age of, 10 years, with a cutaneous burn of any size and type.
- UK parents or carers of burned children of any age with any burn size and type.
- Burn care professionals of any discipline, burn care commissioners, research funders, journal editors and researchers from international settings.

For the interviews described below, patients, carers and HCPs from the UK only, were included.

Participant exclusion criteria:

- Children of less than 10 years of age, due to difficulties in younger children participating in interviews, and independently undertaking a questionnaire survey.
- Those who lack the capacity to consent to qualitative interviews or questionnaires.
- Those who do not speak or read English.

Study setting:

Semi-structured interview patients and HCPs were recruited from four geographically separate National Health Service (NHS) burn services and burn support groups hosted by these services. These included:

- Bristol Royal Hospital for Children, University Hospitals, Bristol NHS Foundation Trust. Frenchay After Burns (FAB) support group.
- North Bristol NHS Trust.
- Chelsea and Westminster NHS Foundation Trust. Burns Family Group and the London Area Burns Adult Support Group.
- The Welsh Burn Centre for Burns & Plastic Surgery, Morriston Hospital, Swansea Bay University Health Board. Welsh Dragons Burns Club.

Delphi HCP respondents were from international burn care research and clinical settings.

Scope: The COS is intended for use in all efficacy *and* pragmatic research studies comparing the effects of interventions for the treatment of patients with burn injuries. This is regardless of aetiology or severity of burn, setting or mode of intervention administration. It will include

surgical and non-surgical (including psychological) care, across all settings and countries of all World Bank income groups.

Study Phases: The study is a mixed-method design, involving the use of qualitative and quantitative methodologies. The methods used to develop a COS are important, as they may influence the final core outcomes(71, 284). The methodology used in this study, is consistent with that prescribed by COMET, and the standards recommended by COS-STAD (published midway through the work undertaken to develop COSB-i)(115, 288).

Development of the COSB-i involved three phases.

1. *Phase 1*: *generation of a comprehensive long-list of outcomes in burn care*, and a questionnaire. Phase 1 aimed to identify all possible outcomes in burn care RCTs, supplemented by outcomes reported and considered important to, and reported by, patients. These outcomes were grouped into domains and operationalised into questionnaire items.
2. *Phase 2*: *a Delphi survey* involving two questionnaire rounds, to prioritise outcomes in terms of importance to both international HCPs and UK families.
3. *Phase 3: COS production*. Using a modification to the Delphi process, the COS was finalised in Phase 3, by undertaking a consensus meeting to agree the most important outcomes(551, 552). The methodology, any changes to the agreed protocol and patient involvement, was overseen by an independent steering group.

Steering group: The COSB-i steering group comprised of four patient representatives (three adult burn patients of which one was burned as a child, one as a teenager and one as an adult, and one parent of a child with a burn), two burn researchers, three COS researchers, one commissioner, one Cochrane wounds group representative, three burn surgeons, a burn nurse consultant, a burn psychologist, a burn therapist and the national burn database chair as recommended by other COS researchers (553). The committee was chaired by an independent COS researcher (Professor Jamie Kirkham, Professor of Biostatistics, University of Manchester).

Patient, parent and public involvement (PPI): Patients and carers were involved in co-designing the study protocol, through active participation in the steering group, through interviews to inform the COS long-list, through domain decision-making, through participation in the Delphi survey, through participation in the consensus meeting, in scientific paper writing and in on-going dissemination and implementation of the COS.

International status: After discussions with NHS England at a meeting to present the COSB-i study in Bristol in January 2017, it was agreed to internationalise and broaden the clinical stakeholder group for the Delphi survey. This was achieved by including as diverse a range of Delphi survey HCP participants, from as many disciplines and countries of varying healthcare income status, as possible. Such international involvement is being increasingly recognised in COS development(554). It was unfortunately not possible to include international patients, as this would require translation of the questionnaire. Due to the time and funding needed, this was not possible for this study. This is the aim for a future project (Future research in Chapter Seven).

6.3.1 Phase 1. Generation of a long-list of outcomes, domain creation and development of a questionnaire

Outcomes were identified from three sources(4, 159, 162):

1. A systematic literature review of clinical outcomes reported in RCTs (Chapter Two).
2. Semi-structured interviews with patients and HCPs.
3. Two published systematic reviews on patient-reported outcomes (PROs) in burn care.

6.3.1.1 Information sources, outcome long-list

Long-list creation: Outcomes were combined across each of the three data sources into an outcome long-list. The extraction of clinical outcomes from the systematic review is described

in Chapter Two. Extraction of outcomes from the patient and HCP interviews and outcome domains from the PRO systematic reviews are detailed below.

Semi-structured interview outcome extraction: Qualitative research is one method for researchers developing COSs to inform the long-list of outcomes, through the exploration of the views of patients, carers, HCPs and other stakeholders. Qualitative research can help to identify what outcomes are important to stakeholders, why some outcomes may be more important than others, identify appropriate language for use in the Delphi survey and inform comparisons between patient, carer and clinician views(555, 556). In COSB-i, the qualitative research was through individual semi-structured interviews (555). The interviews were conducted to identify outcomes important to patients with burn injuries and clinicians working with these patients. As in two other COSs (CONSENSUS (COS for oropharyngeal cancer) and mOMEnt (COS for otitis media with effusion in children)), the interviews were structured as a chronological narrative of recovery after the injury(557, 558). In this way, both patients and HCPs were able to relate how outcomes that were important early after injury, sometimes differed to those that were important at later stages. The interviews were also structured to understand why an outcome is important to patients or carers. In the PARTNERS2 COS (for schizophrenia or bipolar disorders), employment was found to be an important outcome for patients(559). However, it was reported that suitable employment was more important than employment *per se*. Finally, it was important to compare outcomes collected from patients, carers and healthcare professionals, to understand and report areas of disagreement(560, 561).

Potential interview participants were identified by four UK NHS specialised burn services and associated burn support groups, as described above. Participants satisfying the inclusion criteria, were recruited to the qualitative study (Appendices F and G for participant consent and patient information details).

Sample size was determined by data saturation. Non-probabilistic purposive sampling for patients was undertaken, to ensure maximum variation, based on age, sex, ethnicity, burn severity (size and depth), aetiology, time after injury and management at different burn services. Interviews were conducted, at a range of times after injury, to capture different

phases of patient recovery. No interview was undertaken within one month of injury or during an acute period of hospitalisation. Professional participants included doctors of different background specialty, therapists and nurses.

Interviews were conducted on a one-to-one basis by the author of this thesis. As the participants were geographically dispersed, interviews were conducted face-to-face or via the telephone. There is no evidence that data quality is diminished by telephone interviews, when compared to face-to-face meetings(562). All interviewees gave signed, informed consent (by email, hard copy through the post or in person) before the interviews. The interviews were audio-recorded and transcribed verbatim, checked and anonymized before being analysed. Carers were invited to be present for interviews with children between the ages of 10 and 15 years of age, if the children preferred this. However, a focus on the experience and self-reports of the children themselves were maintained whenever possible.

The interview topic guide was informed by the data emerging from the systematic reviews (clinical and patient-reported) and developed iteratively. Interviews were conversational, involving a mix of open questions and more focused prompts. Patients were encouraged to introduce and discuss topics (in terms of recovery outcomes) that were most important to them. All aspects of the patients' life were covered, including, but not limited to, those affecting function, cosmesis and psychological health. Discussion centred around outcomes affected by healthcare treatment, and issues affecting daily life at different time points after injury. Patients who were interviewed earlier after injury were prompted for their thoughts on potential longer-term issues. (Please see Appendix H for the interview topic guide).

Data analysis: A thematic analysis of the transcribed interviews was undertaken. The aim was to identify patterns, or outcome themes, in the interview data(563). The process typically has five steps: data familiarisation, assignment of preliminary codes, pattern or theme searching, theme review and theme defining and re-naming. In terms of this project, themes were outcomes patients felt important in their recovery from a burn injury.

The transcribed interviews were read through to get an overview. More detailed reading of the transcripts followed, allowing familiarisation and initial coding. Outcomes important to patients or HCPs, during recovery or burn care, were coded using QSR NVivo 10 software.

Coding (grouping themes or outcomes) was undertaken by the author of this thesis, with a second reviewer (AD) coding 10% of interviews, to assess agreement. Following a systematic approach to coding, analysis was informed by the constant comparative method, with iterative updating of initial codes, allowing improved specificity and clarity. The constant comparative method involves breaking down the data into discrete incidents (or themes) and coding these into categories (564). Preliminary codes from the transcribed interviews were reviewed, and the final codes applied and grouped into themes reflecting outcomes. By constantly comparing the transcripts, a theory (collection of outcomes and their relative importance) was developed inductively. The framework method of data management was used to chart coded data(565, 566). The framework method of data management allows data to be reduced into a matrix output of rows and columns. Rows represent cases (different participants in this case). Columns represent different themes identified in the raw data.

Data analysis was run in parallel with data collection, so that emerging themes (outcomes) were used to input in an iterative manner into subsequent interviews. In other words, emerging themes would lead to prompts for future interviewees. The appropriateness of outcomes and their respective domains was reviewed and agreed. A final set of outcomes was reviewed, agreed and inputted into the overall outcome long-list.

Patient-reported outcome extraction (PRO): PROs were extracted from two systematic reviews reporting PROs in burn care for adults and children. The review relating to PROs in children and adolescents was published in 2015 and that relating to adults in 2017(159, 162). The reviews report both generic and burn-specific tools. Most of the generic measures reviewed, had only been validated with adults derived from the general population, meaning they were unlikely to be sufficiently sensitive to identify health outcome changes in a burn population(163). It was decided to use outcomes and outcome domains from the burn-specific PRO tools, on advice from the Centre for Appearance research team led by Professor Di Harcourt at the University of the West of England (https://www1.uwe.ac.uk/hls/research/appearanceresearch.aspx), that had undertaken the original reviews. All the outcomes from these tools were assessed with their respective domains for appropriate linkage. The outcome domains reported were added to the list of domains already created in Chapter Two.

In the systematic review of PROs: in child and adolescent burn research, searches of MEDLINE, Social Sciences Index, Cinahl, Psychinfo, Psycharticles, and Allied and Complementary Medicine, were used to identify articles using English-language PROs from January 2001 to March 2013. The inclusion criteria were met by 23 articles reporting 32 different PRO tools. Of these, 31 were generic and one was burns-specific. In the systematic review assessing PRO use in adult burn care, searches of the same databases were used to find PROs from January 2001 to September 2016. In this review, 116 studies met the inclusion criteria and reported 77 different PRO tools. Of these, 71 were generic and six were burns-specific.

The only burns-specific scale identified in review assessing PRO tools for children and adolescents, was:

- *The Children's Burn Outcomes Questionnaire* (CBOQ) for patients aged 11–18 years of age(567). This tool has 52 items which assess physical, psychological and social function outcomes, covering 12 domains (groups of outcomes with similar meanings). The outcomes were generated from a review of the literature and by expert clinician input. Interviews with child and adolescent burn patients were not conducted. All outcome domains were extracted.

Of PROs used with adult burn patients, only four of the six burn-specific PROMs had been validated in English with adults with burns. These were the Burn Specific Health Scale–abbreviated (BSHS-A), the Burn Specific Health Scale-Brief (BSHS-B), the Young Adults Burns Outcomes Questionnaire (YABOQ) and the Burn Specific Pain Anxiety Scale (BSAS)(568-571).

- BSHS-A is an abbreviated version of the Burn Specific Health Scale assessing quality of life after a burn. It has 80 outcomes covering seven domains. The items were developed using a literature review and expert clinician views. Patient interviews were not conducted. However, a group of burn patients reviewed a draft of the scale and suggested additional outcomes.
- BSHS-B is an abbreviated version of the BSHS-A and the BSHS-R (a revised version developed by Blalock *et al*. (1994))(572). The scale has 40 items covering nine domains

- YABOQ measures health outcomes in young adults with burns. It has 47 items covering 15 domains. These outcomes were developed from clinician views and a literature review. Patient interviews were not conducted.
- BSPAS-A measures anxiety related to pain during or after medical treatment for a burn. It is a shortened version of the Burn Specific Pain Anxiety Scale. The outcomes were developed from adult burn patient interview data.

We extracted all the outcome domains from the five tools extracted from the two systematic reviews. The outcome domains were de-duplicated and added to the original list of domains.

6.3.2 Domain creation

Outcome domains: are defined as broad concepts that group similar individual outcomes together(232). The clinical outcomes extracted from the systematic review in Chapter Two had already been grouped into 54 domains. Additional outcome domains from the interviews and PRO data, were added if the domains extracted did not fit into the existing list(464). A second researcher (AD) and I, carried out this process independently and then met to discuss how the outcomes and domains had been merged. A patient representative and independent burn research nurse assisted in the process of categorizing the outcomes into domains and agreeing domain names.

Decision-making regarding the granularity of the outcome domains is challenging. Too many criteria will result in too long a list of domains to operationalise into questions, which is likely to reduce the number of successful survey completions(573). Too restrictive a method will potentially exclude key outcomes. The aim for this COS, was to be inclusive, but to limit the domains to less than 100, in-line with other COSs(573, 574).

6.3.3 Questionnaire formation

The final domains were operationalized into *questionnaire items*, using lay language with medical terminology included in parentheses where necessary (Figures 15 and 16)(575). This

practice was discussed and agreed with our patients at a COSB-i steering group meeting. Patients preferred the sentences and to be clear and understandable at first reading (i.e. without the medical terms in the main sentence). They also appreciated the practical examples under the question. Clinical staff were happy to have the medical term in parentheses. A number of staff commented on the fact that using lay language clarified the issue for themselves as well as the patients. Items were grouped into short-term (before healing) and long-term (after healing), requiring some duplication of items across the questionnaire. This was to improve the ease of understanding and to highlight the recovery phase in which the outcomes may be important. The questionnaire was designed with the input of the COSB-i steering group, including patients, carers and HCPs. It was also discussed with the Bristol Young Peoples Advisory Group (https://generationr.org.uk/bristol/), local nursing and medical teams, and friends and families.

Participant information and consent: a plain English video was conceived and developed by the author of this thesis. This was undertaken, with support from a specialist medical illustrator, to explain the study in plain English: (https://www.youtube.com/watch?v=9DYH072uPrQ). The video was included at the start of the survey alongside age-appropriate written patient information.

Scoring: For each included item, a 9-point Likert-type response scale was provided, with text anchors above the scale to support comprehension, whereby 1 = not at all important, 5 = important but not vital, and 9 = very important. A zero option was provided for participants to indicate that they did not have an opinion about the outcome. One reason for this could be HCPs who did not come across a specific outcome in their work. A coloured traffic-light spectrum to facilitate comprehension among young people was used, following pilot feedback, where red indicated that the item was *not at all important*, amber represented *important but not vital* and green indicated *very important*. At the end of the survey, an option was provided to allow additional outcomes to be suggested. These additional outcomes were reviewed by the author of this thesis and an another researcher, to determine whether they had been included in previously defined items, or whether they were new items to incorporate into round 2 of the survey.

Piloting: The questionnaire survey was piloted in three stages.

1. Initial cognitive interviews were undertaken with six parents. Parents read several questions and fed back to the research nurse what they understood by each question. The questionnaire was modified as a result of this work.
2. Adults (aged over 16 years) and young people aged 10-15 years completed and reviewed the survey, to assess usability, face validity, and acceptability.
3. Following feedback, the survey was piloted again with adults (friends and family), young people and HCPs. The survey was modified as a result of their feedback.

The final questionnaire survey was set up as an online survey using REDCap (Research Electronic Data Capture (https://www.project-redcap.org/)). The set-up was by Ms Alison Hone with input though twice weekly meetings with myself and Dr Anna Davies. Study data were collected and managed using the REDCap electronic data capture tools hosted at the University of Bristol(576, 577). REDCap is a secure, web-based software platform designed to provide:

- An intuitive interface for validated data capture for research studies.
- Audit trails for tracking data manipulation and export procedures.
- Automated export procedures for seamless data downloads to common statistical packages.
- Procedures for data integration and interoperability with external sources.

Consent was taken at the start of the survey after the patient information details, prior to progression to the demographic and outcome sections (Appendix I). To ensure that we had not missed important outcomes, we included an open question at the end of the round 1 questionnaire. Examples of the questionnaire are shown in Figures 15 and 16. The full versions are shown in Appendix J.

Figure 15: Examples of questionnaire items before wound healing.

C2.10 Itch in the burn wound during healing of the burn.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.11 Pain in the burn wound when treatment is <u>not</u> taking place. *For example: pain all the time, pain at night.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.12 The amount of pain caused by medical treatments and tests for a patient with a burn. *For example: pain when having dressing changes, blood tests.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.13 Pain in the donor site *Donor site: is the place from which healthy skin is taken for a skin graft — usually top of the thigh.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

Figure 16: Examples of questionnaire items after wound healing.

D1.9 The effect of the burn (and treatment) on a patient's fitness. *For example: ability to walk as far as normal, being able to do exercise.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D1.10 The effect the burn has on how well a patient's muscles work. *For example: how well a patient can move their face, arms or legs normally.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D1.11 The effect of the burn on the strength of a patient's muscles. *For example: poor muscle strength, difficulty with carrying children or shopping.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D1.12 Whether a patient can maintain their body weight after a burn injury after healing. *For example: weight loss, not able to keep a normal weight.*	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

6.3.4 Phase 2: Prioritisation of outcomes; achieving consensus

Methods used by COS researchers to collect opinions, and to develop consensus on outcome prioritisation, include expert panel meetings, Delphi surveys (modified or not), nominal group techniques, focus groups and individual interviews(71, 578-580). The recommendations from COS-STAD, emphasise that transparency and pre-specification in the consensus process is important, to ensure that the COS has been developed in a rigorous and unbiased way(288). A Delphi survey is an increasingly used method to achieve this(71, 288, 554, 573). The Delphi technique (procedure or process), is a method of collating opinion, with the aim of coming to a group consensus.

It is an iterative process using a systematic progression of voting rounds. It is effective for determining expert group consensus where there is little definitive evidence and where opinion is important. The process was originally developed by Dalkey and Helmer, at the Rand Corporation in the 1950s(115). It can be undertaken without a physical meeting, although the modified Delphi process includes a final consensus meeting(581). One of the strengths of the method, is that, since the responses of the participants are anonymous, opinions are more likely to be true views(582). Performing an anonymous Delphi study by email, may also avoid dominance of certain persons in face-to-face group meetings. Other limitations found with decision-making processes in groups or committees, include, but are not limited to, cost and time constraints(583). Delphi survey feedback is provided in a controlled manner(584-586). The general format of the modified Delphi process, and that used in this COS (known from now on as the Delphi survey), is shown in Figure 17.

Figure 17: Delphi survey flow chart.

Before undertaking a Delphi survey in a COS development study, the following issues need to be considered:

- Participant type (patients, carers and/or HCPs).
- The number of Delphi survey rounds.
- Design and structure of feedback for future rounds.
- Sample size.
- Data analysis and pre-specified criteria for keeping or excluding outcomes.

Delphi survey participants in the COSB-i study, were multi-disciplinary international HCPs working with patients with burns from any setting and at any part of the care pathway. This included clinicians from multiple disciplines, burn researchers, journal editors, research funders, UK health commissioners. UK burns patients aged 10 years or older and UK carers of burned children of any age were also included. Recruitment was through a personal or group email invitation or via social media (Facebook and Twitter). Both included a link to the on-line REDCap survey (https://www.researchgate.net/).

Several methods were used to identify eligible international HCP participants. These included:

- National and international professional burn, plastic surgery and injury organisations.
- UK burn organisational networks.
- National and international burn charitable organisations.
- Key country collaborators known to be leaders in burn care or burn care research, recruited as collaborators to disseminate the survey.
- International burn care contacts of the author of this thesis approached via ResearchGate or personal email.

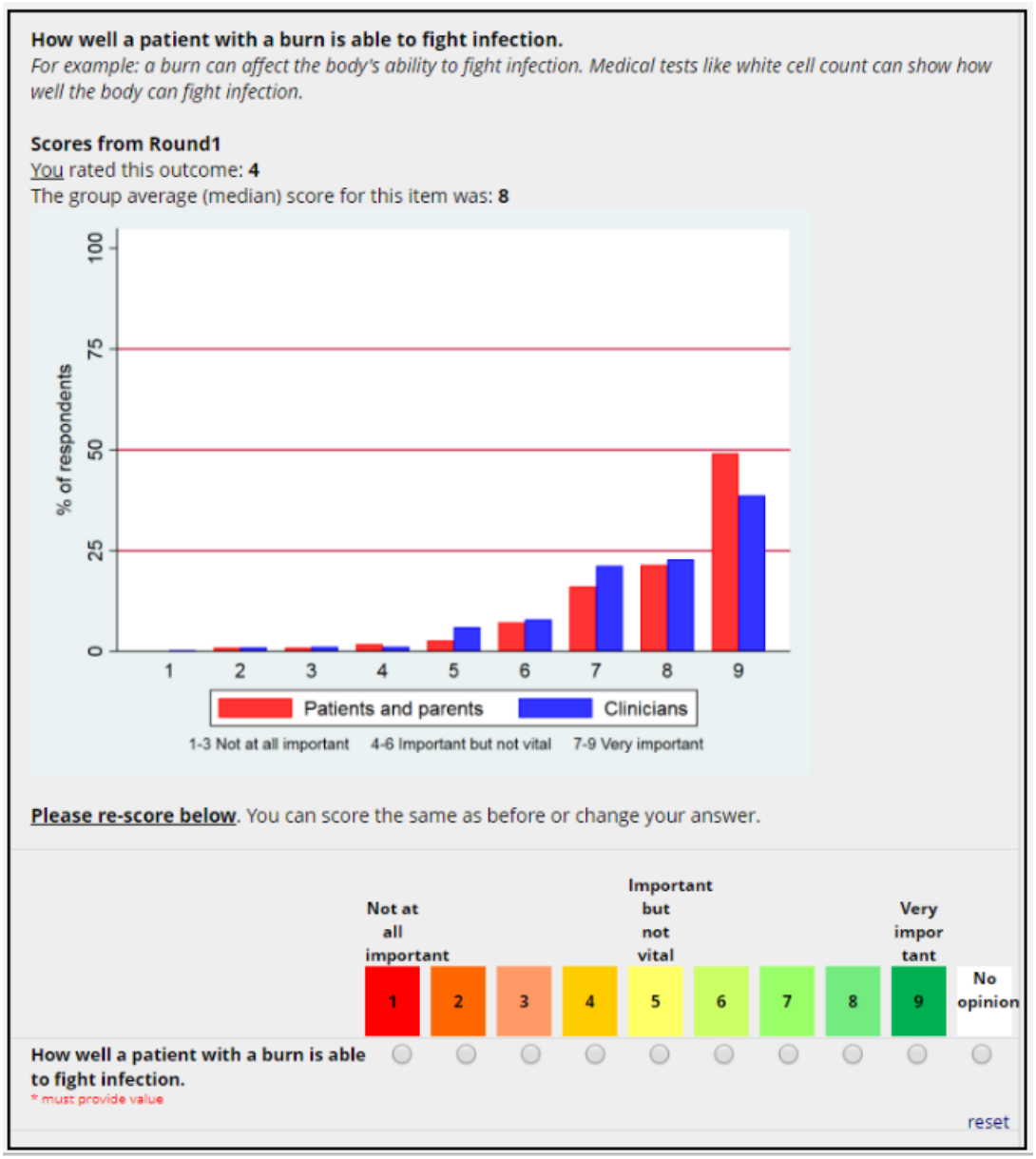
Number of survey rounds: The COSB-i protocol proposed three rounds. The methodology was amended to shorten this to two rounds (named as round 1 and round 2), to reduce potential attrition and mitigate time constraints. This decision was agreed through the COSB-i steering group.

Design and structure of feedback: In round 2 of the survey, all participants who had completed their email address in round 1 of the survey, were emailed a personalised link to round 2 using the REDCap database. This was detailed and consented for in round 1. The round 2 survey used the same format as the round 1 survey, with the following modifications:

- For each item, a value was given indicating the participant's importance rating for the item in the previous round.
- For each item, a value was given indicating the median importance rating score for the item in the previous round. While the median was given, this was referred to as the average, to facilitate comprehension among participants.
- For each item, a histogram of other participants' responses to the item was provided (Figure 18). The graph indicates responses from patients and HCPs using separate colours. Zero responses (no opinion) were not included in the graph. Qualitative work was undertaken with a small group of patients and parents in the burns outpatient clinician in one hospital site as part of public and patient engagement work to agree this feedback format. The patients and parents were presented with a pie chart and two different types of histogram. The version illustrated in Figure 18 was chosen as the most favoured as the most easy to understand.
- Additional inormation was given to participants for round 2 at the start of the survey. The participants were provided with the top ten outcomes from round 1 on a front (cover) sheet to the survey. They were given the following information before this: " In the table below are the most important outcomes as rated by clinicians, patients and parents. These outcomes are highlighted in the survey questions in green.
    - When you complete the survey please consider carefully how important you think these most important are:
    - If you agree these are the most important outcomes to be included in future research trials, please rate them as a '9' (very important).
    - If you think they are not the most important outcomes to include, please rate them as 6 or less, otherwise they are likely to remain as most important."

Sample size: There are no agreed sample size guidelines for the number of participants necessary for consensus methods when developing a COS. The COMET handbook states that "the more participants representing each stakeholder group the better, both in terms of the COS being generalisable to future patients and in convincing other stakeholders of its value" (115). In the absence of agreed methodology, and based on the COMET Handbook, other COSs and the fact that burn injuries are common, we aimed for recruitment of 150 UK patients along with 100 international nurses and therapists and 100 doctors and other HCPs(115).

Figure 18: Example of feedback in the Delphi survey round 2.



6.3.5 Data analysis

Any individual completing the consent form, providing an email address, and rating at least one survey item was considered a study participant.

Delphi survey round 1 and 2 demographics for participants: data collected consisted of the following.

- *HCPs*:
    - Occupation
    - Number of years in burn care
    - Country of origin
    - World Bank income status of country of origin
- *Patients and carers*:
    - Background:
        - Sex
        - Adult, child or carer
        - Ethnicity
        - Education
    - Details of injury:
        - Mechanism of burn
        - Burn severity
        - Time since burn injury

Item data: For the item ratings, any completed datapoint was included, to prevent loss of data. For each item, data were produced consisting of:

- Number of participants completing each item.
- Descriptors of central tendency for items (mean, median).
- Number and percentage of participants rating the item as 1-3, 4-6, and 7-9 in terms of importance.

Where the item was rated as zero (no opinion on the outcome), these data were excluded from the analyses. This may be due to the specialist background of the respondent or the timepoint in the recovery pathway for patients or HCPs. Data were tabulated for the overall sample, and according to stakeholder group. Participants were grouped as HCPs or patients/carers.

Dropping and modification of items between Delphi survey rounds 1 and 2: Criteria for selection of items to be carried through to round 2 were pre-defined and published(229).

Items for which at least 50% of the overall sample rated it above 7-9, and fewer than 15% of the sample rated it as 1-3, were carried through to round 2.

Attrition between survey rounds: Median and mean round 1 survey scores were compared for those who did and did not complete both rounds of the survey. Mann Whitney U tests were used to compare scores, since all outcomes were skewed. The significance level was set at $p<0.05$.

Selection of items for the final consensus meeting: After round 2 of the survey, more stringent criteria were applied for selection of items to carry through to the consensus meeting.

Those items rated 8-9 by more than 70% of the overall sample, or more than 70% of either patients or professionals were carried through to the consensus meeting for further discussion.

Items duplicated for reasons of timing of outcome assessment were combined for the consensus meeting.

6.3.6 Phase 3: Consensus meeting to agree the final COS

A half-day consensus meeting was held in London, UK on October 9th, 2019. An independent chair was appointed from a charity supporting burn care research, Dr Charlotte Coates, research manager, Scar Free Foundation https://scarfree.org.uk/). International HCPs or UK patient or carer participants, who had completed round 2 of the survey, were invited to take

part. Steering group members were invited. Attendance was in-person or by Skype call. Non-professional attendees were met face-to-face or via a telephone call, prior to the meeting, to explain the planned processes and their role. On-line voting software (https://turningtechnologies.com accessed December 2019) was used to enable remote voting at the meeting. Outcome wording was shortened and simplified for the consensus meetings, to allow for ease of reading on Microsoft PowerPoint slides. These were visible to both in-person and telecon attendees, with verbal clarification as needed.

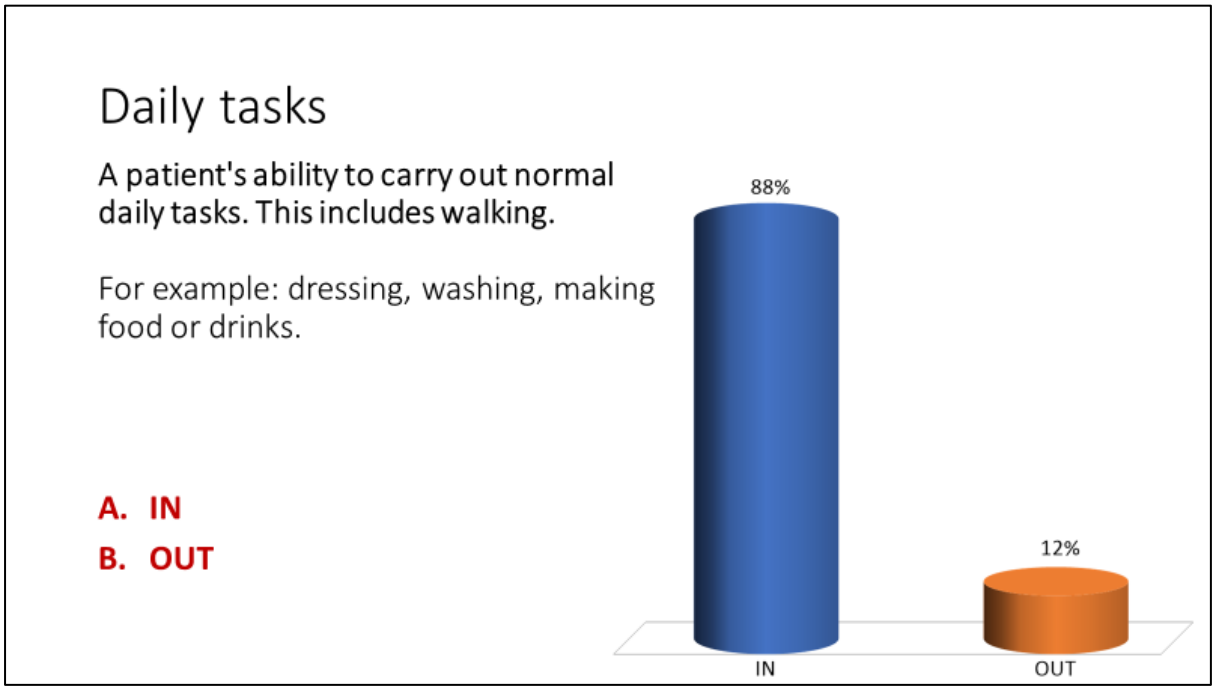
Outcome merging: Prior to voting, a discussion was conducted to determine if any items (from now on called *outcomes*) could be merged, or combined, due to similarity of meaning.

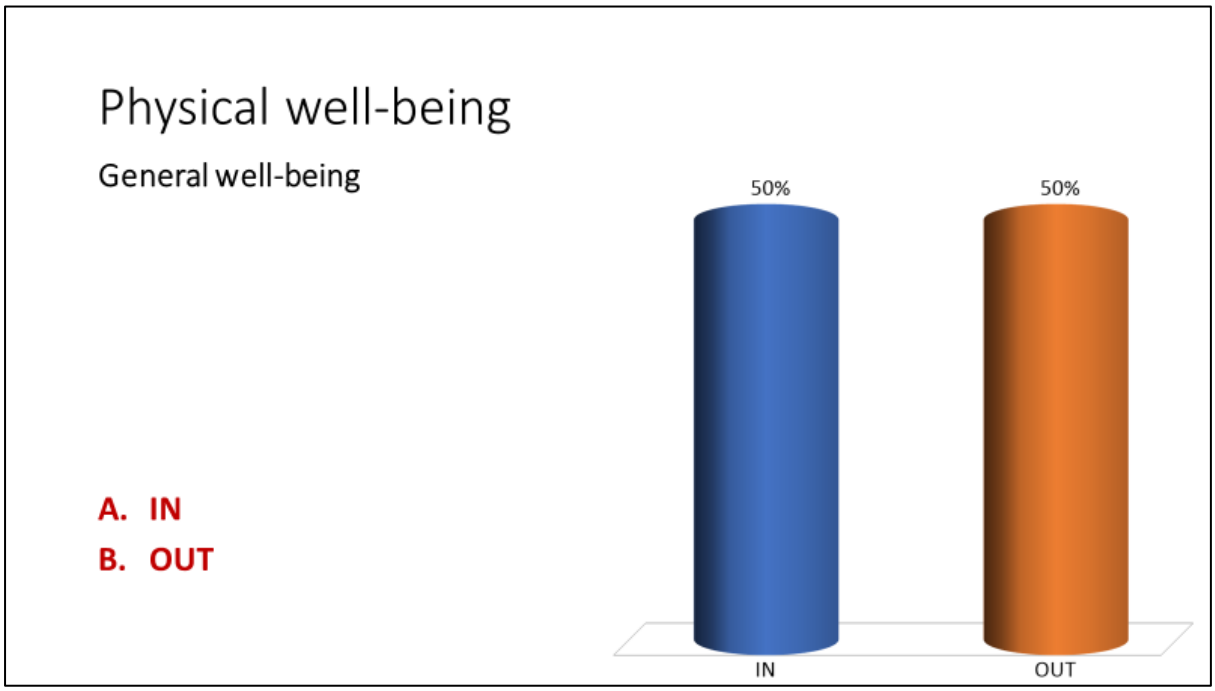
Consensus meeting voting: The final set of outcomes (agreed after the merging exercise) were presented to the meeting to agree the final COS. Two rounds of voting were carried out on the importance of these outcomes. Voting results for each item were presented immediately in the form of a histogram. Outcomes were voted *in or out*, with real-time results shown to all participants (Figure 19).

Decisions regarding maintaining, dropping and agreeing final outcomes through the two voting rounds, were pre-specified prior to the consensus meeting, through steering group and local team meetings involving patients. After the voting for round 1, outcomes where more than 50% of participants had voted it in to include in the COS, were carried through to the next round of voting. For round 2, a more stringent criterion was used to select items to include in the final set. When more than 60% of the participants rated the outcome as important (*voted in*), it was included in the final COS. The final set of outcomes was presented to the participants for sign-off.

Data collection and analysis: Data were collected on participant demographics in terms of country of origin, HCP, patient or carer and HCP profession. Voting was recorded as inclusion (in or out) for each outcome. Voting results for each round were analysed in terms of pre-specified criteria before progression to the next voting round.

Figure 19: Example of consensus voting slides with real-time results.





6.4 Results

6.4.1 Phase 1: Outcome long-list, outcome domain generation and questionnaire creation

The outcome long-list consisted of outcomes from the three sources detailed above.

- For detailed information of the results of the systematic review of clinical outcomes, please see Chapter Two and the published paper(4).
- The PRO domains were extracted from two systematic reviews as described above. Outcome domains from these PRO tools are shown in Table 21.
- Semi-structured interviews were conducted with 25 participants. This included 10 burn care HCPs (one consultant, three nursing staff, four therapists and two other staff), 14 adult patients and one child and parent combination. Interview outcomes are shown in Appendix K. Outcome-related domains from the interviews are shown in the final list of domains in Table 22.

Examination of all three data sources identified 1,187 outcomes which after de-duplication across the sources left 1,021 unique outcomes. These outcomes were grouped into outcome domains (n=68) based on the initial 54 clinical domains described in Chapter Two. Additional domains were added for PROs that did not fit into the existing set. The outcomes extracted from the PRO reviews, from the other two sources and the resulting outcome domains are shown in Table 22.

The 68 outcome domains were converted into 88 questionnaire items, with some necessary duplication between the short- and long-term item sections of the survey.

Table 21: Outcome domains extracted from systematic reviews of PROs in burn care.

PRO tool, author and reference.	**PRO domains (n=45)**
CBOQ Daltroy et al(567)	Self-esteem/self-worth/sense of mastery
	Physical function/athletic competence/mobility/physical health
	Physical Appearance/self-image/weight satisfaction
	Behavioural conduct/social skills/problem behaviours/intrapersonal development/compliance
	Personality/coping styles/emotional functioning/psychological health
	Pain
	Itching
	Satisfaction with treatment/symptoms/status
	Impact on family
	Parental concern
	Quality of life
	Sense of community
BSHS-A Munster(568)	Mobility and self-care
	Hand function
	Role Activities
	Body image
	Affective
	Family and Friends
	Sexual activity
BSHS-B Kildal et al(570)	Heat sensitivity
	Psychological
	Hand function
	Treatment Regimen
	Work
	Sexuality
	Interpersonal relationships
	Simple abilities
	Body image
YABOQ Ryan et al(569)	Physical function
	Fine motor function
	Pain
	Itch
	Social function limited by physical function
	Perceived appearance
	Sexual function
	Emotion
	Family function
	Family concern
	Satisfaction with symptom relief
	Satisfaction with role
	Work reintegration
	Religion
BSPAS Taal et al(571)	Pain
	Pain-related anxiety
	Pain-related disability

Table 22: Final domains with associated outcomes from each source.

	Count of PROM outcomes	Count of review clinical outcomes	Count of Interview outcomes
Ability to carry out daily tasks	3	3	9
Ability to fight infection		40	
Adherence to treatment	1		
Anxiety about medical procedures	1	4	1
Anxiety about and appointments			
Appearance	3	3	14
Blister fluid		3	1
Blood product transfusion		14	
Body temperature issues	1		1
Body weight maintenance		14	
Bone strength		21	
Breathing and lungs		36	2
Bullying	1		4
Burden of care		8	
Burden of care for patients or carers	1		15
Burn smell			1
Burn wound healing		160	7
Burn wound infection		86	2
Burn wound pain	2	48	4
Comfort of dressings		2	2
Complications of drug treatment		36	
Complications of treatment			4
Costs of treatment for NHS/Hospital		14	
Death from any cause		13	1
Death from burn injury		1	
Dignity			1
Donor site healing		17	
Donor site outcomes			1
Donor site pain		10	1
Donor site problems after healing	6	23	
Effect of burn on genes		5	
Effect of scar on movement			3
Effect of scar on movement (contractures)		3	
Effect on heart and blood circulation		36	
Effects of fluid from a drip		22	
Fitness		5	3

Generalised anxiety	2	1	5
Growth after injury			1
Growth in children		12	
How body uses energy		1	
Hair loss			1
How well muscles work		19	
Infections other than burn wound infection		11	
Itch	2	22	3
Kidney function		18	
Length of hospital stay		6	4
Length of stay in intensive care unit		3	1
Length of time on life support machine		3	
Liver function		15	
Medical tests to indicate how unwell a patient is	1	40	
Mental ability		2	1
Mobility	3	11	3
More than one organ failing (multi-organ failure)		6	
Muscle strength		41	
Pain during procedures		7	1
Personal cost for patient			1
Psychological wellbeing	7	1	15
Quality and quantity of sleep		16	1
Relationships	8		8
Return to work/school or previous function	2	1	2
Scar colour		16	1
Scar pain		4	3
Scar size		2	
Scar texture		40	1
Sepsis		10	
Stomach and bowel function		14	5
Thirst			1
Treatment for scars		2	10
Understanding of planned care			3
Use of medicines to treat symptoms	1	4	1
Grand Total	**45**	**955**	**149**

6.4.2 Phase 2: Delphi process to prioritise outcomes

6.4.2.1 Round 1 Delphi survey

Response rate: In round one of the Delphi survey, 794 participants took part.

Participant demographics: Of all participants, 668 (84%) were international HCPs and 126 (15%) were patients or carers. Participants' demographics for the Delphi survey round 1, are provided in Tables 23 and 24, along with those for round 2. For round 1, HCP participants originated from 77 countries from five continents. Of these, 166 (25%) came from lower middle- and lower-income countries (Figures 20 and 21). Of the HCPs, 303 (45%) were doctors, 158 (24%) were allied health professionals, 100 (15%) were nurses and 88 (13%) were burn care researchers. Of these, 377 (56%) worked with adults and children. Of the patients, 97 (77%) were adults, 28 (22%) were carers of a child with a burn injury and one was a young person (1%). Eighty (63%) were of white British origin, and 52 (41%) had a university education. The mean time since injury in the children of carers who responded was 5.5 years (SD 10.7), and for adult patients it was 12.8 years (SD 15.3).

Voting responses (Table 23): In round 1, of all 88 items, 85 were rated as very important (7-9 on the Likert scale), by at least 50% of the sample. Two items did not reach the 50% threshold across both groups (thirst, burn smell). However, more than 50% of the patients and carers, *independently* of the HCPs, rated these items as very important (7-9), and they were therefore carried through to round 2. One item did not reach the 50% threshold for the overall sample, or for either patient/carer or HCP group independently, (mild complications), and was removed. Thirteen additional new outcomes were suggested by participants in round 1. One hundred items were therefore taken forward to round 2 (Tables 23 and 25 and Figure 22).

Figure 20: Round 1 Delphi survey: country of participant origin.

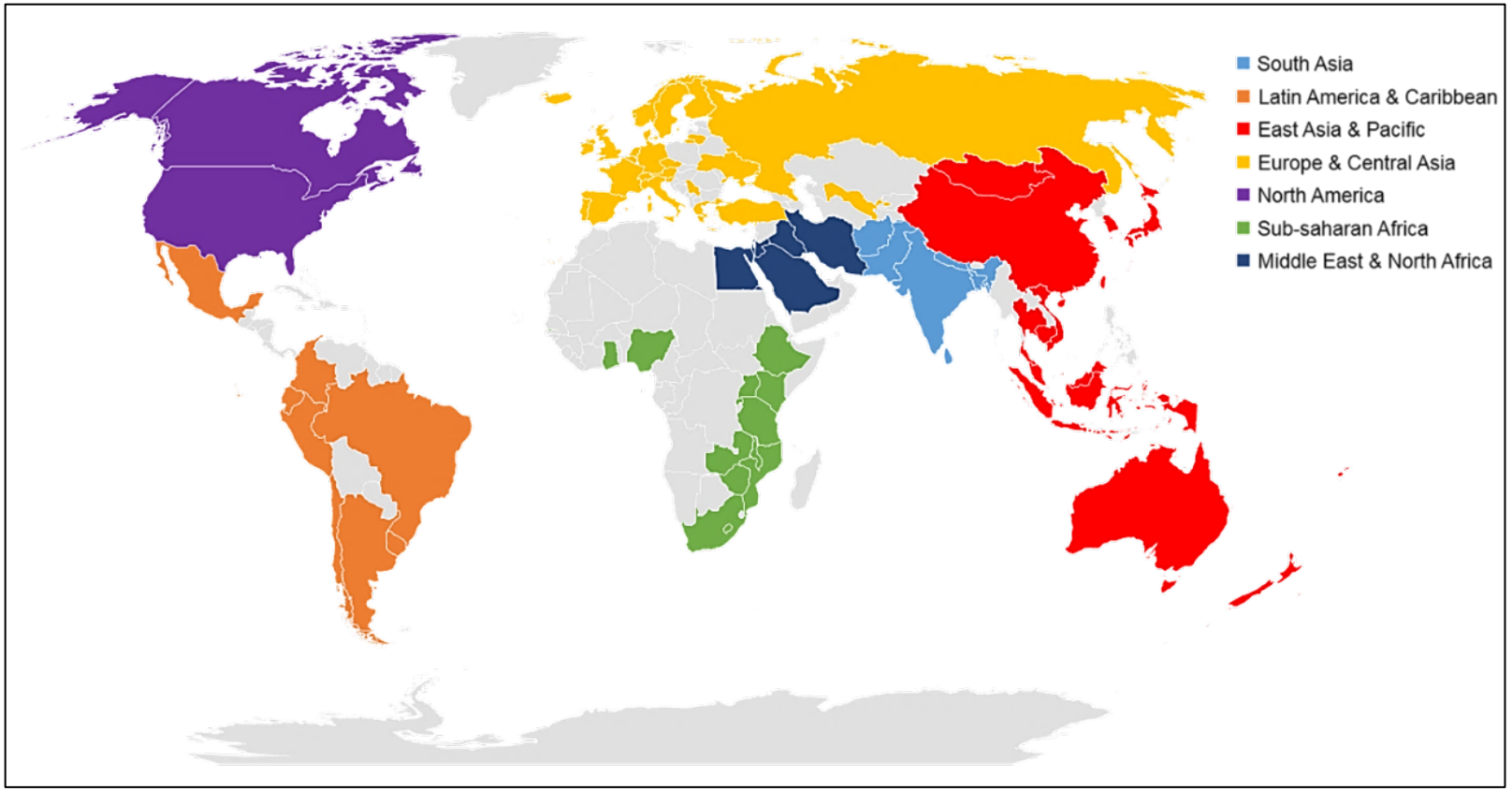


Figure 21: Round 1 Delphi survey: World Bank income status of participant country.

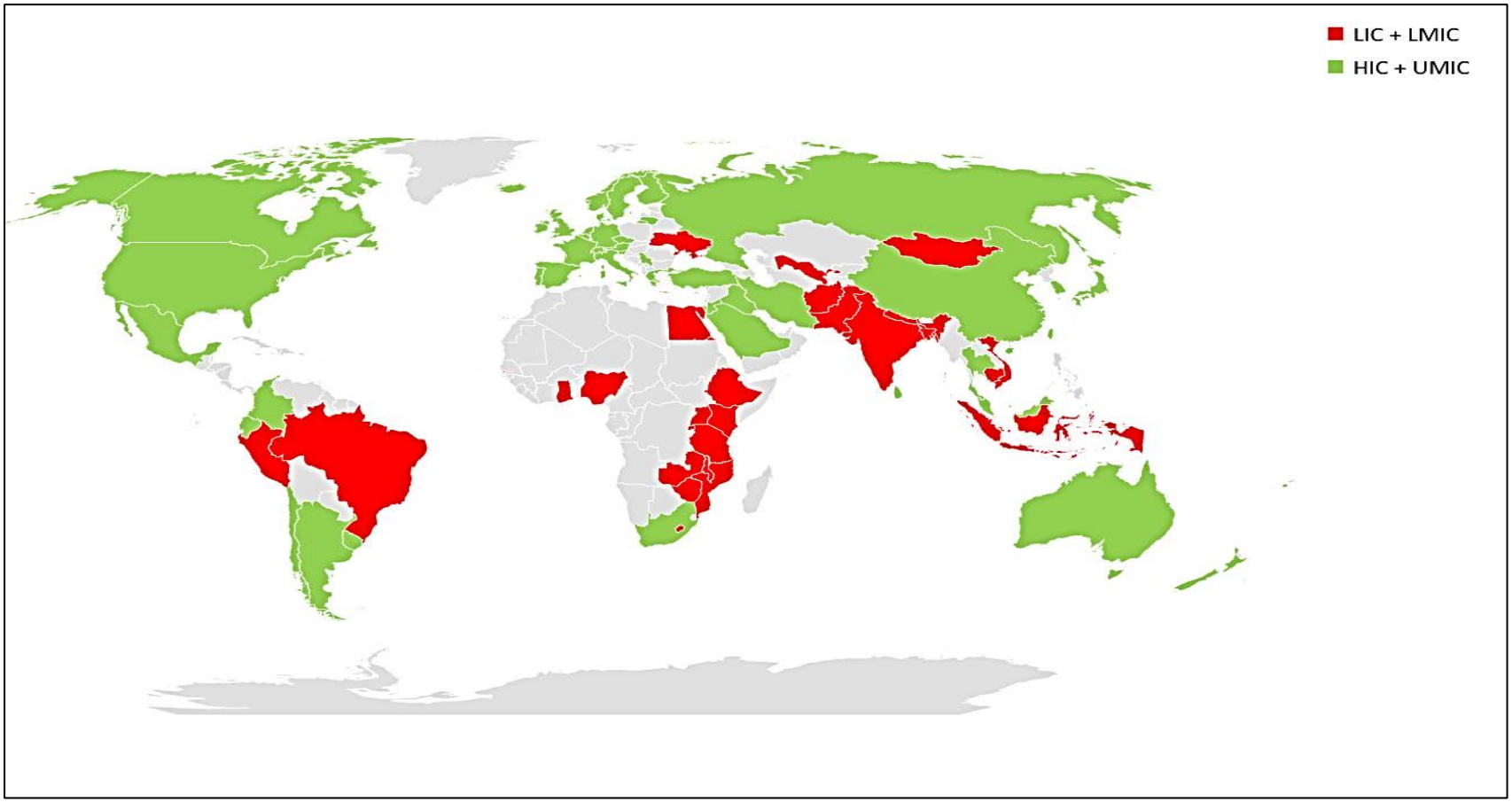

LIC + LMIC
HIC + UMIC

Table 23: Delphi survey round 1 items and voting percentage.

Notes:

- Sorted by % of the total sample scoring the item 7-9.
- Green text: outcomes repeated before and after healing. BH= before healing, AH=after healing.
- Shading: one item at the bottom, rated below 50% by the total sample, and by both patients and carers or clinicians, that was not carried through to round 2 (mild complications).
- Percentages given to two decimal places due to sample size.

Questionnaire item n=88	Whole sample	Patients & carers	Clinicians
Death attributable to the burn injury	94.4%	95.4%	94.3%
Serious complications (e.g. blood clot in lungs or legs)	94.1%	93.5%	94.2%
Sepsis	92.1%	91.6%	92.2%
Burn wound infection	91.8%	92.0%	91.7%
Scar contractures	91.6%	87.5%	92.3%
Ability to carry out daily tasks	90.2%	85.2%	91.1%
Time for a grafted wound to heal	90.1%	91.7%	89.9%
Multiorgan dysfunction	89.7%	88.5%	89.9%
Multiorgan failure	89.7%	90.4%	89.6%
Time for the burn wound to heal	89.4%	90.4%	89.3%
Pain in the scar	88.1%	91.2%	87.6%
Breathing and lung function	87.7%	86.5%	87.8%
Appearance	86.9%	87.0%	86.9%
Serious kidney dysfunction	86.4%	85.0%	86.6%
Return to work/ school/ previous function	86.3%	81.3%	87.2%
BH Death attributable to any cause	85.7%	83.0%	86.2%
Pain during medical procedures	85.1%	89.7%	84.3%
Length of time on a ventilator	84.9%	85.1%	84.9%
Pain when treatment is not taking place	84.7%	86.8%	84.3%
Walking	83.4%	78.4%	84.2%
Length of stay in intensive care unit	83.3%	79.4%	83.9%
Ability of the body to fight infection	83.2%	86.1%	82.7%
Anxiety about the future	82.8%	87.7%	81.9%
BH Functioning of the heart and circulation	82.1%	85.3%	81.6%
BH Anxiety about the future	81.1%	86.1%	80.2%
Physical wellbeing	80.6%	82.5%	80.3%
Donor site infection	80.6%	84.1%	80.0%
Amount of fluid given	80.2%	70.5%	81.9%
BH Effect of burn on metabolism	79.7%	73.4%	80.8%
AH Itch after healing	79.1%	78.6%	79.2%
AH Anxiety about treatment	78.8%	82.6%	78.1%
Growth	78.7%	74.8%	79.4%
Impact on personal relationships	78.5%	79.5%	78.3%
BH Dignity of the patient during and after treatment	77.9%	86.5%	76.3%
BH Anxiety about treatment (e.g. dressing changes, surgeries)	77.6%	82.7%	76.7%
Fitness	77.5%	79.3%	77.2%
BH Number of surgical treatments needed	77.4%	84.5%	76.1%
Comfort of dressings	77.1%	80.9%	76.5%
Unwanted attention	77.0%	81.4%	76.2%

Length of stay in hospital	77.0%	67.3%	78.6%
AH Understanding of treatment	76.5%	80.9%	75.7%
Time for the donor site to heal	76.4%	73.4%	76.9%
Liver function	75.6%	77.6%	75.3%
Muscle strength	75.4%	77.7%	75.0%
AH Number of surgical treatments needed	75.1%	76.3%	74.9%
Number of scar reconstructions	74.7%	72.3%	75.1%
Stomach and bowel function	73.9%	71.0%	74.4%
Sleep quantity and quality	73.6%	79.5%	72.5%
Understanding of treatment	73.5%	85.0%	71.5%
Pain in the donor site	73.5%	73.5%	73.4%
Other infection (e.g. Urinary Tract Infection, Chest infection)	73.2%	66.7%	74.3%
Inflammatory markers	73.1%	79.2%	72.1%
AH Adherence to treatment	73.0%	77.4%	72.2%
Minor kidney dysfunction	72.7%	71.6%	72.8%
BH Itch before healing	72.3%	70.6%	72.6%
AH Dignity of the patient	71.8%	81.4%	70.1%
BH Adherence to treatment	70.8%	80.9%	69.0%
Donor site problems	70.8%	74.8%	70.1%
Number of creams and dressings, time spent in pressure garments	69.6%	75.7%	68.6%
AH Costs to the patient and their family	69.4%	70.5%	69.3%
AH Death attributable to any cause	69.4%	71.2%	69.1%
Need for long-term medication (e.g. pain relief)	68.3%	65.2%	68.9%
Texture of the scar	68.2%	67.3%	68.4%
BH Body temperature regulation	68.1%	73.0%	67.3%
Cognitive functioning (e.g. memory, concentration)	67.1%	74.5%	65.8%
Need for blood transfusion	66.8%	75.0%	65.3%
BH Weight maintenance	66.3%	57.4%	67.8%
Moderate complications (e.g. allergy to medication, bleeding under skin graft)	66.3%	60.6%	67.2%
BH Costs to the patient and their family	65.8%	71.7%	64.8%
AH Body temperature regulation	65.4%	75.7%	63.6%
Number of dressing changes	64.8%	74.3%	63.1%
AH Functioning of the heart and circulation	64.7%	70.3%	63.7%
Scar size	64.3%	65.5%	64.1%
AH Effect of burn on metabolism	63.8%	60.0%	64.5%
Amount of exudate from the wound	62.4%	73.2%	60.4%
Amount of medication needed	61.7%	68.8%	60.5%
BH Costs to the NHS	60.1%	47.6%	62.2%
Hair loss	58.5%	67.3%	57.1%
Nature of exudate from the wound	58.3%	66.1%	56.8%
Burn scar colour	57.7%	61.9%	56.9%
AH Weight Maintenance	54.9%	46.2%	56.3%
AH costs to the NHS	53.7%	48.1%	54.6%
AH Number of outpatient appointments needed	52.7%	59.6%	51.4%
BH Number of outpatient appointments needed	51.9%	58.2%	50.8%
Bone density and strength	51.2%	67.9%	48.4%
Thirst	44.9%	60.0%	42.4%
Smell of the burn wound	41.4%	55.4%	39.2%
Mild complications (e.g. rash from dressing)	41.2%	45.9%	40.4%

6.4.2.2 Round 2 Delphi survey

Response rate: Of those participating in round 1, 431 participants (54%) undertook round 2.

Demographic characteristics of participants: Of all participants, 53 were patients or carers (42% of those completing round 1), and 378 were HCPs (56% of those completing round 1). These data are shown in Tables 24 and 25.

Items for voting and responses: These are shown in Table 26. They consist of those items carried forward from round 1, as well as the 13 additional outcomes added after round 1. The voting is the percentage of respondents

Note: percentages are shown to one decimal point as numbers are larger than those earlier in the thesis.

Table 24: Delphi survey rounds 1 and 2. Demographics of HCPs.

	Survey round 1 n = 668		Survey round 2 n = 378	
	n	%	n	%
HCP occupation				
Doctors				
Consultant burn care (burn surgeon, plastic Surgeon, paediatrician, trauma, pain specialist)	173	25.9	87	23.0
Anaesthetist/ intensivist	84	12.6	46	12.0
Pathologist	1	0.2	0	0
GP	2	0.3	2	0.5
Junior doctor/ registrar	43	6.4	21	5.6
Medical student	1	0.2	1	0.3
Allied Health Professional (AHP)				
Burn AHP: Physiotherapist, occupational therapist, dietician, psychologist, play, speech & language, laser, social worker.	158	23.7	97	25.7
Paramedic	2	0.3	2	0.5
Nursing				
Burn care nurse/ research nurse/ theatre nurse	100	15.0	56	14.8
Burn researchers				
Burn researcher	88	13.2	58	15.3
Other				
Burn charity	1	0.2	1	0.3
Commercial	1	0.2	1	0.3
Burn commissioner/ service manager	2	0.3	2	0.5
Medical education	4	0.6	2	0.5
NIHR	1	0.2	1	0.3
Not stated	5	0.7	1	0.3
Time spent in Burns care				
6-12 months	45	6.7	18	4.8
>1-3 Years	76	11.4	36	9.5
>3-5 years	77	11.5	44	11.6
> 5 years	466	69.8	278	73.5
Not stated	4	0.6	2	0.5
World Bank Income Group				
HIC	473	70.8	306	81.0
UMIC	71	10.6	32	8.5
LMIC	95	14.2	26	6.9
LIC	25	3.7	12	3.2
Missing	4	0.6	2	0.5

Table 25: Delphi surveys rounds 1 and 2. Demographics of patients and burn type.

	Round 1 survey n = 126		Round 2 survey n = 53	
	n	%	n	%
Young person	1	0.79	0.0	0.0
Adult patient	97	77.0	42	79.2
Parent of child with burn	28	22.2	11	20.7
Sex				
Female	83	65.9	36	67.9
Male	43	34.1	17	32.1
Ethnicity				
Asian/ Asian British	1	0.8	1	1.9
Black/ Black British	3	2.4	1	1.9
White British/ White other	114	90.5	48	90.6
Mixed ethnicity	5	4.0	1	1.9
Other	3	2.4	2	3.8
Missing	1	0.8	0	0.0
Education				
No formal qualifications	5	5.0	2	3.8
GCSE or equivalent	23	18.3	10	18.9
A Levels or equivalent	19	15.1	11	20.8
University degree	52	41.3	20	37.7
Vocational qualifications	10	7.9	5	9.4
Higher degree	11	8.7	4	7.6
Other	4	3.2	1	1.9
Missing	2	1.6	0	0.0
Mechanism of burn				
Scald	46	36.5	20	37.7
Contact	8	6.4	2	3.8
Flame	54	42.9	26	49.1
Chemical	5	4.0	2	3.8
Other	13	10.3	3	5.7
Total Body Surface Area of burn				
0-10%	44	34.9	21	39.6
11-20%	20	15.9	7	13.2
21-40%	21	16.7	9	17.0
More than 40%	30	23.8	11	20.8
Not stated / do not know	11	8.7	5	9.4

Table 26: Round 2 Delphi survey items for voting.

Notes:

- Sorted by % of the total sample scoring the item 8-9.
- Green: outcomes repeated before and after healing; BH = before healing; AH=after healing.
- Shading: items carried through after round 2.
- *items added to the survey in round 1.
- Percentages to two decimal points due to sample size.

Outcome	Whole sample	Patients and carers	Clinicians
Death attributable to the burn injury	96.8%	92.0%	97.5%
Serious complications (e.g. blood clot in lungs or legs)	96.3%	98.0%	96.1%
Sepsis	95.3%	98.0%	94.9%
Multiorgan failure	92.9%	85.4%	93.9%
Scar contractures	92.2%	91.5%	92.2%
Ability to carry out daily tasks	91.9%	91.5%	92.0%
Burn wound infection	90.1%	96.1%	89.3%
Multiorgan dysfunction	89.9%	87.8%	90.2%
BH Death attributable to any cause	87.9%	90.0%	87.6%
Time for the burn wound to heal	85.8%	82.4%	86.3%
Pain in the scar	83.9%	87.0%	83.5%
Time for a grafted wound to heal	83.6%	85.7%	83.3%
Breathing and lung function	79.5%	79.6%	79.5%
Pain during medical procedures	79.3%	87.2%	78.3%
Serious kidney dysfunction	77.5%	75.0%	77.9%
Appearance	75.3%	78.7%	74.8%
*Patient psychology	74.6%	75.5%	74.5%
Pain when treatment is not taking place	74.6%	76.6%	74.4%
Length of time on a ventilator	73.7%	65.3%	74.9%
Growth	73.5%	71.7%	73.8%
Return to work/ school/ previous function	73.5%	67.4%	74.3%
Walking	72.8%	72.3%	72.9%
Length of stay in intensive care unit	69.9%	69.4%	70.0%
Amount of fluid given	68.1%	57.1%	69.7%
Physical wellbeing	68.1%	76.1%	67.1%
Donor site infection	68.0%	81.6%	66.1%
BH Dignity of the patient during and after treatment	67.4%	63.8%	67.9%
AH Anxiety about the future	66.8%	71.7%	66.1%
BH Anxiety about the future	66.3%	70.2%	65.8%
Impact on personal relationships	65.9%	63.0%	66.3%
Time for the donor site to heal	65.1%	73.5%	64.0%
Length of stay in hospital	65.0%	59.2%	65.8%
Comfort of dressings	65.0%	66.0%	64.8%
AH Death attributable to any cause	64.0%	53.3%	65.4%
BH Functioning of the heart and circulation	63.0%	66.0%	62.6%
Ability of the body to fight infection	62.2%	76.5%	60.2%
BH Number of surgical treatments needed	62.0%	70.2%	60.9%
Other infection (e.g. Urinary Tract Infection, Chest infection)	60.8%	66.0%	60.1%
BH Effect of burn on metabolism	60.8%	54.0%	61.8%
AH Understanding of treatment	60.1%	80.9%	57.3%
Fitness	59.8%	68.1%	58.7%
AH Anxiety about treatment	58.9%	70.2%	57.3%
AH Itch after healing	58.6%	69.6%	57.1%
Liver function	57.9%	62.5%	57.2%
AH Dignity of the patient	49.9%	54.3%	49.3%
Pain in the donor site	48.7%	52.2%	48.3%
Unwanted attention	48.3%	56.5%	47.3%

BH Anxiety about treatment (e.g. dressing changes, surgeries)	47.6%	50.0%	47.3%
BH Itch before healing	47.1%	44.7%	47.4%
Number of scar reconstructions	47.0%	45.7%	47.2%
Understanding of treatment	46.7%	61.7%	44.7%
*Scar elasticity	46.7%	67.3%	43.9%
*Suicide rate	43.8%	64.6%	41.0%
AH Number of surgical treatments needed	42.6%	46.8%	42.0%
AH Adherence to treatment	42.5%	59.6%	40.2%
Sleep quantity and quality	40.9%	33.3%	41.9%
Muscle strength	40.9%	53.2%	39.2%
*Impact on family	40.7%	56.6%	38.5%
BH Costs to the patient and their family	40.1%	44.7%	39.4%
*Satisfaction with care	40.0%	49.1%	38.7%
Cognitive functioning (e.g. memory, concentration)	38.5%	58.7%	35.8%
AH Costs to the patient and their family	38.0%	45.7%	37.0%
Donor site problems	38.0%	45.7%	37.0%
BH Body temperature regulation	37.9%	50.0%	36.2%
BH Adherence to treatment	37.9%	53.2%	35.8%
Texture of the scar	37.6%	47.8%	36.3%
Stomach and bowel function	37.3%	34.0%	37.7%
*Dysphonia	37.2%	60.0%	34.1%
*Intensive care unit neuropathy	35.3%	36.0%	35.2%
Need for blood transfusion	35.3%	43.8%	34.1%
Inflammatory markers	34.9%	42.9%	33.7%
*Dysphagia	34.7%	48.0%	32.9%
Number of creams and dressings, time spent in pressure garments	33.8%	51.1%	31.5%
Scar size	33.2%	34.0%	33.1%
Hair loss	33.2%	47.7%	31.4%
Need for long-term medication (e.g. pain relief)	33.1%	46.8%	31.2%
*Unplanned readmission to hospital	32.6%	52.0%	30.1%
*Substance Abuse	32.1%	38.0%	31.3%
AH Body temperature regulation	32.1%	61.7%	28.0%
Moderate complications (e.g. allergy to medication, bleeding under skin graft)	31.9%	36.0%	31.4%
Minor kidney dysfunction	31.1%	36.0%	30.4%
BH Costs to the NHS	30.9%	26.1%	31.5%
BH Weight maintenance	30.1%	27.1%	30.5%
*Breast development	29.9%	52.3%	27.2%
*Enteral feeding intolerance	29.8%	45.8%	27.7%
AH Effect of burn on metabolism	29.2%	21.3%	30.3%
Number of dressing changes	28.9%	42.6%	27.0%
AH Functioning of the heart and circulation	28.0%	34.0%	27.1%
*Fatigue	26.5%	32.0%	25.8%
Amount of medication needed	26.4%	36.2%	25.1%
Burn scar colour	24.4%	30.4%	23.6%
AH costs to the NHS	24.2%	22.7%	24.4%
Amount of exudate from the wound	24.1%	31.4%	23.1%
AH Number of outpatient appointments needed	22.1%	31.9%	20.8%
BH Number of outpatient appointments needed	21.3%	34.0%	19.5%
Nature of exudate from the wound	20.8%	35.3%	18.7%
AH Weight Maintenance	19.2%	17.0%	19.5%
Bone density and strength	16.0%	27.7%	14.4%
Smell of the burn wound	14.4%	30.4%	12.2%
Thirst	12.7%	17.0%	12.1%

Voting responses: Using the more stringent criteria described above for items to be carried through to the consensus meeting, 31 outcomes reached the criteria, of which 20 had been voted 8-9 by ≥ 70% of all participants (HCPs and patients or carers) combined (LIST A). An additional 11 outcomes were voted as more than 8-9 by ≥ 70% of either patients or HCPs (LIST B). This resulted in 31 outcomes to be taken to the consensus meeting (Tables 26, 27 and 28).

Attrition of participants between rounds: Demographic characteristics of participants completing both rounds and only round 1 were similar. (Tables 24 and 25).

Analyses examining differences in outcome ratings between participants that completed round 1 only or rounds 1 and 2, were undertaken using Mann Whitney U tests. This demonstrated that 24 outcomes were significantly different at $p<0.05$ (Table 29). However, closer inspection of the data, indicated minimal differences between the medians and means for these outcomes.

Table 27: Outcomes rated 8-9 by more than 70% of patients AND HCPs after round 2.

Note: List A.

Outcome	% rating outcome 8-9	Outcome	% rating outcome 8-9
Death due to burn injury	96.8	Scar pain	83.9
Serious complications (e.g. thrombosis)	96.3	Time to heal a (grafted) wound	83.6
Sepsis (bloodstream infection)	95.3	Breathing and lung function	79.5
Multi-organ failure	92.9	Pain during procedures (dressing changes)	79.3
Scar contractures	92.2	Kidney function	77.5
Daily tasks	91.9	Appearance	75.3
Wound infection	90.1	Pain in the burn wound	74.6
Multi-organ dysfunction	89.9	Patient psychology	74.6
Death from any cause	87.9	Growth (achieving expected height)	73.5
Time to healing	85.8	Walking	72.8

Table 28: Outcomes voted as 8-9 by more than 70% of HCPS OR patients after round 2.

Note: List B.

Outcome	% Patients rating outcome as important (8-9)	% Clinicians rating outcome as important (8-9)
Infection in donor site	**81.6**	66.1
Understanding of treatment received	**80.9**	57.3
Well-being	**76.1**	67.1
Donor site healing	**73.5**	64.0
Anxiety	**71.7**	66.1
Number of surgeries needed	**70.2**	60.9
Anxiety about the future	**70.2**	65.8
Length of stay in ICU	69.4	**70.0**
Time to return to work/school/ previous occupation	67.4	**74.3**
Length of time on ventilator	65.3	**74.9**
Immune response to fighting infection	**76.5**	60.2

Table 29: Outcomes for which there was a significant difference at round 1, between those who did or did not complete both rounds of the survey.

Note: Green: outcomes repeated before and after healing; BH = before healing; AH=after healing.

	Completed round 1 only						Completed rounds 1 and 2						
Questionnaire Item	**N**	**Mean**	**SD**	**Median**	**25th %**	**75th %**	**N**	**Mean**	**SD**	**Median**	**25th %**	**75th %**	**P**
Ability of the body to fight infection	330	7.82	1.47	8	7	9	415	7.63	1.49	8	7	9	0.04
Amount of fluid given	325	7.03	1.76	7	6	9	398	6.56	1.79	7	5	8	0.0002
Nature of exudate from the wound	321	6.93	1.89	7	6	9	398	6.46	1.88	7	5	8	0.0003
Need for blood transfusion	322	7.17	1.78	8	6	9	397	6.99	1.68	7	6	8	0.05
Mild complications	328	6.17	1.84	6	5	7	414	5.85	1.88	6	5	7	0.03
BH Functioning of the heart and circulation	320	7.77	1.33	8	7	9	407	7.49	1.46	8	7	9	0.007
Liver function	300	7.46	1.59	8	7	9	392	7.25	1.61	8	6	9	0.05
Inflammatory markers	309	7.39	1.48	8	7	9	394	7.09	1.59	7	6	8	0.02
BH Costs to NHS	309	6.85	2.07	7	5	9	392	6.46	2.19	7	5	8	0.02
Number of dressing changes	325	7.23	1.59	7	6	9	408	6.72	1.80	7	6	8	0.0002
BH Number of outpatient appointments needed	325	6.63	1.71	7	6	8	413	6.33	1.79	6	5	8	0.02
Smell of the burn wound	319	6.17	2.06	6	5	8	405	5.75	2.15	6	4	7	0.007
BH Adherence to treatment	327	7.32	1.52	7	6	9	413	7.08	1.62	7	6	8	0.05
Pain when treatment is not taking place	322	7.57	1.40	8	7	9	416	7.84	1.23	8	7	9	0.01
Pain during medical procedures	322	7.67	1.39	8	7	9	415	7.93	1.24	8	7	9	0.01
BH Costs to patient and their family	321	7.22	1.72	8	6	9	412	6.98	1.62	7	6	8	0.01
Bone Density and Strength	315	6.50	1.91	7	5	8	407	6.19	1.86	6	5	8	0.03
AH Costs to NHS	313	6.73	1.98	7	5	9	397	6.27	2.15	7	5	8	0.007
AH Effect of burn on metabolism	322	7.11	1.58	7	6	8	411	6.81	1.68	7	6	8	0.02
AH Functioning of the heart and circulation	319	7.13	1.59	7	6	9	411	6.85	1.64	7	6	8	0.02
AH Adherence to treatment	335	7.47	1.42	8	7	9	420	7.10	1.59	7	6	8	0.002
Number of creams and dressings, time spent in pressure garments	333	7.30	1.49	7	6	9	418	7.01	1.66	7	6	8	0.04
AH Number of outpatient appointments needed	332	6.69	1.62	7	6	8	414	6.40	1.74	6	5	8	0.02
AH costs to the patient and their family	327	7.32	1.57	7	6	9	416	7.06	1.67	7	6	8	0.04

6.4.3 Phase 3: COSB-i Consensus meeting

Participant demographics: The meeting was attended by 28 HCPs and 4 patients and carers, with 19 international HCPs joining by teleconference. Details of the consensus meeting attendees are shown in Table 29.

Table 30: Consensus meeting. Participant type and country.

Country of participant	**n (%)**
UK	28 (60)
Australia	6 (13)
USA	4 (9)
Belgium	1 (2)
Indonesia	1 (2)
Japan	1 (2)
Netherlands	3 (6)
Norway	1 (2)
Sweden	1 (2)
Not reported	1 (2)

Participant group	
Health care professional including commissioners, researchers, charity sector staff	43 (92)
Patient or carer	4 (9)

Participant group profession / role	
Researcher, academic or journal editor	11 (23)
Consultant plastic surgeon involved in burn care	5 (11)
Registrar/junior doctor with at least 6 consecutive months' burn care experience	2 (4)
Burn care research nurse or nurse	8 (17)
Psychologist or counsellor working with patients with burns	1 (2)
Physiotherapist or occupational therapist working with patients with burns	5 (11)
Patient and carers	4 (9)
Not reported	11 (23)

De-duplication of outcomes due to repetition in short and long-term sections: Prior to discussion on outcome merging and the subsequent voting, the final set of 31 items (from now on called outcomes) were de-duplicated (for outcomes repeated in short- and long-term sections). This resulted in one outcome listed at both times being combined (anxiety about the future).

Merging of outcomes: A discussion to determine outcomes that could be merged due to similarity in meaning was undertaken. Items were merged in List A (Table 27) and in List B (Table 28).

The following nine merging actions were taken:

1. To combine death due to the burn with death from other causes.
2. To combine multi-organ failure and multi-organ dysfunction into organ dysfunction, as these terms are often used interchangeably.
3. To combine kidney and lung function into the organ dysfunction outcome.
4. To expand burn wound healing, to incorporate burn wound, grafted wound and donor site healing.
5. To combine procedural and background pain under one heading (acute pain).
6. To combine scar pain with itch (both address long-term pain, differentiated from acute pain) into neuropathic pain.
7. To merge length of stay in ICU with length of time on a ventilator.
8. To combine anxiety with psychological impact into psychology.
9. To merge complications under one heading, with the formal inclusion of sepsis, wound infection and thrombosis.

Of the 20 outcomes, rated as very important (8-9) by more than 70% of both patients and HCPs in List A, merging outcomes with a similar meaning resulted in 11 outcomes to vote on (Table 31). It was also agreed that any outcomes that were voted as being important by either patients or HCPs (List B) should be added to the voting after a similar merging exercise (Table 32). This resulted in another resulting in six outcomes to add to the voting list. The final list of 17 outcomes to vote on are shown in bold in both tables 31 and 32, and in Table 33.

Table 31: Merged Outcomes from List A to vote on in the consensus meeting.

Note: List A fits *include* criteria from both patients *and* HCPs.

- **Death (all causes)**
- **Serious complications (to include sepsis, wound infection)**
- **Multi-organ dysfunction (combined with multi-organ dysfunction, lung and kidney dysfunction)**
- **Scar contractures**
- **Ability to do daily tasks (to include walking)**
- **Time to heal (combined healing of burn wound and healing of grafted wound)**
- **Long term pain (to include itch)**
- **Acute pain (include background and procedural)**
- **Appearance**
- **Psychology**
- **Growth**

Table 32: Merged outcomes (in bold) from List B to be added to List A.

Note: List B fits *include* criteria from both patients *or* HCPs both lists.

- Wound infection- this was merged under serious complications in List A
- **Understanding of treatment received**
- **Physical well-being**
- **Number of surgeries needed**
- **Length of stay in ICU** – this was merged with length of time on ventilator
- **Immune response to fighting infection**
- **Time to return to work/school/previous occupation**
- Anxiety about future, anxiety – these were merged under *psychology*.
- Donor site healing - this was merged under 'wound healing' in List A above

The final group of 17 outcomes to be voted on, agreed after the merging exercise, are shown in Table 33.

6.4.3.1 Consensus meeting voting

Round 1: Of the 17 outcomes voted in on round 1 of the consensus meeting, those where at least 50% of the participants stated that they should be included in the COS, were carried through to round 2. Using these criteria, five outcomes were removed prior to the round 2 vote of voting. Twelve outcomes were carried though to round 2 (Table 33).

Round 2: In round 2 of the consensus meeting voting, 45 people joined (range 43-45 votes per item). Table 34 shows the 12 items that were voted on in round 2 and the seven outcomes reached the criteria to be included in the final COS.

It is important to note that outcomes 1,2 and 4 are short-term and outcomes 3,5,6 and 7 are longer-term in relation to the burn injury.

Figure 22 shows the COSB-i outcome inclusion or exclusion flow chart over the whole study.

Table 33: Consensus round 1 outcomes and definitions and percentage voting.

Shading indicates outcomes *not* meeting the 50% cut-off for inclusion in consensus meeting voting round 2.

Outcome	Definition	n voting	n (%) voting on inclusion in COS
Death	Death of a patient from any cause soon after the patient is injured. Death due directly to the burn injury soon after the patient is injured. *For example: death due to 'burn shock' or due to a burn wound infection or sepsis or death from a heart attack.*	41	36 (88)
Organ failure/ dysfunction	Whether the burn causes several of the patient's organs to fail/not work at all or stop working well (dysfunction). *For example: kidney failure alongside liver failure, where it is unlikely to get better, or will need long-term care or poor kidney function and poor liver function at the same time. This is likely to get better following treatment.*	39	28 (72)
Serious complications	Includes: blood clot, sepsis, wound infection but not organ dysfunction/failure.	39	36 (92)
Scar contractures	The effect of the burn scar on a patient's ability to move joints (contractures). *For example: inability to straighten arm, difficulty moving fingers normally, limited range of motion of joints.*	41	28 (68)
Daily tasks	A patient's ability to carry out normal daily tasks. This includes walking. *For example: dressing, washing, making food or drinks.*	41	36 (88)
Time to heal (incl. wound graft and donor site)	How quickly a patient's burn wounds heal. This includes wounds after receiving a skin graft (A skin graft is when healthy skin is taken from another party of the body and placed over the burn wound to help it heal). *For example: how many days or weeks does it take for the burn to heal completely or how well a burn that has needed a skin graft heals.*	41	29 (71)
Pain acute	Pain in the burn wound. This includes background and procedural pain. *For example: pain all the time, pain at night.*	39	23 (59)
Pain long-term	The amount of pain caused by a burn scar. This includes itch.	41	31 (76)
Appearance	Patients' appearance after a burn injury. *For example: appearance of the scar, facial appearance, body image.*	44	27 (62)
Patient psychology	The psycho-emotional effect a burn has on patients. Distress and anxiety can often be consequences of a burn and affect patient well-being. *For example: anxiety triggered by reminders of how the burn happened or low self-esteem in case of a visible scar.*	43	32 (74)

Growth	The effect a burn has on a child's growth. *For example: not achieving potential height, slowing of growth.*	43	4 (9)
Understanding treatment	How much a patient understands of the treatment.	43	8 (18)
Physical wellbeing	General Physical well-being	42	20 (47)
Immune response	Ability to fight infections	42	6 (14)
Number of surgeries	Number of surgeries	43	16 (37)
Time to return to work/school/previous occupation	Time to return to work/school/previous occupation	43	34 (79)
Length of stay in ICU	This includes length of time on a ventilator.	44	19 (43)

Table 34: Consensus meeting voting round 2 outcomes.

Shading shows those outcomes to be included in the final COS.

Outcome	**Numbers voting**	**Numbers (%) voting to include in COS**
Death	43	34 (79)
Organ failure/ dysfunction	44	20 (46)
Serious complications including wound infection, sepsis or thrombosis	45	41 (91)
Scar contractures	44	23 (52)
Ability to do daily tasks	44	36 (82)
Time to wound healing (including graft or donor site).	44	27 (61)
Pain acute	45	21 (46)
Pain long-term including itch	45	30 (67)
Patient psychology	45	37 (82)
Physical wellbeing	45	15 (33)
Time to return to work or school or previous occupation	44	37 (84)
Appearance	44	24 (55)

Figure 22: COSB-i outcome flow chart.

The seven outcomes reaching the threshold for inclusion were presented to the meeting and agreed as the final core outcome set and are shown in Table 35. The final COS was sent to the group after the meeting via a consensus report so that people could have further time to consider their decisions and confirm (Appendix L). Participants confirmed agreement. All responses to the consensus report from the meeting were positive.

Table 35: COSB-i Final Core Outcomes.

1. **Death: to include death from any cause and death from the burn.**
2. **Serious complications: to include wound infection, sepsis, venous thrombosis.**
3. **Ability to do daily tasks: to include walking.**
4. **Time to heal: to include wound healing, grated wound healing and donor site wounds.**
5. **Neuropathic pain and itch.**
6. **Patient psychology: to include anxiety and anxiety about the future.**
7. **Time to return to work or school or previous occupation.**

6.5 Discussion

This study is the first to develop a COS to standardise, but not restrict, outcome reporting in trials of burn care interventions. It was developed throughout, using shared decision-making, by UK patients and international HCPs. The COS was prioritised from an initial list of 1,021 clinical and patient-reported outcomes, generated systematically from three information sources. These individual outcomes were grouped into 88 questionnaire items. To achieve prioritisation of these items in terms of importance to stakeholders, a modified Delphi survey, consisting of two on-line questionnaire rounds with a final face-to-face consensus meeting was undertaken. Using a web-based survey to achieve consensus, meant that many international stakeholders were able to participate. Voting in the final consensus meeting generated a COS that all stakeholders supported. The final COS of seven outcomes is illustrated in Table 35. The COSB-i COS is a new COS for burn care research. It is hoped that the chosen outcomes, should be assessed and reported, in all trials assessing the effect of interventions in burn care.

New COS are increasingly being developed, and are widely recognised in specialties such as dermatology, rheumatology, paediatric, breast and colorectal surgery(111, 419, 541, 587-590). Funding bodies are now advocating the use of COSs, and uptake among triallists is increasing(591). Importantly, COSs are now more commonly developed using international participants, with the recognition that global agreement will increase dissemination of the COS, support the applicability of the COS in global healthcare settings and make it more likely that they will be used in future trials wherever these take place (554, 592, 593). The COMET Handbook highlights the logistical and organisational challenges of international COS development projects, as well as issues regarding generalisability of small international participant numbers(115). This COS included 794 Delphi survey participants of which 668 were international HCPs, researchers, journal editors and commissioners, from 77 countries of all four world income groups. The large numbers of international participants, and variation in country income status and participant type recruited in this COS, compared to other COSs, should increase the external validity of the COSB-i(594-597).

The core outcomes chosen for this COS, clearly reflect priorities in recovery for both patients, carers and HCPs. The likely reason for this, was the shared decision-making used throughout the development of the COS. This diversity of stakeholder involvement is increasingly common in COS development(554, 598). Shared-decision making has a more traditional definition as discussed earlier in this chapter. The author of this this thesis believes that the use of the term, implies joint decisions in study methodology and outcome choice, weighing the views of all stakeholder groups equally. This is the way this COS has been developed. Interestingly, stakeholders agreed on outcomes that span both short and long-term recovery. Death, pre-specified acute complications including infection and time to heal, are outcomes to measure the effect of interventions in short-term efficacy RCTs. The other four outcomes, (ability to undertake tasks of daily living, neuropathic pain and itch, psychological well-being and time to return to work, school or previous occupation), are patient-important and more likely to be of value when assessing clinical interventions in longer-term pragmatic trials. A remaining question, is whether all the COSB-i core outcomes should be in be used in all trial types? In other words, would it be useful to develop or encourage the use of the short-term outcomes in efficacy trials and the longer-term outcomes in pragmatic trials. This is an area for future work after completion of this thesis.

The outcomes chosen, are similar in type and number to those agreed in other trauma-related COSs. In a COS for traumatic dental injuries, the outcomes chosen include healing, pain, complications (side effects), functional status of teeth and quality of life including return to work. It is interesting that this COS also covers outcomes in both short and longer-term recovery(599). The COSB-i outcomes are also similar to the core outcomes chosen for trials of interventions in hip fracture management(600). These include mortality, pain, activities of daily living, mobility, and health-related quality of life. The participants for the whiplash injury COS agreed on six core outcomes: physical functioning, perceived recovery, work and social functioning, psychological functioning, quality of life, and pain(601). The differences are in the increased granularity of the outcomes in COSB-I, compared to those in the whiplash COS. Interestingly, our COS also overlaps with outcome choice for COSs in non-traumatic healthcare areas(602, 603). This implies that many core outcomes are similar across different healthcare areas of research. This will be explored further in Chapter Seven.

6.5.1 Strengths and limitations

The broad range of stakeholders that participated in the Delphi survey is one of the strengths of this study (553). Diversity is present in terms of UK patient (and carer) age, cause, severity of burn, time after injury, and the involvement of international HCPs of different disciplines and from a variety of countries of different income status. A related strength is that every stage of the process, including merging, addition and exclusion of outcomes, and final decision-making, was performed by consensus and always included patient and/or carer representation. The impact of involving multidisciplinary clinical staff, researchers, commissioners, patients, parents and charitable organisation representatives to be involved in all aspects of this study, will allow easier and more influential and effective dissemination, a more meaningful result for international research and an emerging shared decision-making burn network researching outcomes after injury(604).

Further strengths lie in the comprehensive search for potential outcomes, through three sources, including patient-reported outcomes. The study has followed the standards set for COS development and previous practice endorsed by the COMET initiative. Methodology changes from the published protocol, including the involvement of international HCPs and a change from three survey rounds to two, were based on consensus being achieved earlier than anticipated. All protocol changes have been explicitly described and agreed by the steering group. We agreed at steering-group level that outcomes would be dropped from the first Delphi survey round if they did not fulfil pre-specified and published criteria. There is discussion in the academic literature as to whether this is the correct methodology. Dropping outcomes from round one allows round two to be shorter and less burdensome to participants. Maintaining all the round one outcomes for round two, will allow aprticpants to see other participants' views on outcomes that may have been dropped if the former methodology is followed.

A potential study limitation is that the descriptive text detail for the semi-steucture interviews could have been broadened to give more detail on the qualitative methodology. The aim of this work was to extract outcomes to add to the COS long-list and not to develop in-depth themes about burn recovery. This is part of a furture project and will be important to explore

at this stage. A further limitation of the study was the impracticality of including international patients. Recruiting global patients incurs costs and time for questionnaire translation and validation, along with ethical research permissions to achieve in many countries. This was beyond the scope of this project and pre-specified. We would aim to consider international patients' views in a future study, with several countries already expressing interest.

Other next steps will include agreement on the timing of outcome assessment, definitions and parameters of the individual outcomes and the agreement of measures to assess the seven chosen outcomes.

Evidence to support burn care decision-making is vital, as burn care is currently inconsistent. This impacts patient management and results in varying healthcare outcomes. Reporting data for these core outcomes, will make burn trial design more relevant, the ability to synthesise evidence more effective and reduce research waste.

6.6 Conclusion

This is the first study, using rigorous methodology and international shared decision-making, to agree a minimum set of core outcomes to be reported in trials assessing burn care interventions. The development of this COS was undertaken to promote the standardised reporting of outcomes and facilitate the robust evaluation of burn care. It is recommended that future trials include measures of these seven outcomes. This will enable consistent reporting and effective data synthesis to support evidence-based healthcare for patients with burns. Future work is needed to validate the COS internationally and determine how these outcomes are best measured and timed.

The next chapter will summarise the work presented in thesis, answer the thesis research question and explore the implications and impact of the work undertaken.

Chapter 7 Discussion

7.1 Introduction

The aim of this thesis is to explore the reasons that limit researchers' ability to synthesise data in global burn care.

The research question that this thesis has aimed to answer is:

Is it possible to increase the provision of data from burn care randomised controlled trials, that can be synthesised into evidence to answer clinical questions, through the development of a Core Outcome Set (COS)?

A COS is a scientifically agreed set of the most important outcomes. These outcomes are intended to be reported consistently across trials of one healthcare area, and developed to improve evidence synthesis(71). Effective evidence synthesis will inform global burn care treatment strategies. The knowledge will reduce wasted research effort and improve patient outcomes through standardisation of evidence-based care. The research presented here has demonstrated specific challenges in aggregating data from RCTs in burn care research. All the issues relate to outcome reporting. The work has highlighted the need to understand how to resolve these issues, to achieve a true understanding of the effects of interventions in burn care. One solution to the methodological challenges presented in this thesis is the development of an international COS for burn care.

This chapter summarises and critically explores the work conducted for the thesis. The context and relevance of the research findings are considered in the setting of the global challenge of burn injury. The impact of the research findings on burn care is presented, alongside current evidence in other clinical areas. This chapter examines the benefit to clinical decision-making, by optimising outcome selection, definition and timing of outcome assessment in RCTs, through the development of a COS. Ideas to take the work forward after submission of this thesis are also discussed.

The following are the main thesis findings, which are detailed in Table 36. The strengths and limitations of the research are separately presented for each study, in each chapter.

The under-pinning methodological work in this thesis has demonstrated, through four literature reviews, a variation in outcome reporting in burn care. This is novel. Although variation in burn care clinical practice and patient recovery outcomes, has been well recognised, the challenges with outcome reporting heterogeneity have not been studied.

The systematic reviews showed that:

1. There is a wide variation in the choice of outcomes across trials in burn care research.
2. Investigators have difficulty in defining a unique outcome, through:
    a. A variation in numbers and type of indicators to define one outcome (e.g. burn wound infection (BWI)).
    b. A variation in the timepoints for assessment of the same outcome across trials in burn care.

This work has proposed that one solution to these methodological challenges, is the development of the first international COS in burn care research.

7.2 Summary of findings.

Table 36: Summary of findings from the work presented in this thesis.

Thesis objective.	Study undertaken to answer thesis objective.	Study findings.	Clinical implication and impact of the findings.	Comments and future work.
1. An exploration of the variation in clinical outcome reporting across burn care RCTs. (Chapter Two).	Systematic review (SR) of clinical outcomes reported in burn care RCTs over five years.	Numbers of burn care RCTs across a recent five-year period reported 955 unique outcomes extracted from 147 trials. This study demonstrated a variation in clinical outcome reporting across RCTs in terms of outcome choice, timing of assessment and definition of each outcome.	The magnitude of the variation of clinical outcome reporting will impact on evidence synthesis and limit the evidence base in burn care research. This limit to the evidence produced from trials will maintain the variation in patient care and outcomes. This is the first study to demonstrate this in global burn research.	Challenges and future work: • The level of granularity required to define a single (unique) outcome. • Understanding and agreeing the above, would allow an accurate determination of the magnitude of outcome variation across trials (defined as ORH in Chapter Three). • Variation in the timing of outcome assessment impacts the numbers of outcomes reported across and within trials. There is a need to agree a small number of assessment timings for each core and non-core outcome. • Definitions of the same outcome vary across trials. There is a need to agree international definitions for core and non-core burn outcomes for consistent reporting across trials.
2. The development of an understanding of what makes an outcome unique. (Chapter Three).	SR to examine methods used to extract and combine outcomes with the same or similar meaning, from published research papers to inform how to establish a reproducible	Methods were proposed for the grouping of similar outcomes into unique outcomes, following verbatim outcome extraction from a literature review to develop a COS.	Clarifying what makes one outcome different from another; what makes an outcome unique. This knowledge directly impacts the magnitude of outcome reporting variation across trials.	The start of an international attempt to propose a definition for a unique healthcare outcome and how this impacts COS long-lists and ORH. This work will be taken further through COMET and other international outcome research partners.

	and quantifiable long-list of unique outcomes. Work to define a unique outcome and define outcome reporting heterogeneity (ORH).	Working definition was proposed for a unique outcome and ORH.		
3. An analysis of how the variation in the definition of a specific outcome (acute burn wound infection (BWI)) across trials in burn care impacts evidence synthesis (Chapter Four).	SR to explore how challenges with the definition of one unique outcome (BWI) impacts evidence synthesis.	The number and type of clinical and patient-reported indicators to define BWI across trials varied significantly. Proposed definitions for clinical indicator and Core Indicator Set were discussed through this work.	This is another type of variation in outcome reporting that impacts data collation and comparison. It limits the ability to interpret effects of interventions in burn care to detect or treat BWI.	A pilot study to determine a CIS (minimum set of indicators required to be reported when using BWI as an outcome) has been undertaken separately from this thesis. Further work is required to agree this internationally.
4. An analysis of how variation in the timepoints for the assessment of unique outcomes across trials impacts relevance to patients (Chapter Five).	SR to understand any variation in outcome assessment timing across trials of burn care interventions and the relevance of this to patients.	Timing of outcome assessment is used in a variable manner to define unique outcomes. 69% of outcomes were last assessed at less than six months after injury. Only one study followed patients for more than three years.	This is the third type of variation in outcome reporting across trials. It impacts aggregation of data and patient relevance.	Timing of outcome assessment is not an important determinant of a unique outcome (as discussed in Chapter Three). However, when used to determine the measure for the final COS, it is important in terms of collation and comparison of data, in terms of relevance to patients and in the use of the outcome in effectiveness or efficacy trials. Further work needs to determine whether a short and long-term COS for burn care research is required.
5. A consensus on which burn care outcomes are most important to patients, carers, and international burn HCPs (Chapter Six).	Development of an international Core Outcome Set for burn care research (COSB-i).	A consensus on which burn care outcomes are most important to stakeholders has been achieved. Seven outcomes were agreed.	The COSB-i will standardise outcome reporting in burn trials, while not limiting the reporting of other outcomes. This will allow more effective evidence synthesis, impacting positively on patient care and outcomes.	Future work to implement the COS: • Agree the measures for COSB-i. • Validate the COS with international patients. • Implement the COS though work with international stakeholders to ensure uptake and embedding into future burn care trials.

7.3 Relevance and context of research findings

It was known that there was a lack of standardised care for patients with burns, prior to the work undertaken for this thesis. Outcomes for these patients vary internationally, in terms of function, cosmesis and psychological well-being, despite the same injury severity. It is accepted that a lack of evidence-based care impacts on this variation in patient outcomes.

Recent publications provide the evidence to support this issue. Research shows that burn management varies within and between countries in terms of mortality, surgical and scar management and rehabilitation provision (13, 30, 605-607). Kazis has shown that adherence to 36 pre-specified burn care process indicators varies across the United States (50). The variation was shown to occur in burn evaluation, resuscitation, debridement, critical care, psychosocial and pain control, and reconstruction surgery. Papers, written by the author of this thesis, link a similar variation in UK practice with variation in patient outcomes.

- Patients with the same severity small area burns vary in their need for skin grafting and future scar presence and quality.
- Outcomes of patients managed with different fluid management with the same severity burns vary in terms of length of hospital stay.
- Variation exists in the diagnosis of burn wound infection (BWI) and the use of antibiotics (11, 12, 208, 608).

Advances in clinical practice have led to improved patient outcomes after burn injury. These advances have resulted from internationally agreed principles in resuscitation, improved coverage of wounds, treatment of infections, better management of the hypermetabolic response and early functional and psychological rehabilitation(16, 609). However, high quality evidence, in terms of valid data from systematic reviews, is still lacking for the clinical detail of these strategies(610-613). New surgical techniques and advances in understanding of the wound environment, critical care and dressing technology, continue to be introduced(522, 614). Synthesised evidence from well-conducted and reported RCTs, for short and longer-term benefit and cost-effectiveness for this new innovative care, is lacking(611, 615).

Achieving high quality evidence to answer clinical questions is known to be challenging in burn care research. Since 2000, 12 Cochrane reviews have had direct relevance to the management of patients with cutaneous burns(8, 10, 89, 237-245). None could draw firm conclusions due to methodological issues including heterogeneity of outcome reporting. Table 37 highlights issues with outcome selection, measurement and reporting in Cochrane reviews directly related to burn care.

If clinical-effectiveness cannot be determined through evidence-based medicine, care will not be optimised, and patient outcomes will remain variable. Blocks to effectively synthesising evidence will result in persisting clinical uncertainty and research waste(616-620). One of the blocks or challenges to evidence synthesis is the variation in outcomes reported across trials and the need for a COS in burn care research

The impact of the findings of this thesis are detailed below in the context of the current literature.

Table 37: Methodological issues in outcome reporting in burn care Cochrane reviews.

Cochrane reviews on burn care listed in ascending date order.	Outcomes assessed	Outcome reporting methodology (extracted verbatim)	Conclusion
Hyperbaric oxygen therapy for thermal burns (HBOT)2004. (242)	• Mortality rate. • Major morbidity rate (wound infection, haemodynamic instability).	• "There were no outcome measures in common with the two included trials so pooling of data was impossible."	"This systematic review has not found enough evidence to support or refute the effectiveness of HBOT for the management of thermal burns."
Early versus delayed enteral nutrition support for burn injuries 2006. (243)	• All-cause mortality at end of follow-up. • Length of hospital stay. • Frequency of infection. • Number of adverse events.	• "There was wide variation amongst the studies in …. the type of clinical, metabolic and hormonal outcome measures used to determine effectiveness."	"…. need for ongoing future research that includes conducting large multi-centre, randomised, double-blind studies, coupled with a number of key outcome measures is needed which in turn would allow for pooling of data in a meta-analysis."
High-carbohydrate, high-protein, low-fat versus low carbohydrate, high-protein, high-fat enteral feeds for burns. 2012. (245)	• Mortality. • Incidence of sepsis or pneumonia. • Time to healing. • Number of days on ventilator.	• "No conclusions could be drawn about the risk of death in patients receiving the different feeding regimens." • "No meta-analysis could be performed on the remaining outcomes data due to lack of similar outcomes reported between the two available studies."	"The available evidence is inconclusive regarding the effect of either enteral feeding regimen on mortality."
Dressings for superficial and partial thickness burns 2013. (8)	• Time to complete wound healing /proportion of burns completely healed in a specified time period. • Change in wound surface area over	• "The studies summarised in this review evaluated a variety of interventions, comparators and clinical endpoints and all were at risk of bias." • "The studies summarised in this review evaluated a variety of interventions, comparators and clinical endpoints and all were at risk of bias."	"In conclusion, a number of dressings may have some benefit over other products in the management of superficial and partial thickness burns. However, our confidence in these conclusions is reduced by the low quality of the evidence and small sample sizes of these trials."

	time/proportion of wounds partly healed in a specified time period.	• "The evidence for the effectiveness of the different dressings .....is limited by the inconsistent measurement and reporting of this outcome." • ".....the time to wound healing data ..... were often not reported in a way that allowed the results to be reproduced by the review authors." • "Poor measurement of outcomes that are important". • "The limited use of objective outcome measures and insufficient reporting of results makes the analysis and usefulness of these results doubtful."	
Antibiotic prophylaxis for burn wound infection 2013. (238)	• Burn wound infection. • Invasive infections. • Infection-related mortality. • Adverse events.	• "Consensus is needed amongst researchers and clinicians regarding valid and reproducible criteria for diagnosis of infection of the burn and a consistent and standardised approach to outcome reporting." • "The results given in this review are still limited; few data could be pooled in most comparisons. • "Outcome measures and follow-up times were heterogeneous, or not even defined, which made it difficult to interpret the results of the review and to determine their applicability." • "There was a high degree of heterogeneity between studies in terms of interventions evaluated, types of burn, and outcomes assessed. This made it difficult to determine the effectiveness of antibiotic prophylaxis."	"The available evidence is limited ....."
Topical treatment for facial burns. 2013. (239)	• Time to complete wound healing. • Change in wound surface area over time, or the proportion of the burn wound surface area that had healed within a specified time period. • Wound infection.	• "Heterogeneity of interventions and outcomes prevented pooling of data." • "Future trialists might give some extra thought to the outcome wound healing, as this outcome can be reported in numerous ways and it is not always analysed correctly (i.e. survival analyses)." "Four studies included time to complete wound healing as an outcome of interest but differed in their definition of this outcome." • "Ideally, all trialists should use the same measurement for wound healing, and as a result, allow comparisons to be made." • "Heterogeneity of studies with regard to interventions and outcomes prevented assessment of reporting biases and limited data synthesis to a narrative overview, structured by the type of comparison."	"There is insufficient high quality research and evidence to enable conclusions to be drawn about the effects of topical interventions on wound healing in people with facial burns."

Recombinant human growth hormone for treating burns and donor sites. 2014. (237)	• Burn wound healing. • Donor site healing. • Wound infection (as defined by the trial authors). • Mortality rate.	• "Not all trials reported on all outcome measures." • "Twelve of the excluded studies addressed none of the pre-specified outcome measures." • "The included studies often could not be pooled because they used different methods to measure outcomes." • "For the primary outcome of the healing rate of burn wounds in adults, four studies .... measured the outcome in three different ways." • "Burn scar formation: Three of the studies involving children reported this outcome, but these studies could not be pooled because they used different methods to measure the outcome."	"This evidence is based on studies with small sample sizes and risk of bias and requires confirmation in higher quality, adequately powered trials."
Negative pressure wound therapy for partial thickness burns (NPWT). 2014. (10)	• Time to complete healing. • Rate of change in wound area. • Proportion of wound completely healed within the trial period.	• "We undertook a narrative synthesis of results, as the absence of data and poor reporting precluded us from carrying out any formal statistical analysis." • "Time to complete healing: no data were reported for this outcome. • "Proportion of wounds completely healed within the trial period: no data were reported for this outcome." • "Other weaknesses included: the absence of reporting on clinically relevant outcomes, such as rate of healing, time to complete healing, rate of change in wound area, and proportion of the wound completely healed within the trial period; lack of clarity regarding the definition and reduction of oedema formation."	"There was not enough evidence available to permit any conclusions to be drawn regarding the use of NPWT for treatment of partial-thickness burn wounds."
Immuno-nutrition as an adjuvant therapy for burns. 2014. (241)	All-cause mortality.	• "Overall mortality rate was reported in 13 studies but was not reported in three. Fourteen studies reported hospital length of stay, but two did not." • "One study reported only hospital length of stay as "Length of stay per percentage burn"." • Five studies reported on rate of burn wound infection. Rates of other non-wound infections such as pneumonia, urinary tract infection and bacteraemia were reported in four studies." • "....some of the outcome measures used are subject to a high degree of variability (e.g. time to healing). It is for this reason that only four included outcomes were used in this review, with the greatest quantity of evidence found for mortality and length of stay."	"Although we found evidence of an effect of glutamine on mortality reduction, this finding should be taken with care".

		• "Many articles were excluded because they reported only biochemical markers of immune activity—not clinically significant outcomes."	
Interventions for treating phosphorus burns 2014. (244)	• Death. • Time to complete wound healing/proportion of burns completely healed in a specified period of time.	"Neither study reported the primary outcome of wound healing."	"The conduct of high-quality randomised controlled trials to address the uncertainties around the management of people with phosphorus burns, is highly desirable...".
Intravenous lidocaine for the treatment of background or procedural burn pain. 2014. (240)	• Pain measured by a visual analogue scale (VAS) or verbal rating scales (VRS), a numerical rating scale, or other validated assessment tool. • Time to re-medication. • Requirements for rescue analgesia.	• "No information is available from the published RCTs or CCTs on clinically relevant primary outcome measures which can influence current burns care practice and management." (2007 version) • 2014 version: only one RCT included.	"As current clinical evidence is based on only one RCT as well as case series and reports, intravenous lidocaine must be considered a pharmacological agent under investigation in burns care, the effectiveness of which is yet to be determined with further well-designed and conducted clinical trials."
Antiseptics for burns 2017.(89)	Primary outcomes were wound healing and infection.	• "Primary outcomes were not reported or were reported incompletely." • "Most studies reported some data on wound healing with this being presented in different ways." • "Usable data on key outcomes were limited and often unavailable." • "Much of the evidence is of low certainty or very low certainty because of indirectness and imprecision."	"It was often uncertain whether antiseptics were associated with any difference in healing, infections, or other outcomes."

7.4 Impact of the research findings

The primary output from this thesis, is a COS for burn care research. Methodological work on outcome reporting, has under-pinned this work. The impact of both are described below.

7.4.1 Methodological work

7.4.1.1 Impact of the variation in outcome choice across trials in burn research (relating to Thesis Objective 1)

The literature review undertaken in Chapter Two, is the first to demonstrate, using systematic methodology, the scale of heterogeneity of outcome reporting in global burn care research(4). Across 147 RCTs, 955 different, unique outcomes were reported. The high number of outcomes reported across the studies, is supported by reviewers of burn care RCTs, who have consistently shown that there is difficulty in collating evidence to support clinical care, despite increasing numbers of trials(8, 219, 220, 240, 446).

A published literature search, including 50 studies (1966–2003) on short-term and long-term functional outcomes after burn injury, was unable to summarise current knowledge due to the variety of outcomes assessed across trials. The authors stated that "the current state of knowledge on the functional outcome of burns was hard to summarise, due to the wide variety in study designs and outcome assessment methods"(150). A Cochrane review of 30 randomised controlled trials (RCTs) concluded that it was impossible to draw firm conclusions about the effectiveness of burn dressings, as the studies evaluated a variety of clinical end points(8). A 2012 systematic review on scarring, identified 48 articles. Most had methodological limitations including a lack of standardised outcome measures, which was a major barrier to the authors drawing conclusions(33). Between 2012 and 2017, nine Cochrane reviews with direct relevance to the management of patients with burns were published(8, 10, 89, 237-241, 245). None of the reviews could draw firm conclusions about the topic studied, due to varying study design and poor outcome reporting. No Cochrane reviews have been

undertaken in burn injury over the last three years. One reason for this is likely to be the scale of inconsistency in outcome choice across burn trials, demonstrated by the systematic literature review in Chapter Two.

Burn care research is not an outlier in terms of the presence and scale of this variation in outcome reporting. Inconsistency in outcome choice and reporting across trials is supported by the literature in other healthcare areas(227, 621-623). In studies, looking at pediatric eosinophilic esophagitis, sub-arachnoid haemorrhage, Hirschsprung's disease and colorectal cancer surgery, the number of outcomes reported across the included reviews varied from 25 (from 11 studies), 95 (from 35 studies), 285 (from 129 studies) and 766 (from 194 studies) respectively. In the literature review in Chapter Three, the number of reported outcomes across studies in COS development reviews, varied from 12 to 5,776 (median: 82 IQR: 261). The variation in numbers of outcomes reported is striking. Possible reasons for this variation are discussed further below, and in Chapters Two and Three.

The impact of this finding in burn research, is the need for an international agreement on a minimum set of the most important outcomes through the development of a COS. Data on these outcomes, despite the intervention chosen, need to be reported in all trials of burn care.

7.4.1.2 Impact of the need to understand the nature of a unique outcome (relating to Thesis Objective 2)

The variation in outcome choice and numbers of outcomes reported in COS development literature reviews, can be partially explained by the difficulty in determining what makes an outcome unique. In other words, what makes one outcome different to another. Difficulties in understanding the nature of a unique outcome is an important challenge when developing a valid long-list for COS development, and in reporting an accurate magnitude of the variation in outcome reporting across trials. It also impacts the identification of trials reporting the same outcome, and comparison and collation of treatment effects across trials.

In this thesis, the definition of an outcome reported by Chan *et al.* was initially used: "a variable measured at a specific time point to assess the efficacy or harm of an intervention"

(116). The use of this, and other definitions, by COS researchers, explain what a generic outcome is. They do not explain the difference between one unique outcome, and another outcome with a similar meaning. Different researchers define a unique outcome in different ways. The results of the review in Chapter Three illustrate this, by demonstrating a variation in the methods used in COS development studies to combine outcomes with the same meaning. The work in Chapter Three makes the definition of an outcome by Chan difficult to use in COS development literature reviews and in this thesis. The work undertaken suggests that this should be amended to:

"a trial outcome is one that has original meaning and context",

with the word *outcome* as defined by Chan:

"a variable measured to assess the efficacy or harm of an intervention."

The COMET Initiative has identified a lack of clarity in other aspects of COS development: the scope, stakeholder involvement and consensus processes (284, 285, 288, 289). COMET has worked to provide methodological guidance for these COS stages, through the COMET Handbook and Standards for COS development (COS-STAD) (115, 286-291). They have not focussed to a similar degree on the early part of COS development. Verbatim outcome extraction is recommended: "The first step is to group these different definitions together (extracting the wording description verbatim) under the same outcome name" (71, 115). However, a lack of detail exists in the COMET methodology for grouping similar outcomes and variation in the level of granularity used in the grouping process is common(574, 624). Some researchers developing COSs, use a *high-level* of outcome definition (e.g. wound infection), while others report more detailed outcomes in their long-lists (e.g. numbers of bacteria in the wound). A reproducible and quantifiable COS long-list of unique outcomes is, therefore, difficult to produce. This results in inaccurate numbers of unique outcomes reported across trials.

The magnitude of outcome reported heterogeneity (ORH) quoted by COS researchers, will depend upon outcome grouping methodology (definition of a unique outcome) and the inclusion criteria for the systematic review(625). The work in Chapter Three, demonstrates that no true understanding of the scale of outcome reporting variation can be presented in current COS literature reviews. The magnitude of ORH quoted, is an approximation, a

number without scale or context. It will not be possible to quantify this variation in burn care or other research areas, until a definition of a unique outcome and consistent methodology for grouping similar outcomes is agreed.

A further impact, is that there is no guidance on determining when outcomes that appear to be similar, are similar enough to combine and inform a meta-analysis. From the Cochrane handbook: "meta-analysis should only be considered when a group of studies is sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary"(626). Clinical heterogeneity is defined as "differences in participant, treatment, or outcome characteristics or research setting"(627). Clinical heterogeneity can lead to statistical heterogeneity, inaccurate summary effects and findings. The latter can be mitigated by using, for example, pre-planned subgroup analyses. The better option would be to use the whole sample and ensure that outcomes are reported in a standardised and consistent manner.

The inability to determine a magnitude for ORH, will prevent prioritisation of the topics requiring a COS. This is important, as the costs and researcher time for COS development, are significant and should be channelled into those healthcare areas that are most needy in terms of the scale of ORH across trials. The novel work in Chapter Three aimed to resolve this issue by suggesting a working definition for defining a unique outcome and ORH. Draft methodology for the grouping of verbatim-extracted outcomes into unique outcomes is also proposed.

Chapters Four and Five, describe two other types of heterogeneity in outcome reporting. In these examples however, the variation is regarding a single outcome, rather than the choice of different outcomes, across trials.

7.4.1.3 Impact of a variation in the definition of one single outcome across trials (relating to Thesis Objective 3)

Another challenge to outcome reporting, is the variation in the definition of a single outcome across trials. An example is burn wound healing, which was defined in 166 different ways across 147 trials, as reported in Chapter Two(4).

Understanding and standardising terminology for defining an outcome is an important impact of the work undertaken for Chapter Four. Clinicians use one or more indicators to diagnose burn wound infection (BWI), as there is no reference standard for the clinical diagnosis. A clinical indicator was defined in Chapter Four, as a clinical sign, laboratory test or patient-reported symptom. There is no agreement on the type or number of indicators required to define BWI in the research literature. Some authors have used a formal collection of indicators (a clinical consensus diagnostic tool) for reporting. However, these tools are not in standard clinical use and incorporate several practical challenges. The review in Chapter Four showed that more than one third of studies reporting BWI as an outcome, did not report how this outcome was defined, despite reporting data on its presence. In those studies that *did* report a definition for BWI, there was considerable heterogeneity in the numbers and types of indicators used. This issue will impact the assessment of treatment effect sizes across trials and is a novel finding.

This heterogeneity in the definitions of one outcome across trials, in other clinical areas, is common. Bruce *et al*. describes 41 different definitions of surgical site infections in 90 studies which reported this as an outcome(223). The Centres for Disease Control and Prevention criteria are the most widely implemented standard definition for surgical site infection(628). Another frequently used quantitative scoring system for surgical site infection is the ASEPSIS score (Additional treatment, presence of Serous discharge, Erythema, Purulent exudate, Separation of the deep tissues, Isolation of bacteria and duration of Stay)(629). However, despite more clarity in the definition of wound infection in surgical sites compared to burns, the incidence of surgical site infection across trials, still differs according to the definitions used(630).

In COS development, Blencowe *et al*., in a review of outcomes reported in trials of oesophagectomy management, showed that anastomotic leak was assessed in 80 articles. Definitions were reported in 28 of the 80 studies. Of these, only six were similar. In another paper by Bruce *et al*., a total of 56 definitions for anastomotic leak were identified from 97 studies. This was observed, despite publication of a standard definition two years before the beginning of the review(224). Similar findings were noted by Jacxens and Potter in varying and inconsistent definitions for post-surgical complications, including humeral loosening and fat necrosis(317, 631).

The impact of heterogeneity in the definition of one outcome, will limit the validity of evidence synthesis in the size of the effects of interventions on the presence of this outcome. This will hinder the identification of the most effective treatments for patients with a common complication after burn injury. The impact of this work has led to the need to develop a Core Set of indicators (CIS) to pre-specify and standardise reporting in trials in which data for BWI is presented. A systematic review demonstrating the need for such a CIS, undertaken outside of this thesis, has been accepted for publication. The methodology to develop a CIS has been published in protocol form and is discussed in future work below(328).

7.4.1.4 Impact on variation in the timing of assessment of one outcome across trials (relating to Thesis Objective 4)

A final challenge in standardising the reporting of unique outcomes in trials, is the use of the timepoint of outcome assessment, as part of the definition of a unique outcome.

The literature review undertaken in Chapter Two, showed that if the same outcome measured at different timepoints across the 147 RCTs were included as different unique outcomes, then 2,743 outcomes would have been reported, instead of 1,494. If the timing of outcome assessment is included in the definition of a unique outcome in some COS literature reviews and not in others, the magnitude of ORH will not be comparable. There is no consensus in the literature about this issue.

Whether or not to include a timing element to the definition of an outcome is explored in Chapter Three. Chan recommends this by adding a temporal element to the definition of a trial outcome: "a variable measured at a specific time point to assess the efficacy or harm of an intervention" (116). However, the work in Chapter Three suggests that this is not useful when measuring the numbers of unique outcomes at the early stages of COS development. In contrast, at the later stages of COS development, the core outcomes will ultimately need a timepoint for their measurement. The COMET handbook states: "Many COS developers have identified an agreed set of outcomes to measure, leaving the timing of assessment as an issue for trialists to decide subsequently depending on their particular context of use"(115). In terms of timing, an outcome may need to be measured at one, or a small number of timepoint(s),

relevant to the chosen outcome. Examples of timepoints for outcome assessment could include:

- *Immediate*: showing the very short-term impact of the intervention (e.g. blood loss).
- *Intermediate:* weeks to months (e.g. wound healing).
- *Longer-term*: 12 months or longer (e.g. scarring).

These timepoints will relate to the outcome chosen and may relate to national reporting timepoints or times of routine follow-up. As shown by the work undertaken for this thesis, there is a difference, in terms of the use of the timing of outcome assessment, in the definition of a unique outcome, the calculation of ORH across studies and the measurement of a core outcome.

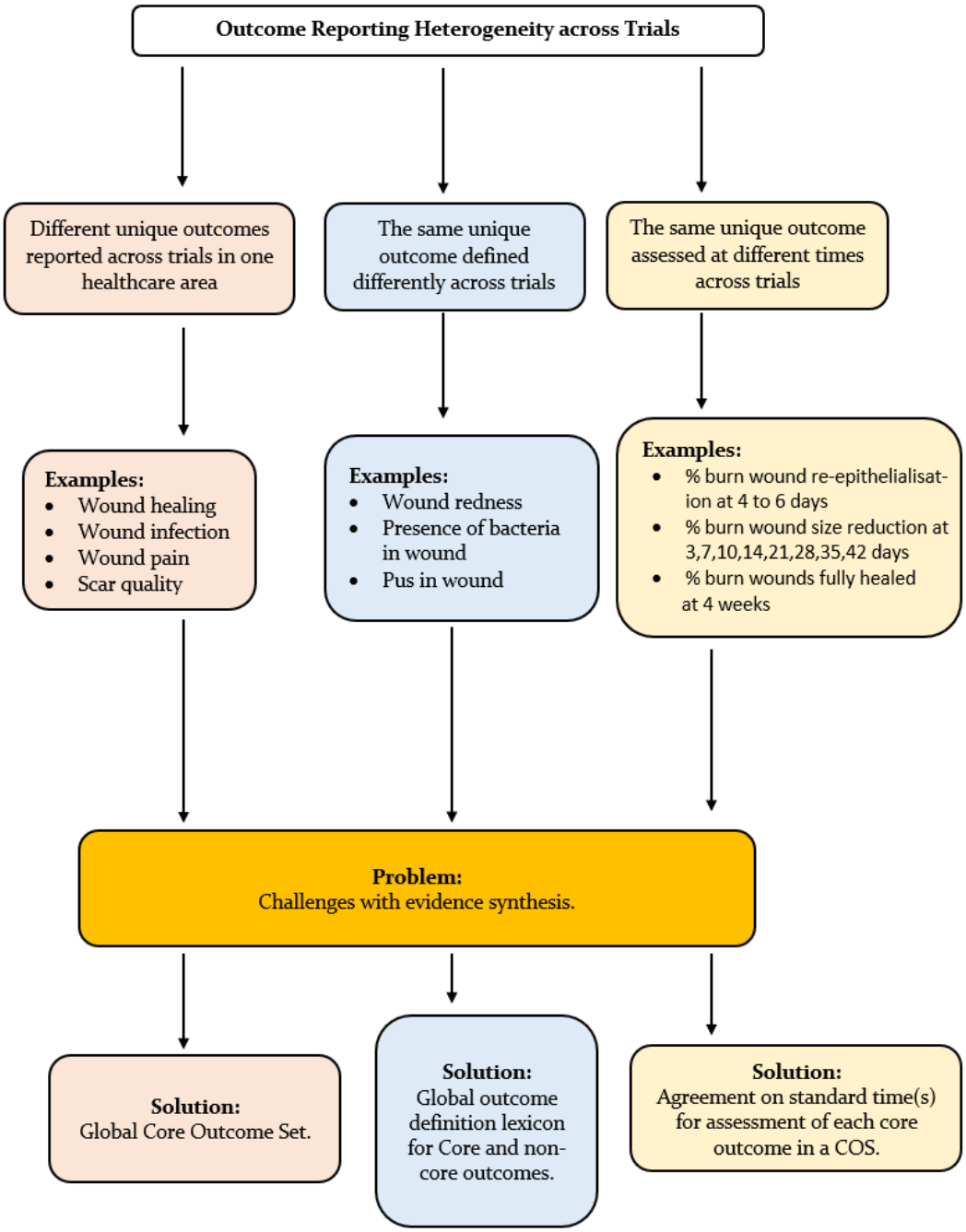
This work demonstrates, that, as well as a need to standardise timing of outcome assessment across trials to improve collation of data, it is also important that that patient relevance is considered in terms of the timing of outcome assessment. Outcomes measured shortly after injury have importance in assessing surgical technique, health care costs or adverse events. Most patients are, however, more interested in the impact of interventions on their life many years later (106, 149).

There is a need for *validated surrogate outcomes* in burn care to ensure patient relevance. The systematic review presented in Chapter Five, explored the impact of timing of outcome assessment on relevance to stakeholders. The review showed that, of the 103 included studies, only 29 (28%) reported outcomes last assessed at more than six months after burn injury. Only one study followed patients for more than three years. This finding has important implications. It is well known that longer-term outcomes are more important to patients. For this reason, whilst it is appropriate that efficacy trials include shorter-term outcomes, there is a need to get longer-term data as well. There are financial and practical constraints to collecting this information. If longer-term data capture collecting cannot be achieved through time or funding constraints, then more research on the formal associations between surrogate and longer-term burn care outcomes needs to be undertaken. If short-term outcomes can be validated as surrogate outcomes and represent a true proxy for longer-term outcomes, then it will be possible to extrapolate data from short-term studies to understand impact on patient longer-term outcomes.

This finding highlights the need for trials in burns care to agree a standardised set of outcome assessment timings for each core and non-core outcome. When debating this, consideration of the trial design and the relevance to patients is important.

This work demonstrates three different challenges to evidence synthesis. This is illustrated pictorially below (Figure 37).

Table 38: Versions of variation in outcome reporting across trials.



7.4.2 The impact of the development of an international Core Outcome Set for burn care research (COSB-i) (Thesis Objective 5)

A potential solution to the methodological challenges in outcome reporting described above, is the use of a minimum set of the most important outcomes to be reported in all trials; a Core Outcome Set (COS)(71, 632).

"The choice of outcome is critical when testing a hypothesis, and significant energy is devoted by investigators to ensure that their prespecified outcomes are appropriate, relevant, and support or disprove the stated hypothesis"(633). "A lack of adequate attention to the choice of outcomes in clinical trials has led to avoidable waste in both the production and reporting of research"(318). These two contrasting quotes from papers on trial outcomes, show that although individual researchers may spend much time in choosing outcomes, little effort has been spent to date on understanding the impact of individual researcher outcome choice. The issue of multiple researchers choosing different outcomes in the same healthcare area impacts negatively on evidence synthesis. The work on developing COSB-i is an important step to resolve this gap in burn care research.

One of the first attempts to standardize outcome reporting in clinical trials was by the World Health Organization in 1981, when Miller and colleagues published recommendations for standardised approaches to recording data for cancer patients(634). His statement "The guidelines (in outcome reporting and patient demographics) given here are meant to be minimal requirements, leaving the investigator free to add any variable he deems necessary". This fits particularly well with the subsequent development of COSs. Since 1992, Outcome Measures in Rheumatology (OMERACT, http://www.omeract.org) has led COS development(111, 160, 253, 254, 635-639). This work is thought to have begun as an international initiative in 1992, in collaboration with the World Health Organization (WHO)(640).

The beneficial impact of standardising outcome reporting has been illustrated by Kirkham and colleagues. The authors reported that uptake of a COS in trials in one healthcare area, supported by the OMERACT Initiative (rheumatoid arthritis), increased from 40% in 1995 to 81% in 2016(641). The OMERACT work, impacts positively on meta-analyses of rheumatoid

arthritis studies. After introduction of the COS, meta-analyses were able to include 87% of trials and 93% of patients(642, 643). In contrast, a review of systematic reviews with meta-analyses of reno-protection (a COS was only agreed in this healthcare area from 2014) showed that from 66 reviews, 609 outcomes had been reported for 20 outcome domains(538). The median proportion of reviews in which these outcomes had been meta-analysed was 8%.

The development of COSs has rapidly grown over recent years with the support of the COMET Initiative(115, 644-648). At the end of 2015, there were 720 COSs listed in the COMET database(286). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) group (http://www.gradeworkinggroup.org) have recognised the need to identify core outcomes. COMET is working with the GRADE working group of the Cochrane Collaboration to achieve three strategic goals:

- To increase the number of COS developed using evidence-based methods.
- To increase their impact on the quality of research by raising awareness and increasing their use.
- To establish methods for the development of COS(649).

This work is supported by the WHO, in developing guideline recommendations(650, 651). The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement also recommends the use of core outcome sets where they exist(652).

In burn care, agreeing a COS by triallists, has been hampered by a multiplicity of outcomes, by a lack of agreement between clinical professionals, by limited patient involvement and by varying national and international practice. The work presented in this thesis, has shown that these challenges in burn care and in other healthcare areas, can be overcome. Patients and international professional collaborators have shown that they understand the concept and problem of ORH in research. They have shown themselves to be keen to overcome the issue, through the development of a COS. This has been demonstrated by the ability to recruit hundreds of HCPs across 77 countries to prioritise outcomes. UK patients have also been vocal and interested in taking part in the research. A set of seven important outcomes for consistent reporting across trials in the burn care research have now been agreed (Table 39).

The most common outcome domains reported in the trials included in the systematic literature review in Chapter Two were:

- Burn wound healing (48% of studies)
- Burn wound infection (43% of studies)
- Complications of treatment (42% of studies).

Death was reported in 21% of studies. These commonly reported outcomes align well with three of the agreed COS outcomes. In contrast, ability to carry out daily tasks and return to school or employment were reported in only one study each. Chapter Five reported that longer-term patient-important outcomes are less commonly reported in burn care RCTs. There may, therefore, be challenges in implementing the whole COS in every trial. This will be the subject of future work.

Table 39: Final COSB-i Core Outcome Set.

1. Death: to include death from any cause and death from the burn.
2. Serious complications: to include sepsis, wound infection, thromboses.
3. Ability to undertake daily tasks: to include walking.
4. Time to heal: to include wound healing, grafted and donor site wound healing.
5. Long term pain and itch.
6. Patient psychology: to include general anxiety and anxiety about the future.
7. Time to return to work/school/previous occupation.

Table 40: Comparison between COS outcome domains.

Outcome domain	**Burn injury (COSB-i)**	**Hip fracture COS(600)**	**Shoulder disorders(635)**	**Cauda Equina COS(653)**	**Bariatric COS(603)**	**Gastroschisis COS(654)**
Short-term						
Complications / adverse events	Serious pre-specified complications		Adverse events	Adverse events	Technical complications of surgery, re-operation, dysphagia	Sepsis, no. of operations, G-I complications Liver disease
Intermediate-term						
Death	All-cause mortality	Mortality	Death		Mortality	Mortality
Weight/growth					Weight	Growth
Healing	Time to wound healing					
Longer-term						
Daily tasks, physical function	Ability to do daily tasks.	Activities of daily living and mobility	Physical function, activity.	Power		
Pain	Long-term pain and itch	Pain	Pain	Pain and sensation		
Psychology	Including anxiety					
Time to return to school / work	Time to return to school or work.					
Health-related quality of life (HRQL)		HRQL		HRQL		HRQL
Other			Global perceived effect	Bladder, bowel and sexual, function.	Micronutrient status, diabetes, cardiovascular risk	Time on TPN

The outcomes chosen for COSB-i are similar, in terms of numbers and topic area, to other recent COSs (Table 40). In the COS for shoulder disorders (OMERACT group), the following outcomes were agreed: pain, physical function/activity, global perceived effect and adverse events including death, emotional wellbeing, sleep and participation (recreation and work)(635). In the COS for hip fracture trials, consensus supported five outcomes: mortality, pain, activities of daily living, mobility, and health-related quality of life (HRQL)(600). In bariatric surgery the following nine COS outcomes were agreed: weight, diabetes status, cardiovascular risk, quality of life (QOL), mortality, technical complications of the specific operation, any re-operation/re-intervention, dysphagia/regurgitation, and micronutrient status(654). Other examples are shown in the table above.

It is interesting to note that several outcomes are important across different COSs. Examples include daily activities and pain. Other core outcomes are healthcare area-specific such as time to wound healing. A number of these outcomes imply a shorter time to assessment than the burn care core outcomes. One reason for this could be that burns commonly happen in childhood and the impact is therefore life-long and that longer-term outcomes are more important to patients. Interestingly, only one of the COSs in Table 40, discussed or reported, the timepoint of assessment of the agreed core outcomes. Allin, when reporting the gastroschisis COS, proposed that: "Appropriate time-points for reporting these core outcomes were also discussed, and it was unanimously agreed that these should be kept as close as possible to standard time-points for reporting surgical and paediatric outcomes. In order to make future meta-analysis more meaningful, studies using the developed COS should report on outcomes using at least one of these time points."

The use of a COS in burn research, will advance the volume and relevance of research able to inform clinical practice and improve patient outcomes. It will also allow improvements in medical indexing, referencing, and identifying relevant clinical trials and reviews though keywords and MESH terms(655). Other impacts will include linking the agreed core outcomes with the national burn database (iBID; international burn injury database; http://www.ibidb.org/) and, through this, to NHS England quality indicators in burn care (the burn injury dashboard https://www.england.nhs.uk/wp-content/uploads/2018/03/specialised-burn-care-adults-metric-definitions-2018-19.pdf). These have the benefit of being endorsed through a robust, transparent, multi-stakeholder process to ensure that they are relevant,

reliable and efficient. They allow for comparisons across providers and can be aggregated across multiple providers to generate data on trends in process and outcomes. The author of this thesis was the first chair of the NHS England commissioning group for burns, and co-developed the first quality dashboard for burns, agreeing process and outcome indicators. Through this, and her role as a burn network lead, she worked closely with the chair of the national burn injury database. This work has begun, out with this thesis, and is discussed further in future research (section 7.5).

7.4.3 Dissemination of the Core Outcome Set for burn care research (COSB-i)

Dissemination of the COSB-i will be improved by the diversity of stake-holders involved in its development(643). The stakeholders include a senior member of the Cochrane wounds group, national and international burn and plastic surgery professional groups, research funders and burns journal editors, all of whom have been involved with the development and have committed to assist in implementing the COS. One way to actively collaborate with such stakeholders is to develop an initiative such as CROWN (CoRe Outcomes in WomeN's health; http://www.crown-initiative.org/)(656). One of the aims of CROWN, is to "Facilitate embedding of core outcome sets in research practice, working closely with researchers, reviewers, funders and guideline makers". In 2014, CROWN had the support of the editors of over 50 journals related to women's health. There are other similar initiatives including OMERACT (described above), the Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN), the Standardised Outcomes in Nephrology-Haemodialysis (SONG-HD) and the Harmonising Outcome Measures for Eczema (HOME) groups(232, 648, 657). This approach would be an important method to take forward and facilitate the dissemination of the COSB-i project.

Global stakeholder involvement in COS development has been limited until recently (642). Increasing stakeholder diversity has been achieved through the COSB-i project by working with more than 750 participants across 77 countries from all World Bank income statuses and all five continents. An additional way to achieve international implementation of the COS, will

be through publication in widely-read and high quality peer-reviewed journals. At the time of writing, publication has been achieved for:

- Two protocols (COSB-i (Chapter Six)) and the BWI definition project (ICon-B) (Chapter Four). These have both been published in *BMJ Open*(229, 328).
- The systematic literature review of clinical outcomes reported in burn care RCTs has been published in B*MJ Open*(293).
- The study to define a unique outcome was published in the *Journal of Clinical Epidemiology*(293).
- The systematic review for Infection Consensus in burn care (ICon-B) has been accepted for publication in the *Burns* journal (March 2020).
- The COSB-i final paper is ready for submission to PLOS Medicine.

The work has been presented at international conferences including COMET (Amsterdam, November 2018), the British and Canadian Burn Associations (Leeds May 2019; Toronto, October 2018), International Clinical Trials Methodology Conference (Brighton, October 2019) and the European Paediatric Burn Association (Cologne, September 2018).

We have formal support for COSB-i development, from the British Burn Association, the American Burn Association, the Australia and New Zealand Burn Association, the African Burn Association, the UK Paediatric Intensive Care Society, the Reconstructive Surgery Trials Network, the Swansea Centre for Global Burn Injury, the Hong Kong Children's burn support group, the Calgary Firefighters' Burn Treatment Centre, the European Scar Academy, the USA Phoenix patient burn society, the Surgical Society of Kenya, and other international burn and plastic organisations. Researchers from Cochrane wounds, the Burns journal editor and a member of the NIHR Health Technology Assessment funding team were also collaborators in this study (please see the collaborator list Appendix M).

Important research to implement the COSB-I, will be undertaken after submission of this thesis. The methodlogical details for this work are described under 'Future work' in section 7.5.1.

7.4.4 Patient and public involvement in COSB-i

Implementation requires support from patients, their carers and charitable burn care organisations. These stakeholders have been involved in all study aspects, including the methodology (and publication of the protocol), the consensus process (the Delphi survey and final consensus meeting) and in the readability and understanding of all written materials. Outcomes were included for discussion at the final consensus meeting if they fulfilled the inclusion criteria by patient *or* HCP prioritisation. Young people and adult burn patients were vocal at the consensus meeting about the need to *exclude* scar contractures but instead to *include* the longer-term outcome of function (ability to do daily tasks) and the exclusion of acute pain, but instead to include the longer-term outcome of neuropathic pain and itch.

A large group of interested patients in the UK has been engaged with, as a result of the COSB-i work. We are planning to increase this patient population, with international patient and carer input. We have already started to develop contacts through international burn support groups (see future work). Global patient input in the future, will be facilitated by (as requested by burn support groups internationally) a translation of the Delphi survey. We have had to date, requests from Hong Kong, Germany and Brazil to do this. As a result of the inclusion of more than 120 UK burn care patients and carers and members other international patient organisations, we now have a global network of patients, carers and charitable burn support groups, who are all willing and keen to be involved in burn research and the implementation of COSB-i. This is a significant achievement for this project.

7.5 Future research

The work presented in this thesis, is the beginning of a potentially much larger programme of research. Ideas for possible future projects are presented in the following sections. The aim of the work presented in this thesis is to increase usable data from burn care trials. Follow-on work will aim to further improve the ability to aggregate data from well-conducted RCTs. In this way, the volume and validity of systematic reviews in burn care and other healthcare research will be improved. The work will have two objectives:

1. *Primary work*: To operationalise and implement COSB-i for burn care research.
2. *Secondary work*: To address the methodological challenges relating to outcome reporting as identified in this thesis.

7.5.1 Primary work: to operationalise and implement COSB-i

For COSB-i to achieve benefits in burn care research, it needs to be operationalised and implemented. While a COS is important in determining what outcomes should be measured consistently across trials in research, it does not describe how these key outcomes should be defined and measured, and at what timepoints they should be measured. Operationalisation will need to agree these important next steps(658). Agreeing the measure for each core outcome is known as developing a Core Measurement Set (CMS); the *how* in COS development. International collaboration and involvement will impact on measures chosen in burn care and will need to be carefully considered through the work described below. If new technology allows outcomes to be measured accurately and consistently, a compromise will need to be made in the use of a different outcome measure in a low-income country. In this case, it would be important to undertake work to ensure comparability between the two methods(659).

The COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments; https://www.cosmin.nl/) have agreed methodology to assist and standardise the process to agree core outcome measures(303, 660). COSMIN aims to improve the selection of outcome measurement instruments, both in research and in clinical practice, by developing methodology and practical tools that select the most suitable outcome measurement tool. The OMERACT filter and OMERACT Handbook provide important methodological help for this process(642, 661, 662). The Harmonising outcome measures for eczema roadmap (HOME) also provides information on processes and decision-making regarding outcome measures(648).

The work to agree a Core Measurement Set (CMS) for COSB-i, will involve SRs, a Delphi survey with patients, carers and HCP input and consensus meetings to determine the final

CMS including outcome definition and timepoint of assessment(111, 648, 663, 664). This will be the most important work to be undertaken after thesis submission.

The work is being planned and will consist of three work packages (WP):

WP One: Systematic reviews:

1. An SR will be required to identify all relevant measurement instruments, and gaps where new tools are needed, for the seven core outcomes in COSB-i. The existing review of clinical outcomes (reported in Chapter Two) will need to be updated and a verbatim list of reported outcome definitions, outcome measures, timing of outcome measurement and methods for measurement, extracted by two researchers. Extracted data will be reviewed for completeness and relevance, prior to progression to WP 2.

2. An SR of the measurement properties of patient-reported outcome measures (PROs) developed for, or validated in, patients with burns, will also be required. An update to the two systematic reviews published in 2015 and 2017 and used in Chapter Six to identify PROs for COSB-i will be undertaken(665). Tables will be constructed to summarise study and instrument characteristics, measurement properties and interpretability(666). The COSMIN checklist will be used to assess the methodological quality of included studies(667). If more than one instrument is considered valid, details of candidate instruments will be included in the Delphi process to determine which tool should be used. If no suitable instrument is identified, this will be acknowledged.

WP 2: Delphi consensus process:

A Delphi process to establish consensus among stakeholders (patients and healthcare professionals) regarding which outcome definitions, measurement instruments and standardised timepoints for assessment should be used. The methodology will be similar to that used to develop the COSB-i detailed in Chapter Six. The need for this work is illustrated by a COS on peri-operative outcomes after hip fracture(668). Despite the short-term nature of this COS, and the involvement of stakeholders in its development, there is still an issue about definitions and measures for several of the outcomes chosen for this COS. There are unresolved discussions as to whether mortality should be assessed at day 30, day 90, in-

hospital, or peri-operatively(633). The group have agreed that until further work is undertaken, they will maintain consistency between the national groups regularly reporting hip fracture outcome data, and report 30 day, 120 day, and one year mortality. This pragmatic methodology is in-line with the work by Allin *et al*., as discussed above(654). There are no agreed reporting times for burn care clinical outcomes. Further work will need to be undertaken to agree these timepoints and link them to practical patient reviews or national benchmarking data timepoints.

Agreeing the timing of outcome assessment needs to ensure engagement, in terms HCPs and patients and carers. There needs to be an understanding and agreement about research undertaken for efficacy trials and the more patient-important effectiveness trials. The former trials are less costly in terms of funding and time. However, the latter will make the greater impact on patient care, as discussed in Chapter Five and in the paper by Tunis and colleagues(318).

WP 3: A final consensus meeting:

This will be undertaken to agree and ratify the decisions on outcome definitions, measurement instruments and standardised timepoints of assessment. It will be held after the conclusion of the Delphi survey.

COSB-i bolt-on projects: It has become clear through the work in this thesis and through other COSs, that the first *generic* COS for burn care may require bolt-ons or supplements. It is possible that we will need to work on a more detailed short-term COS assessing outcomes for efficacy trials. This work has achieved further funding, out with the work for this thesis through the Scar Free Foundation, and will be finalised this year. There may also need to be different COSs for patients with different severity burns and possibly for children and adults. The need for these bolt-on projects remains to be explored.

International patient validation of COSB-i: One limitation of the above work, is that, although there was collaboration with more than 650 HCPs, only patients from the UK were included. We have had requests from countries including China (Hong Kong), Germany and Brazil to translate the COSB-i Delphi survey into the native languages of these countries. We will explore taking this work further.

7.5.2 Secondary work: to address the methodological challenges with outcome reporting

In parallel with the implementation of COSB-i, outcomes research will continue as a second priority. *Outcomes research* can be defined as the study of the end results of healthcare. It can also be described as the effect of treatments on endpoints important to patients and society(669-671). It is therefore crucial that this work takes patients' preferences and values into account. The follow-on methodological work will, with the involvement of patients and other stakeholders, focus on describing the definitions of specific burn care-related outcomes and generic definitions of terms associated with outcomes and COS research.

The objectives of this work are to:

1. *Determine definitions for core and non-core outcomes in burn care research.*

It is important that clarity is achieved, in terms of definitions for core and non-core outcomes in burn care. COSs do not restrict researchers to reporting of core outcomes alone, and researchers will continue to use non-core outcomes. It is important that the most commonly used non-core outcomes, have clarity of meaning, to allow comparison and collation of data. OMERACT have formalised this process, by describing an inner, middle and outer core set of outcomes. These are ranked in terms of importance from inner to outer(635). This still requires standard outcome definitions, and, ultimately, standard measures.

A lexicon of definitions: for the commonly used outcomes in burn care, would be one solution to this issue. This would allow aggregation of data across trials for non-core outcomes. There is precedence for this in paediatric palliative care(672). The authors of this work define a lexicon as: "a shared vocabulary using a stock of terms that carry a particular meaning for those working within the field". They developed, through multidisciplinary consensus processes, international agreement on definitions for 18 terms of importance (http://pediatricpalliative.com/publications).

In Chapter Four, results from an SR showed, that in studies reporting burn wound infection (BWI), the outcome is defined variously, if at all, across studies. There was heterogeneity in

types and numbers of indicators used for the definition. This supports the need for a Core Indicator Set to standardise the reporting of BWI, across trials presenting data for this outcome. This work has been started through the UK-based ICon-B (Infection Consensus in Burn care research) group led by the author of this thesis. The protocol for this work has been published(328). The national work is completed with four chosen indicators. Further work will be undertaken through the collaborative burn research network developed through the work to develop the COSB-i. This will be to validate the findings of the UK work and agree any changes internationally. This would be the first important step, using BWI as an example, towards agreeing definitions of commonly-used outcomes in burn care research internationally.

Agreeing a common language in clinical burn care: consensus on definitions of burn care outcomes, in terms of meaning and context, will create clinical impact as well as standardising research outcome reporting. It will allow clinicians to speak to each other using the same language and promote the development of guidelines, in which there is clarity about the chosen outcomes. For example, it will be easier to standardise the use of antibiotics in burn services, when there is clarity about what is meant by a burn wound infection. There will be the facility to compare different wound dressings, when it is clear what we mean by wound healing and when clinicians have a standardised measure to reflect this. Conversations with patients and carers will be clearer and, ultimately, more accurate comparisons will be possible between healthcare provision across services.

2. Unique outcomes and ORH.

In determining standard definitions for unique, healthcare area-specific outcomes, a clear understanding as to what makes one outcome different to the next, is needed. This was explored in Chapter Three. Work to establish this, needs to be continued internationally with collaboration across researchers with an interest in outcomes research, and through COMET. The impact will affect COS long-lists, the magnitude of ORH (as defined in Chapter Three), prioritising healthcare areas for COS requirement and formal searching for trials reporting specific outcomes. There is also a need to standardise other terms used in outcome research. These include, as discussed in Chapter Four, clinical indicators, clinical consensus diagnostic

tools, outcomes, outcome domains, outcome definitions and outcome measures. Despite the comprehensive work by COMET, there is still confusion regarding these terms in the literature(673). Work has been undertaken in terms of defining and classifying outcome domains through the efforts of Williamson and colleagues(115, 674). Less work has been undertaken in studying specific outcome definitions and differentiating between these and outcome measures. An example is wound healing (outcome or outcome domain), percentage wound healed in two weeks (outcome definition) and measurement of unhealed wound area using tracing and computer software (outcome measure).

Clarifying what makes one outcome different to another will allow an understanding of ORH. Qualitative reporting of ORH across trials is reported in COS-development reviews. However, authors often put a number to this, implying that they can accurately report the scale of the variation. The magnitude of ORH hinges on agreeing the granularity required when defining an outcome. If COS developers can determine how many verbatim outcomes can be grouped under one term, they can then report ORH quantitatively, and compare these results with other COS developers. This would mean that researchers and research funders could prioritise healthcare areas for COS development. Future work will take this discussion further with COS researchers, COMET and other international interested parties.

Through the specific and under-pinning methodological work described above, limiting research waste in burn care and other healthcare research will increase the synthesised evidence base, allowing more clinical decisions to be evidence-based.

7.6 Recommendations

Through the research in this thesis, the following recommendations for future work can be made:

1. *To operationalise and implement the COSB-i*, through agreeing outcome definitions, measures and timepoint(s) of assessment for the seven chosen outcomes.
    a. Agree whether there is a need for a more detailed short and longer-term COS for burn care research as a bolt-on project.

2. *Agree international definitions for commonly reported outcomes in burn care research* (core and non-core), using burn wound infection as an example (lexicon of definitions).
3. *Agree a definition for a generic unique outcome,* to allow the quantification of outcome variation across trials and to determine the healthcare areas, where the scale of ORH makes it a priority for COS development.

Chapter 8 Conclusions

This thesis has explored the reasons that limit researchers' ability to synthesise RCT data to support clinical decision-making in burn care. It has answered the thesis research question:

It is possible to increase the provision of data from burn care RCTs, that can be synthesised into evidence to answer clinical questions.

Four methodological challenges in aggregating outcome data from trials have been highlighted in this thesis. These include the variation in choice and definition of outcomes, the timing of outcome assessment and agreeing what makes one outcome different to another. One solution to these methodological challenges is the development of a COS.

Development of the international COS in burn care research (COSB-i), has utilised shared decision-making across more than 750 HCPs and patients across 77 countries of varying income status. Involvement of patients and multidisciplinary HCP stakeholders, including clinicians, researchers, research funders, research commissioners and journal editors, is likely to optimise implementation and use of the COS in future RCTs. The first global COS for burn care research, reflects the priorities of patients and burn care professionals.

The COSB-i project has led to agreement on seven core outcomes to be reported in all burn care trials internationally. These include death, serious complications, ability to do daily tasks, time to heal, neuropathic pain and itch, patient psychology and time to return to work, school or previous occupation. It is now necessary to determine definitions, measures and timepoints of assessment for each core outcome and to validate the COS with international patients.

The conclusion of the work in this thesis, is that, knowledge of challenges in outcome choice and reporting in burn care research, support the development of COSB-i. It is hoped that the first COS for patients with burn injuries will, through standardised outcome reporting, improve evidence synthesis. This should increase the evidence base for burn care, resolve persisting uncertainty over clinical management and ultimately improve the recovery of more than 11 million patients with burns globally. Future research is now needed to implement the COSB-i.

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Appendix A Publications

A.1 First author papers published in peer-reviewed journals:

- Young A, Brookes S, Rumsey N, Blazeby J. Agreement on what to measure in randomised controlled trials in burn care: study protocol for the development of a core outcome set. BMJ Open. 2017 Jun 1;7(6):e017267.
- Young AE, Davies A, Bland S, Brookes S, Blazeby JM. Systematic review of clinical outcome reporting in randomised controlled trials of burn care. BMJ Open. 2019 Feb 1;9(2):e025135.
- Young AE, Brookes ST, Avery KN, Davies A, Metcalfe C, Blazeby JM. A systematic review of core outcome set development studies demonstrates difficulties in defining unique outcomes. Journal of clinical epidemiology. 2019 Nov 1;115:14-24.
- Young A, Reeves BC, Cheng HY, Wasiak J, Muir D, Davies A, Blazeby J. Risk of bias and reporting completeness of randomised controlled trials in burn care: protocol for a systematic review. BMJ Open. 2019 Dec 1;9(12). Note: this paper is directly related to the work in this thesis but is not reported here and relates to an on-going project.

A.2 Senior author paper published in a peer-review journal with work led by the thesis author:

- Davies A, Teare L, Falder S, Coy K, Dumville JC, Collins D, Moore L, Dheansa B, Jenkins AT, Booth S, Agha R, Mamta Shah, Karen Marlow, Amber Young. Protocol for

the development of a core indicator set for reporting burn wound infection in trials: ICon-B study. BMJ Open. 2019 May 1;9(5):e026056.

A.3 Paper In Press in a peer-reviewed journal:

- A systematic review of intervention studies demonstrates the need to develop a minimum set of indicators to report the presence of burn wound infection. Accepted by Burns in March 2020. In press.

A.4 Paper submitted to a peer-reviewed journal:

- Amber Young, Fatima Yaqub, Chris Metcalfe, Sarvnaz Sepehripour, Jane Blazeby. Clinical trials in burns care primarily focus on short-term outcomes of uncertain longer-term patient benefit: a systematic review. Submitted to the Journal of Clinical Epidemiology December 2019. Not peer-reviewed. Returned with the suggestion to submit to a specialist burns journal. This will occur April 2020.

Appendix B Studies included in the systematic review in Chapter Two.

Trial title	First Author	Year of publication
1. Comparison of silver nylon wound dressing and silver sulfadiazine in partial burn wound therapy. (377)	Abedini F	2012
2. Healing of burn wounds by topical treatment: A randomized controlled comparison between silver sulfadiazine and nano-crystalline silver. (675)	Adhya A	2015
3. An analysis of deep vein thrombosis in burn patients (Part 1): Comparison of D-dimer and Doppler ultrasound as screening tools. (676)	Ahuja R	2016
4. An analysis of deep vein thrombosis in burn patients (part II): A randomized and controlled study of thrombo-prophylaxis with low molecular weight heparin. (677)	Ahuja R	2016
5. A four arm, double blind, randomized and placebo-controlled study of pregabalin in the management of post-burn pruritus. (678)	Ahuja R	2012
6. Propranolol attenuates haemorrhage and accelerates wound healing in severely burned adults. (679)	Ali A	2015
7. Aerobic exercise training in modulation of aerobic physical fitness and balance of burned patients. (680)	Ali Z	2015
8. Silk sericin ameliorates wound healing and its clinical efficacy in burn wounds. (380)	Aramwit P	2013
9. A Randomized Controlled Trial Comparing Endoscopic-Assisted Versus Open Neck Tissue Expander Placement in Reconstruction of Post-Burn Facial Scar Deformities. (681)	As'adi K	2016
10. A prospective, randomised study of a novel transforming methacrylate dressing compared with a silver-containing sodium carboxymethylcellulose dressing on partial-thickness skin graft donor sites in burn patients. (682)	Assadian O	2013
11. Multimodal quantitative analysis of early pulsed-dye laser treatment of scars at a pediatric burn hospital. (683)	Bailey J	2012
12. Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial. (684)	Bechir M	2013
13. A prospective randomized trial comparing silver sulfadiazine cream with a water-soluble poly-antimicrobial gel in partial-thickness burn wounds. (685)	Black J	2015
14. Clinical effectiveness of dermal substitution in burns by topical negative pressure: a multi-center randomized controlled trial. (686)	Bloeman M	2012
15. Effect of subcutaneous epinephrine/saline/local anesthetic versus saline-only injection on split-thickness skin graft donor site perfusion, healing, and pain. (687)	Blome Eberwein S	2013
16. A randomized controlled study of silver-based burns dressing in a pediatric emergency department. (345)	Brown M	2016
17. Cost-Effectiveness of a Nonpharmacological Intervention in Pediatric Burn Care. (688)	Brown N	2015
18. Play and heal: randomized controlled trial of DittoTM intervention efficacy on improving re-epithelialization in pediatric burns. (689)	Brown N	2013
19. The implementation and evaluation of therapeutic touch in burn patients: an instructive experience of conducting a scientific study within a non-academic nursing setting.	Busch M	2012
20. Prophylactic sequential bronchoscopy after inhalation injury: results from a three-year prospective randomized trial. (690)	Carr J	2013
21. Burns injury in children: is antibiotic prophylaxis recommended? (382)	Chahed J	2014

22.	A randomized controlled trial to compare the effects of liquid versus powdered recombinant human growth hormone in treating patients with severe burns. (691)	Chen G	2016
23.	The Effect of Continuous Sedation Therapy on Immunomodulation, Plasma Levels of Antioxidants, and Indicators of Tissue Repair in Post-Burn Sepsis Patients. (692)	Chen Li	2015
24.	Application of acellular dermal xenografts in full-thickness skin burns. (693)	Chen X	2013
25.	Effectiveness of medical hypnosis for pain reduction and faster wound healing in pediatric acute burn injury: study protocol for a randomized controlled trial. (694)	Chester S	2016
26.	Safety of recombinant human granulocyte-macrophage colony-stimulating factor in healing pediatric severe burns. (695)	Chi Y	2015
27.	Comparison of three cooling methods for burn patients: A randomized clinical trial. (696)	Cho Y	2016
28.	The effect of burn rehabilitation massage therapy on hypertrophic scar after burn: a randomized controlled trial. (697)	Cho YS	2014
29.	Effect of extracorporeal shock wave therapy on scar pain in burn patients: A prospective, randomized, single-blind, placebo-controlled study. (698)	Cho YS	2016
30.	Characterization of early thermal burns and the effects of hyperbaric oxygen treatment: a pilot study. (383)	Chong SJ	2013
31.	Effects of different duration exercise programs in children with severe burns. (508)	Clayton RP	2016
32.	The effect of healing touch on sleep patterns of pediatric burn patients. (699)	Cone L	2014
33.	Effect of N-acetylcysteine treatment on oxidative stress and inflammation after severe burn. (700)	Csontos C	2012
34.	The effects of intravenous glutamine supplementation in severely burned, multiple traumatized patients. (701)	Cucerean-Badica	2013
35.	A comparison between occlusive and exposure dressing in the management of burn wound	Dallal MMS	2016
36.	Evaluation of the "Early" Use of Albumin in Children with Extensive Burns: A Randomized Controlled Trial	Dittrich MH	2016
37.	Interim pressure garment therapy (4-6 mmHg) and its effect on donor site healing in burn patients: study protocol for a randomised controlled trial. (702)	Donovan M	2016
38.	Effect of whole body vibration on leg muscle strength after healed burns: a randomized controlled trial. (703)	Ebid AA	2012
39.	Effect of isokinetic training on muscle strength, size and gait after healed pediatric burn: a randomized controlled study. (704)	Ebid AA	2014
40.	Effect of 12-week isokinetic training on muscle strength in adult with healed thermal burn. (705)	Ebid AA	2012
41.	Effects of whole-body vibration exercise on bone mineral content and density in thermally injured children. (706)	Edionwe J	2016
42.	Efficacy of platelet rich plasma application in comparison to conventional dressing therapy in partial thickness burn wound. (707)	Ehmer al Ibran	2014
43.	Effect of probiotic administration in the therapy of pediatric thermal burn. (708)	El-ghazely MH	2016
44.	Heparin/N-acetylcysteine: an adjuvant in the management of burn inhalation injury: a study of different doses. (709)	Elsharnouby NM	2014
45.	The effect of levamisole on mortality rate among patients with severe burn injuries. (710)	Fatemi MJ	2013
46.	Impact of stress-induced diabetes on outcomes in severely burned children. (370)	Finnerty CC	2014
47.	Outcome of Burns Treated With Autologous Cultured Proliferating Epidermal Cells: A Prospective Randomized Multi-center Intra-patient Comparative Trial. (711)	Gardien KL	2014
48.	Randomized controlled trial of three burns dressings for partial thickness burns in children. (712)	Gee Kee EL	2015
49.	Topical petrolatum gel alone versus topical silver sulfadiazine with standard gauze dressings for the treatment of superficial partial thickness burns in adults: a randomized controlled trial. (713)	Genuino GAS	2014
50.	HEPBURN - investigating the efficacy and safety of nebulized heparin versus placebo in burn patients with inhalation trauma: study protocol for a multi-center randomized controlled trial. (714)	Glas GJ	2014
51.	A multi-center study on the regenerative effects of erythropoietin in burn and scalding injuries: study protocol for a randomized controlled trial. (715)	Gunter CI	2013
52.	Early rehabilitative exercise training in the recovery from pediatric burn. (716)	Hardee JP	2014
53.	Quality of pediatric second-degree burn wound scars following the application of basic fibroblast growth factor: results of a randomized, controlled pilot study. (717)	Hayashida K	2012
54.	Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. (718)	Herndon DN	2012

55.	Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. (719)	Herndon DN	2016
56.	Cost-Effectiveness of Laser Doppler Imaging in Burn Care in The Netherlands: A Randomized Controlled Trial. (720)	Hop MJ	2016
57.	Effect of music intervention on burn patients' pain and anxiety during dressing changes. (721)	Hsu K	2016
58.	Low dose of glucocorticoid decreases the incidence of complications in severely burned patients by attenuating systemic inflammation. (722)	Huang G	2015
59.	An assessment of early Child Life Therapy pain and anxiety management: A prospective randomised controlled trial. (723)	Hyland E	2015
60.	Prospective, randomised controlled trial comparing Versajet™ hydrosurgery and conventional debridement of partial thickness paediatric burns. (724)	Hyland EJ	2015
61.	Construction of skin graft seams in burn patients: A prospective randomized double-blinded study. (725)	Isaac K	2016
62.	Multi-axis shoulder abduction splint in acute burn rehabilitation: a randomized controlled pilot trial. (726)	Jang KU	2015
63.	Glucose control in severely burned patients using metformin: An interim safety and efficacy analysis of a phase II randomized controlled trial. (363)	Jeschke MG	2016
64.	The effect of ketoconazole on post-burn inflammation, hypermetabolism and clinical outcomes. (337)	Jeschke MG	2012
65.	The Effect of Distraction Technique on the Pain of Dressing Change among 3-6 Year-old Children. (727)	Kaheni S	2016
66.	Prospective randomize-controlled comparison between sillCone plus herbal extract gel versus Aloe Vera gel for burn scar prophylaxis. (728)	Keorochana K	2015
67.	Effects of Enteral Glutamine Supplementation on Reduction of Infection in Adult Patients with Severe Burns. (338)	Kibor DK	2014
68.	Effects of sustained release growth hormone treatment during the rehabilitation of adult severe burn survivors. (729)	Kim J	2016
69.	Virtual reality for acute pain reduction in adolescents undergoing burn wound care: a prospective randomized controlled trial. (730)	Kipping B	2012
70.	The effects of splinting on shoulder function in adult burns. (731)	Kolmus AM	2012
71.	Prospective study on burns treated with Integra, a cellulose sponge and split thickness skin graft: comparative clinical and histological study--randomized controlled trial. (732)	Lagus H	2013
72.	Evaluation of an oxygen-diffusion dressing for accelerated healing of donor-site wounds. (733)	Lairet KF	2014
73.	Anti-inflammatory effect of taurine in burned patients. (734)	Lak S	2015
74.	A randomized controlled pilot study comparing aqueous cream with a beeswax and herbal oil cream in the provision of relief from postburn pruritis. (735)	Lewis PA	2012
75.	Human acellular dermal matrix allograft: A randomized, controlled human trial for the long-term evaluation of patients with extensive burns. (736)	Li X	2015
76.	Selective digestive decontamination attenuates organ dysfunction in critically ill burn patients. (737)	Lopez-Rodriguez L	2015
77.	Results of a prospective randomized controlled trial of early ambulation for patients with lower extremity autografts. (738)	Lorello DJ	2014
78.	Moist occlusive dressing (Aquacel(Â®) Ag) versus moist open dressing (MEBO(Â®)) in the management of partial-thickness facial burns: a comparative study in Ain Shams University. (739)	Mabrouk A	2012
79.	Enhancement of burn wounds healing by platelet dressing. (740)	Maghsoudi H	2013
80.	Effect of immune-enhancing diets on the outcomes of patients after major burns. (741)	Mahmoud WH	2014
81.	Silver-coated nylon dressing plus active DC microcurrent for healing of autogenous skin donor sites. (742)	Malin EW	2013
82.	The application of platelet-rich plasma in the treatment of deep dermal burns: A randomized, double-blind, intra-patient-controlled study. (743)	Marck RE	2016
83.	Clinical safety and efficacy of probiotic administration following burn injury. (391)	Mayes T	2015
84.	Three donor site dressings in pediatric split-thickness skin grafts: study protocol for a randomised controlled trial. (744)	McBride CA	2015
85.	Evaluation of who oral rehydration solution (ORS) and salt tablets in resuscitating adult patients with burns covering more than 15% of total body surface area (TBSA). (745)	Moghazy AM	2016

86.	Efficacy and adverse events of early high-frequency oscillatory ventilation in adult burn patients with acute respiratory distress syndrome. (746)	Mohamed SA	2016
87.	Effect of amniotic membrane on graft take in extremity burns. (747)	Mohammadi AA	2013
88.	Comparison of the application of allogeneic fibroblast and autologous mesh grafting with conventional method in the treatment of third-degree burns. (748)	Moravvej H	2016
89.	Effect of low-intensity laser on the neuropathic common peroneal nerve post burn. (749)	Mowafy ZM	2016
90.	Clinical Efficacy Test of Polyester Containing Herbal Extract Dressings in Burn Wound Healing. (750)	Muangman P	2016
91.	Effect of oral olive oil on healing of 10-20% total body surface area burn wounds in hospitalized patients. (353)	Najmi M	2015
92.	Double-blind, randomized, pilot study assessing the resolution of postburn pruritus. (751)	Nedelec B	2012
93.	Comparing outcomes of sheet grafting with 1:1 mesh grafting in patients with thermal burns: a randomized trial. (752)	Nikkah D	2014
94.	Comparison of hydrogel produced by radiation as applied at the research center (Yazd branch) with maxgel and routine dressing for second-degree burn repair in Yazd burn hospital. (753)	Noorbala MT	2016
95.	Effectiveness of cerium nitrate-silver sulfadiazine in the treatment of facial burns: a multi-center, randomized, controlled trial. (754)	Oen IMMH	2012
96.	Influences of purposeful activity versus rote exercise on improving pain and hand function in pediatric burn. (755)	Omar MTA	2012
97.	Botulinum toxin and burn induces contracture. (756)	Omranifard M	2016
98.	Results of a pilot multi-center genotype-based randomized placebo-controlled trial of propranolol to reduce pain after major thermal burn injury. (757)	Orrey DC	2015
99.	A proper enteral nutrition support improves sequential organ failure score and decreases length of stay in hospital in burned patients. (758)	Ostradrahimi A	2016
100.	Topical silver sulfadiazine vs collagenase ointment for the treatment of partial thickness burns in children: a prospective randomized trial. (354)	Ostlie DJ	2012
101.	Prospective randomized phase II Trial of accelerated re-epithelialization of superficial second-degree burn wounds using extracorporeal shock wave therapy. (759)	Ottomann C	2012
102.	A randomized and controlled multi-center prospective study of the Chinese medicinal compound Fufang Xuelian Burn Ointment for the treatment of superficial and deep second-degree burn wounds. (760)	Ouyang J	2014
103.	Prospective comparison of packed red blood cell-to-fresh frozen plasma transfusion ratio of 4: 1 versus 1: 1 during acute massive burn excision. (761)	Palmieri T	2012
104.	A herbal cream consisting of Aloe Vera, Lavandulastoechas, and Pelargonium roseum as an alternative for silver sulfadiazine in burn management. (355)	Panahi Y	2012
105.	Interactive gaming consoles reduced pain during acute minor burn rehabilitation: A randomized, pilot trial. (762)	Parker M	2016
106.	A Pilot Prospective Randomized Control Trial Comparing Exercises Using Videogame Therapy to Standard Physical Therapy: 6 Months Follow-Up. (763)	Parry I	2015
107.	An open, prospective, randomized pilot investigation evaluating pain with the use of a soft sillCone wound contact layer vs bridal veil and staples on split thickness skin grafts as a primary dressing. (764)	Patton ML	2013
108.	Effects of community-based exercise in children with severe burns: A randomized trial. (765)	Pena R	2015
109.	Effects of propranolol and exercise training in children with severe burns. (766)	Porro LJ	2013
110.	Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. (767)	Porro LJ	2012
111.	Clinical effectiveness, quality of life and cost-effectiveness of Flaminal versus Flamazine in the treatment of partial thickness burns: study protocol for a randomized controlled trial. (768)	Rashaan ZM	2016
112.	Five-Year Outcomes after Long-Term Oxandrolone Administration in Severely Burned Children: A Randomized Clinical Trial. (769)	Reeves PT	2016
113.	A novel rapid and selective enzymatic debridement agent for burn wound management: a multi-center RCT. (770)	Rosenburg L	2013
114.	Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. (771)	Rousseau AF	2014

115.	Evaluation of Amniotic Membrane Effectiveness in Skin Graft Donor Site Dressing in Burn Patients. (772)	Salehi SH	2015
116.	A feasibility study assessing cortical plasticity in chronic neuropathic pain following burn injury. (773)	Santos Portilla A	2013
117.	Perioperative treatment algorithm for bleeding burn patients reduces allogeneic blood product requirements. (774)	Schaden E	2012
118.	A prospective clinical trial comparing Biobrane, Dressilk, and PolyMem dressings on partial-thickness skin graft donor sites. (775)	Schulz A	2016
119.	Effectiveness of Aloe Vera gel compared with 1% silver sulphadiazine cream as burn wound dressing in second degree burns. (266)	Shahzad M	2013
120.	The comparison between modified kligman formulation versus kligman formulation and intense pulsed light in the treatment of the post-burn hyperpigmentation. (776)	Siadat A	2016
121.	A comparative study of spray keratinocytes and autologous meshed split-thickness skin graft in the treatment of acute burn injuries. (777)	Sood R	2015
122.	Long-Term Administration of Oxandrolone Improves Lung Function in Pediatric Burned Patients. (778)	Sousse LE	2016
123.	An open, parallel, randomized, comparative, multicenter investigation evaluating the efficacy and tolerability of Mepilex Ag versus silver sulfadiazine in the treatment of deep partial-thickness burn injuries. (779)	Tang H	2015
124.	Non-ablative fractional laser provides long-term improvement of mature burn scars - A randomized controlled trial with histological assessment. (780)	Taudorf EH	2015
125.	Fluid therapy lidco controlled trial - Optimization of volume resuscitation of extensively burned patients through noninvasive continuous real-time hemodynamic monitoring LiDCO. (781)	Tokarik M	2013
126.	Burn donor site dressing using melolin and flexigrid versus conventional dressing. (782)	Vejdan SA	2015
127.	Laser Doppler imaging as a tool in the burn wound treatment protocol. (783)	Venclauskiene A	2014
128.	Low-dose hydrocortisone reduces norepinephrine duration in severe burn patients: a randomized clinical trial. (784)	Venet F	2015
129.	A Comparative Study of Paediatric Thermal Burns Treated with Topical Heparin and Without Heparin. (785)	Venkatachalapathy TS	2014
130.	Aquacel() Ag dressing versus ActicoatTM dressing in partial thickness burns: a prospective, randomized, controlled study in 100 patients. Part 1: burn wound healing. (249)	Verbelen J	2013
131.	Skin stretching for primary closure of acute burn wounds. (786)	Verhaegen PDHM	2014
132.	Xbox KinectTM based rehabilitation as a feasible adjunct for minor upper limb burns rehabilitation: A pilot RCT. (787)	Voon K	2016
133.	Local application of low-dose insulin in improving wound healing after deep burn surgery. (357)	Wang C	2016
134.	Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period. (788)	Wibbenmeyer L	2014
135.	A prospective randomised clinical pilot study to compare the effectiveness of Biobrane (R) synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. (789)	Wood F	2012
136.	Effective symptomatic treatment for severe and intractable pruritus associated with severe burn-induced hypertrophic scars: A prospective, multicenter, controlled trial. (790)	Wu J	2016
137.	Propranolol reduces cardiac index but does not adversely affect peripheral perfusion in severely burned children. (791)	Wurzer P	2016
138.	A new method of microskin autografting with a Vaseline-based moisture dressing on granulation tissue. (792)	Xiao H	2014
139.	Recombinant human granulocyte-macrophage colony-stimulating factor hydrogel promotes healing of deep partial thickness burn wounds. (406)	Yan H	2012
140.	A comparative study of the dressings silver sulfadiazine and Aquacel Ag in the management of superficial partial-thickness burns. (793)	Yarboro D	2013
141.	A clinical trial designed to evaluate the safety and effectiveness of a thermosensitive hydrogel-type cultured epidermal allograft for deep second-degree burns. (794)	Yim H	2014
142.	Study of the use of recombinant human granulocyte-macrophage colony-stimulating factor hydrogel externally to treat residual wounds of extensive deep partial-thickness burn. (402)	Yuan L	2015
143.	Effect of Olea ointment and Acetate Mafenide on burn wounds - A randomized clinical trial. (795)	Zahmatkesh M	2015

144.	Effects of puerarin on the inflammatory role of burn-related procedural pain mediated by P2X7 receptors. (796)	Zhang J	2013
145.	Effects of early enteral nutrition on the gastrointestinal motility and intestinal mucosal barrier of patients with burn-induced invasive fungal infection. (797)	Zhang Y	2016
146.	Maximizing the safety of glycerol preserved human amniotic membrane as a biological dressing. (798)	Zidan SM	2015
147.	Therapeutic Value of Blood Purification and Prognostic Utilities of Early Serum Procalcitonin, C Reactive Protein, and Brain Natriuretic Peptide Levels in Severely Burned Patients with Sepsis. (799)	Zu H	2015

Appendix C Studies included in the systematic review in Chapter Three.

Trial title	First Author	Year of publication
148. Defining clinically important peri-operative blood loss and transfusion for the StEP collaborative: protocol for a scoping review(800)	Bartoszko J	2017
149. Reporting Clinical Outcomes of Breast Reconstruction: A Systematic Review(317)	Potter S	2010
150. Assessment of Cosmesis After Breast Reconstruction Surgery: a Systematic Review (801)	Potter S	2011
151. Development of a core outcome set for research and audit studies in reconstructive breast surgery(589)	Potter S	2015
152. Systematic review and critical appraisal of the impact of acellular dermal matrix use on the outcomes of implant-based breast reconstruction(802)	Potter S	2015
153. 2017 EULAR recommendations for a core data set to support observational research and clinical care in rheumatoid arthritis(803)	Radner H	2018
154. A core outcome set for adult cardiac surgery trials: A consensus study(804)	Benstoem C	2017
155. Evaluating Outcomes Used in Cardiothoracic Surgery Interventional Research: A Systematic Review of Reviews to Develop a Core Outcome Set(805)	Benstoem C	2015
156. A Core Outcome Set for Children With Feeding Tubes and Neurologic Impairment: A Systematic Review(806)	Kapadia M	2016
157. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review(807)	Johnston B	2010
158. A core outcome set for clinical trials in acute diarrhoea(808)	Karas J	2015
159. Choice of primary outcomes in randomised trials and SRs evaluating interventions for preterm birth prevention: a systematic review(809)	Meher S	2014
160. A Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth.(810)	Van't Hooft J	2016
161. Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer(811)	Wilt T	2008
162. A COS for localised prostate cancer effectiveness trials: protocol for a SR of the literature and stakeholder involvement through interviews and a delphi survey (812)	Maclennan S	2015
163. A COS for localised prostate cancer effectiveness trials(813)	Maclennan S	2017
164. Symptomatic and QoL outcomes after treatment for clinically localised prostate cancer; a SR(814)	Whiting P	2016
165. Effectiveness of prepregnancy care for women with pregestational diabetes mellitus: protocol for a systematic review of the literature and identification of a core outcomes set using a Delphi survey(815)	Egan A	2015
166. A core outcome set for studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes(816)	Egan A	2017
167. A Core Outcome Set for the Benefits and Adverse Events of Bariatric and Metabolic Surgery: The BARIACT Project.(603)	Coulman K	2016
168. Patient-reported outcomes in bariatric surgery: a systematic review of standards of reporting(817)	Coulman K	2013
169. Outcome reporting in bariatric surgery: an in-depth analysis to inform the development of a core outcome set, the BARIACT Study(230)	Hopkins J	2015
170. A core outcome set for clinical trials of interventions for young adults with type 1 diabetes: an international, multi-perspective Delphi consensus study.(818)	Byrne M	2017

171.	SR of interventions to improve outcomes for young adults with type 1 diabetes(819)	O'Hara M	2017
172.	A scoping review of outcomes related to orthodontic treatment measured in cleft lip and palate.(820)	Tsichlaki A	2017
173.	A Systematic Review of Outcome Measures Employed in Aneurysmal Subarachnoid Hemorrhage (aSAH) Clinical Research(262)	Andersen C	2018
174.	A systematic review of outcome measures used in clinical trials of treatment interventions following traumatic dental injuries(821)	Sharif M	2015
175.	A systematic review of outcomes in postoperative pain studies in paediatric and adolescent patients: towards development of a core outcome set.(272)	Ross A	2018
176.	A systematic review of outcomes reported in small bowel obstruction research.(822)	Mellor K	2018
177.	Are dental researchers asking patient-important questions? A scoping review(421)	Fleming P	2016
178.	Assessing outcomes of alcohol-related brain damage (ARBD): What should we be measuring?(823)	Horton L	2015
179.	Cardioplegia in paediatric cardiac surgery: a systematic review of randomized controlled trials(824)	Drury N	2018
180.	Choice of primary outcomes evaluating treatment for heavy menstrual bleeding: a systematic review(825)	Herman M	2016
181.	Developing a core outcome set for chronic rhinosinusitis: a systematic review of outcomes utilised in the current literature(826)	Soni-jaiswal A	2017
182.	CHronic Rhinosinusitis Outcome MEasures (CHROME) – developing a core outcome set for trials of interventions in chronic rhinosinusitis(827)	Hopkins C	2018
183.	Clinical endpoints in trials of chemoradiation for patients with anal cancer.(828)	Glynne-Jones R	2017
184.	Completeness of main outcomes across randomized trials in entire discipline: survey of chronic lung disease outcomes in preterm infants(549)	Ioannidis J	2015
185.	Completeness of Outcomes Description Reported in Low Back Pain Rehabilitation Interventions: A Survey of 185 Randomized Trials(829)	Gianola S	2016
186.	Complications associated with arthroscopic rotator cuff tear repair: definition of a core event set by Delphi consensus process(830)	Audige L	2016
187.	Complications Following Arthroscopic Rotator Cuff Tear Repair A Systematic Review of Terms and Definitions With Focus on Shoulder Stiffness(831)	Audige L	2015
188.	Variation of clinical outcomes used in glaucoma randomised controlled trials: a systematic review(832)	Ismail R	2014
189.	Outcome measures in glaucoma: SR of cochrane reviews and protocols(673)	Ismail R	2015
190.	Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors. An International Modified Delphi Consensus Study(833)	Needham D	2017
191.	Outcome measurement in ICU survivorship research from 1970-2013: a scoping review of 425 publications(834)	Turnbull A	2016
192.	Core outcome domains in incontinence-associated dermatitis research(835)	Van Den Bussche K	2018
193.	CONSIDER – Core Outcome Set in IAD Research: study protocol for establishing a core set of outcomes and measurements in incontinence-associated dermatitis research(836)	Van Den Bussche K	2017
194.	Core outcome set for gene therapy in haemophilia (hemophilia): Results of the coreHEM multistakeholder project(837)	Iorio A	2018
195.	Interventions to improve the appropriate use of polypharmacy for older people (Review)(838)	Patterson S	2012
196.	COS for trials aimed at improving the appropriateness of polypharmacy in older people in primary care(839)	Rankin A	2018
197.	Development of a COS for effectiveness trials aimed at optimising prescribing in older adults in care homes.(840)	Millar A	2017
198.	Choice of primary outcomes in randomised trials and systematic reviews evaluating interventions for preterm birth prevention: a systematic review(809)	Meher S	2014
199.	Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study(841)	Meher S	2018

200.	Core Outcomes and Common Data Elements in Chronic Subdural Hematoma: A Systematic Review of the Literature Focusing on Reported Outcomes(842)	Chari A	2016
201.	An Updated Systematic Review and Meta-analysis of the Predictive Value of Serum Biomarkers in the Assessment of Fever During Neutropenia in Children with Cancer(843)	Haeusler G	2013
202.	Core Outcomes for Colorectal Cancer Surgery: A Consensus Study(541)	McNair A	2016
203.	Synthesis and summary of patient-reported outcome measures to inform the development of a core outcome set in colorectal cancer surgery(844)	McNair A	2015
204.	A SR of outcome reporting in colorectal cancer(623)	Whistance R	2013
205.	COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation(845)	Haywood K	2018
206.	A SR of the outcomes reported in cardiac arrest clinical trials: need for a COS(846)	Whitehead L	2015
207.	Defining a core outcome set for adolescent and young adult patients with a spinal deformity(847)	De Kleuver M	2017
208.	Defining a standard set of patient-centred outcomes for lung cancer(420)	Mak K	2016
209.	Developing a core outcome set for fistulising perianal Crohn's disease(277)	Sahnan K	2018
210.	Reporting Outcome Measures in Trials of Infant Colic(848)	Steutel N	2014
211.	Developing a core outcome set for infant colic for primary, secondary and tertiary care settings: a prospective study(849)	Steutel N	2017
212.	A systematic review of the outcomes reported in multimodal pain therapy for chronic pain(260)	Deckert S	2016
213.	Developing a core outcome domain set to assessing effectiveness of interdisciplinary multimodal pain therapy: the VAPAIN consensus statement on core outcome domains.(850)	Kaiser U	2018
214.	Developing a core set of patient-reported outcomes in pancreatic cancer: A Delphi survey.(851)	Gerritsen A	2016
215.	Developing a Set of Core Outcomes for Trials in Hemodialysis: An International Delphi Survey (852)	Evangelidis N	2017
216.	Range and Heterogeneity of Outcomes in Randomized Trials of Pediatric Chronic Kidney Disease(279)	Chong L	2017
217.	Developing a Standard Set of Patient-Centred Outcomes for Inflammatory Bowel Disease—an International, Cross-disciplinary Consensus(853)	Kim A	2017
218.	Developing core economic outcome sets for asthma studies: a protocol for a systematic review(854)	Hounsome N	2017
219.	Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus(855)	Eleftheriadou V	2015
220.	Which outcomes should we measure in vitiligo? Results of a systematic review and a survey among patients and clinicians on outcomes in vitiligo trials(856)	Eleftheriadou V	2012
221.	Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study(857)	Al Wattar B	2017
222.	Variation in the reporting of outcomes among pregnant women with epilepsy: a SR(263)	Al Wattar B	2015
223.	Development of a core set of outcome measures for OAB treatment(858)	Foust-Wright C	2017
224.	Development of a provisional core domain set for polymyalgia rheumatica: Report from the OMERACT 12 Polymyalgia Rheumatica Working Group(859)	Helliwell C	2016
225.	Development of a Standardized Set of Patient-centered Outcomes for Advanced Prostate Cancer: An International Effort for a Unified Approach(860)	Morgans A	2015
226.	Evaluating physical activity in dementia: a systematic review of outcomes to inform the development of a core outcome set.(273)	Goncalves A	2017
227.	Reporting of symptoms in randomized controlled trials of atopic eczema treatments: a systematic review(861)	Gerbens L	2016
228.	Heterogeneity in Definitions of Endpoints for Clinical Trials of Ulcerative Colitis: A Systematic Review for Development of a Core Outcome Set.(225)	Ma C	2018
229.	Heterogeneity in post-intervention prolapse and urinary outcome reporting: a one-year review of the International Urogynecology Journal.(862)	Globerman D	2015

230. Heterogeneity of wound outcome measures in RCTs of treatments for VLUs: a systematic review(863)	Gethin G	2015
231. Outcomes mapping study for childhood vaccination communication: too few concepts were measured in too many ways(274)	Kaufman J	2016
232. Identification of preliminary core outcome domains for communication about childhood vaccination: An online Delphi survey(864)	Kaufman J	2017
233. A Preliminary Core Domain Set for Clinical Trials of Shoulder Disorders: A Report from the OMERACT 2016 Shoulder Core Outcome Set Special Interest Group(635)	Buchbinder	2018
234. Creation of a core outcome set for clinical trials of people with shoulder pain: a study protocol(865)	Gagnier J	2017
235. Outcome Reporting in Randomized Trials for Shoulder Disorders: Literature Review to Inform the Development of a Core Outcome Set(866)	Page M	2018
236. Identifying a core set of outcome domains to measure in clinical trials for shoulder disorders: a modified Delphi study.(867)	Page M	2016
237. Inconsistent selection of outcomes and measurement devices found in shoulder arthroplasty research: An analysis of studies on ClinicalTrials.gov(868)	Sims M	2017
238. Infants at risk of cerebral palsy: a systematic review of outcomes used in Cochrane studies of pregnancy, childbirth and neonatology(869)	Hines M	2015
239. International and Interdisciplinary Identification of Health Care Transition Outcomes(870)	Fair C	2016
240. International expert consensus on endpoints for full thickness laparoendoscopic colonic excision (871)	Currie A	2016
241. Clinical Outcomes in Psoriatic Arthritis: A Systematic Literature Review(872)	Palominos P	2012
242. Systematic literature review of domains assessed in psoriatic arthritis to inform the update of the psoriatic arthritis core domain set(873)	Kalyoncu U	2015
243. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials(594)	Orbai A-M	2016
244. Meaningful health outcomes for paediatric neurodisability: Stakeholder prioritisation and appropriateness of patient reported outcome measures(874)	Morris C	2015
245. Variability of outcome reporting in Hirschsprung's Disease and gastroschisis: a systematic review(227)	Allin B	2016
246. NETS1HD study: development of a Hirschsprung's disease core outcome set(419)	Allin B	2017
247. No common denominator: a review of outcome measures in IVF RCTs(275)	Wilkinson J	2016
248. Outcome Measures in Polymyalgia Rheumatica. A Systematic Review(875)	Duarte C	2015
249. Outcome reporting in randomised controlled trials and meta-analyses of appendicitis treatments in children: a systematic review(876)	Hall N	2015
250. The Importance of Integration of Stakeholder Views in Core Outcome Set Development: Otitis Media with Effusion in Children with Cleft Palate(877)	Harman N	2015
251. MOMENT – Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey(878)	Harman N	2013
252. Patient-reported outcomes in randomised controlled trials on age-related macular degeneration(879)	Krezel A	2015
253. Pharmacists' interventions on clinical asthma outcomes: a systematic review. (880)	Garcia-Cardenas V	2016
254. Quality of outcome reporting in phase II studies in pulmonary tuberculosis (881)	Bonnett L	2015
255. Quality of reporting of outcomes in phase III studies of pulmonary tuberculosis: a systematic review(882)	Bonnett L	2018
256. Reported Outcome Measures in Degenerative Cervical Myelopathy: A Systematic Review(883)	Davies B	2016
257. Reporting on Outcome Measures of Functional Constipation in Children-A Systematic Review(884)	Kuizenga-Wessel S	2016

258.	Reporting outcomes of definitive radiation-based treatment for esophageal cancer: a review of the literature.(885)	Main B	2015
259.	Scoping review of patient- and family-oriented outcomes and measures for chronic pediatric disease(886)	Khangura S	2015
260.	SCORE-IT (Selecting Core Outcomes for Randomised Effectiveness trials In Type 2 diabetes): a systematic review of registered trials(261)	Harman N	2017
261.	Social network analysis identified central outcomes for core outcome sets using systematic reviews of HIV/AIDS(887)	Saldanha I	2016
262.	Functional outcome measures in contemporary stroke trials(888)	Quinn T	2009
263.	Survival, morbidity, growth and developmental delay for babies born preterm in low- and middle-income countries - a systematic review of outcomes measured.(889)	Gladstone M	2015
264.	Systematic review of outcome domains and instruments used in clinical trials of tinnitus treatments in adults.(890)	Hall D	2016
265.	Systematic review of outcome measures following chemoradiotherapy for the treatment of anal cancer (CORMAC)(891)	Fish R	2018
266.	Systematic review of outcome measures in pediatric eosinophilic esophagitis treatment trials(622)	Rubin T	2016
267.	Validated Outcomes in the Grafting of Autologous Fat to the Breast: The VOGUE Study. Development of a Core Outcome Set for Research and Audit(892)	Agha R	2018
268.	The Need for Core Outcome Reporting in Autologous Fat Grafting for Breast Reconstruction(282)	Agha R	2016
269.	Use of autologous fat grafting for reconstruction postmastectomy and breast conserving surgery: a systematic review protocol(893)	Agha R	2013
270.	The consistency and reporting of QoL outcomes in trials of immunosuppressive agents in kidney transplantation: A systematic review and metaanalysis(894)	Howell M	2016
271.	Quality and consistency of outcome reporting in clinical trials of immunosuppression in renal transplantation(895)	Hussain S	2016
272.	Variability in the reporting of renal function endpoints in immunosuppression trials in renal transplantation: time for consensus(280)	Knight S	2016
273.	Standardized outcomes in nephrology-transplantation: a global initiative to develop a COS for trials in kidney transplantation(896)	Tong A	2016
274.	Towards a core outcome set for hemorrhoidal disease—a systematic review of outcomes reported in literature(897)	Van Tol R	2018
275.	Variation in hyperemesis gravidarum definition and outcome reporting in randomised clinical trials: a systematic review(898)	Koot M	2018
276.	Variation in outcome reporting in endometriosis trials: a systematic review(283)	Hirsch M	2016
277.	An International Collaborative Standardizing a Comprehensive Patient-Centered Outcomes Measurement Set for Colorectal Cancer(899)	Zerillo J	2017
278.	Development of a core outcome set for use in determining the overall success of gastroschisis treatment(588)	Allin B	2016
279.	Outcome reporting in randomized controlled trials and systematic reviews of gastroschisis treatment: a systematic review(276)	Ross A	2016

Appendix D COSB-i HRA and IRAS approvals

Appendix E Letter from study sponsor

Appendix F Patient interview consent form

University of BRISTOL

COSB

Consent Form (Adult Participant)

Study Title: COSB Core Outcomes for Burn Care Research.

Study ID						Initials			

Please read this consent/assent form carefully and <u>put your initials in the boxes</u> by the items to which you agree or give your consent. We are asking you to sign to show you understand what taking part in the study means and that you are happy to do so.

1. I confirm that I have read and understand version 1.0 of the information sheet dated 06/01/17 for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. I know who to contact if I have any further questions.

2. I agree to take part in an interview with the research team about what recovery issues (outcomes) are important during recovery from a burn injury.

3. I understand that I am taking part voluntarily and that I am free to withdraw from the study at any time, without giving any reason, and without my medical care or legal rights being affected.

4. I agree that the interview can be audio-recorded.

5. I understand that information from my medical notes will be recorded and processed by members of the research study team within the National Health Service and I am willing for them to do this.

6. I understand that my information will be anonymised with a study number and kept strictly confidential and used only for the purposes of this study. My consent depends on the University Hospitals Bristol NHS Foundation Trust complying with its duties and obligations under the 1998 Data Protection Act.

7. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

8. I agree to my General Practitioner being informed of my participation in the study.

9. I understand that people who monitor research and make sure it is being done properly, may need to, see information about me to check the study**.**

10. I agree to take part in this study.

Full name: _____ Signature: _____ Date:

Full name of researcher: ___Dr Amber Young_____ Signature: __  Date: 5th June 2017_____

Appendix G Patient information for semi-structured interviews.

Trust logo

Patient Information Sheet
Qualitative Interviews (Adult)

Study Title: Core Outcomes for Burn Care Research.

Agreeing how to measure recovery from a burn.

We would like to ask if you would be happy to participate in this research study.

This leaflet will explain why the study is being done and what will happen if you take part.

Please take time to read the following information carefully and feel free to ask your doctor or nurse for more information.

What is the reason for this study?

There are different ways to treat patients after a burn injury. Doctors need to test whether new treatments are better than older treatments. To do this we need to measure how well patients recover with different care. People with burns have different experiences during their recovery. This could include issues such as the side effects of treatment including scarring, pain or itching or quality of life. We want to know which recovery issues or outcomes are most important to patients.

Why have I been chosen?
You have been chosen because you have had a burn injury. Your contact details were obtained via the medical team looking after you.

Do I have to take part?
No. It is up to you to decide whether to take part. We will explain the study to you and go through this leaflet. If you decide to take part, you will be asked to sign a form and we recommend you keep this information sheet for reference. If you don't want to take part, you don't need to give a reason and your hospital care will stay the same.

Can I change my mind?
That's fine. You can say no at any time.

What will happen if I take part?

The research team will contact you to arrange an interview. This can take place at a time and location convenient to yourself. This could be in the hospital, University or at your home. The interview will last about one hour and no longer than 2 hours. You are free to stop the interview at any point. We will ask you about your recovery from the burn and what matters to you. This could include complications of treatment, what stops you doing what you enjoy or other issues affecting your daily quality of life. With your permission we will record the interview.
If you undertake an interview at a time separate to a hospital appointment, you will be reimbursed for any travel costs. This will be undertaken on the basis of receipts provided to the study researchers. Petrol costs will be reimbursed at the rate 40p/ mile.

What are the possible risks or disadvantages of taking part?
There are very few risks of taking part in this study. If you agree to take part in the study, the disadvantages include the possible anxiety caused by answering questions about what is important to you during your recovery from the burn. We can arrange support for you if this is the case. However, many patients find it helpful to talk about their recovery. You will have the opportunity to discuss any queries, anxieties or issues with a study researcher, for whom we will provide contact details. We will also inform your GP that you are taking part in this study.

What are the possible benefits of taking part?
The information we obtain from the study will help us to improve ways that doctors and health personnel measure the most important recovery issues or outcomes for patients when developing new treatments and deciding on the best care after burn injuries.

Will my taking part in this study be kept confidential?
All information that is collected about you during the research will be kept strictly confidential. Information will be collected, stored and analysed by the study researchers at the Hospital Trust and the University of Bristol. Any information collected about you will have your name and address removed so that you cannot be recognised from it. Access to this information will be restricted to members of the research team alone. You will never be identified in any publications. Audio tapes will be destroyed after 10 years in line with Data Protection Act regulations.

What will happen to the results of this research study?
The main results of the study will take 2-3 years to become available. We will send you a letter with what we have found out if you wish. We will also send regular updates to participants in a newsletter. We will publish results in scientific journals, as well as present reports at various local, national and international scientific meetings. You will not be identified in any report or publication.
Who is organising and paying for this research?
The research is being run by the University of Bristol and is funded by the National Institute for Health Research. The study is led by the Chief Investigator, Dr Amber Young, who is a Senior Research Fellow at the University of Bristol and Professor Jane Blazeby, who is a Professor of Surgery at the University of Bristol.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by the xxxxxx Research Ethics Committee (reference number). Approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

Who do I contact if I want more information, have concerns or want to make a complaint?
If you have any further questions concerning this study, please contact your consultant, nurse or the study contact below. If you remain unhappy about any aspects of the study, you can do so through the Patient Advice and Liaison Service (PALS). Details are on the NHS Choices website www.nhs.uk.

Study contact: Dr Amber Young 0117 3427017

Appendix H Interview Topic Guide

COSB Interview Topic Guide – patient, parent and child participants.

Introduction

- Thank you for coming. My name is Amber Young and I'm a researcher at the University of Bristol.
- I am working on the COSB project. I am undertaking a programme of research with the aim of achieving agreement about the most important areas of your recovery during recovery from a burn. Researchers and clinicians will then use these to evaluate the impact of existing and new treatments. I want to agree these using knowledge from both patients and professionals
- I would like to discuss with you what you thought were important areas of recovery to you during your (or your child's) recovery from a burn.
- There are no right or wrong answers or views, I just want to understand your thoughts on what was and is important during your recovery. I appreciate these issues can be difficult topics (for parents, children) and you can stop our discussion at any time. This should take no longer than an hour.
- Do you have any questions at this point?
- I will check that they are happy for me to record the interview and I will take verbal consent. Written consent will be taken beforehand.

Questions:

- Opening: Could you tell me a bit about you?
    - Prompt: do you work, do you have children etc

- Could you tell me about how you/your child came to have the burn?

- What was your experience of being treated in hospital?
    - Prompts:
        - Do you know how long you spent in hospital and what sort of treatment you received?
        - Did you need to go to intensive care?
        - Have you needed much medical care since you left hospital?

- When you were burned, did you experience any worries about the effects of the burn at that time or for the future? If so, what were these?
    - Prompt:
        - Eg survival, scarring, pain?
        - Areas of your life that it was most important to ensure the burn didn't affect eg function (eg related to work, school), the look of the burn (confidence, work, school, friends)?
        - Did the worries change over time?

- What were the most important areas of your recovery to you after you got home?
    - Prompt:
        - Was your daily life affected? If so, in what ways?

        - Prompts could include work life; social life; family life; relationships (including intimacy)
    - Were you worried about the future? If so, in what way(s)?
    - Were there any issues that affected you that the doctors didn't ask about at your out-patient appointments?
    - Were there issues that bothered you more than they seemed to bother the medical staff?
    - Were there issues that the doctors asked about that didn't worry you?

- Were your family and friends worried about any effects of your burn at any time after the burn injury? If so, what were they worried about?
    - Prompt: (as above; work life; social life; family life; relationships (including intimate relationships)
- What matters to you now while you are getting better?

- If there are any areas of healthcare that could have been improved, what would that/they be?
    - Prompt: treatment of infection, management of pain, improving success of skin-grafting?

- Are there any other aspects of your recovery that you thought were important and we haven't talked about?

- To finish with, could we summarise what the most important areas of your recovery after the injury were to you?

- Closing: Researcher thanks interviewee and asks if they would like a summary of the study results once complete

Check any remaining demographic information eg: date of burn, age of patient etc for CRF

Appendix I Delphi Participant Information

Study Title: Core Outcomes for Burn Care Research.
Invitation to a questionnaire survey for adult patients or parents/carers.

You are being invited to take part in a research study. Before you decide, it is important for us to explain clearly why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, if you wish. Thank you for reading this.

What is the reason for this study?
There are different ways to treat patients after a burn injury. Doctors need to test whether new treatments are better than older treatments. To do this we need to measure how well patients recover with different care. People with burns have different experiences during their recovery. This could include issues such as scarring, pain or itching or quality of life. We want to know which recovery issues or outcomes are most important to patients.

Why have I been chosen?
You have been chosen because you or your child have had a burn injury. Your contact details were obtained via the medical team looking after you or your child.

What will happen if I take part?
If you agree to take part, you will be sent two sets of questionnaires by email over the following months. We would like you to complete the questionnaires (they take about 15-30 minutes), which ask you to rate how important you think each outcome is to include in a minimum (core) outcome set ie how important each issue is to patients recovering from a burn. The questionnaire has been designed based on all the many different outcomes currently reported in the research literature. If there are any outcomes you think we may have missed, please add these in the space provided at the end of the questionnaire.
Please return the questionnaire to us in the enclosed stamped addressed envelope. A second questionnaire will be sent in the next few months.
If you are able to participate in this study we will also invite you to a meeting (with expenses covered) to select the final core outcome set.

Do I have to take part?
No. It is up to you to decide whether to take part. If you agree to participate please sign and return one copy of the enclosed Consent Form in the prepaid envelope (at no cost to yourself). Please sign and keep the other copy for your own records. On receiving this form, a member of the research team will send you the first questionnaire to complete. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time or a decision not to take part

will not affect the standard of care you or your child receive. If you do decide to take part we recommend you keep this information sheet for reference.

What are the possible risks or disadvantages of taking part?
There are very few risks of taking part in this study. If you agree to take part in the study, the disadvantages include the possible anxiety caused by answering questions about what is important to you during your recovery from the burn. We can arrange support for you if this is the case. However, many patients find it helpful to talk about their recovery. You will have the opportunity to discuss any queries, anxieties or issues with a study researcher, for whom we will provide contact details. We will also inform your GP that you are taking part in this study.

What are the possible benefits of taking part?
The information we obtain from the study will help us to improve ways that doctors measure the most important recovery issues or outcomes for patients when developing new treatments and deciding on the best care after burn injuries.

Will my taking part in this study be kept confidential?
All information that is collected from you during the research will be kept strictly confidential. Information will be collected, stored and analysed by the study researchers at the University of Bristol. Any information collected from or about you or your child will have your names and addresses removed so that neither of you can be recognised from it. Access to this information will be restricted to members of the research team alone. You will never be identified in any publications.

What will happen to the results of this research study?
The main results of the study will take 2-3 years to become available. We will send you a letter with what we have found out if you wish. We will also send regular updates to participants in a newsletter. We will publish results in scientific journals, as well as present reports at various local, national and international scientific meetings. You will not be identified in any report or publication.

Who is organising and paying for this research?
The research is being run by the University of Bristol and is funded by the National Institute for Health Research. The study is led by the Chief Investigator, Dr Amber Young, who is a Senior Research Fellow at the University of Bristol and Professor Jane Blazeby, who is a Professor of Surgery at the University.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by the xxxxxx Research Ethics Committee (reference number). Approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

Who do I contact if I want more information, have concerns or want to make a complaint?
If you have any further questions concerning this study, please contact your consultant, nurse or the study contact below. If you remain unhappy about any aspects of the study, you can do so through the Patient Advice and Liaison Service (PALS). Details are on the NHS Choices website www.nhs.uk.

Thank you so much for helping us with this research.
Study contact: Dr Amber Young 0117 3427017

Appendix J Delphi questionnaires.

SECTION C: Before wound healing

This Section asks you about what outcomes occurring before wound healing are important to measure in research trials.

C1: Medical outcomes affecting a patient's burn or body during the process of healing

How important is it to measure the following outcomes in research about burns?

C1.1 How well a patient with a burn is able to fight infection.

For example: a burn can affect the body's ability to fight infection. Medical tests like white cell count can show how well the body can fight infection.

Please mark a cross under the number that best represents your view about how important this outcome is.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.2 The amount of fluid coming from the burn wound (exudate).

For example: whether and how much the burn leaks fluid.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.3 The nature of the fluid coming from the burn wound.

For example: what colour is the fluid coming from the wound, and has it changed?

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.4 The need for blood transfusions during treatment for a burn.

For example: does a patient need to be given blood or blood products during their treatment. This sometimes happens if the burn is large or a patient needs an operation for a skin graft.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.5 The difficulty patients have with body temperature

For example: A burn can affect the way the body handles temperature by increasing a patient's sensitivity to heat or by being unable to sweat.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.6 How quickly a patient's burn wounds heal.

For example: how many days or weeks does it take for the burn to heal completely.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.7 How quickly a patient's burn wound heals after receiving a skin graft.

A skin graft is when healthy skin is taken from another part of the body and placed over the burn wound to help it heal.

For example: how well a burn that has needed a skin graft heals.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.8 How quickly the donor site heals in patients who have had a skin graft.

Donor site: is the place from which healthy skin is taken for a skin graft – usually top of the thigh

For example: how soon does the site where the skin graft has come from heal.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.9 Whether the donor site becomes infected.

Donor site: is the place from which healthy skin is taken for a skin graft — usually top of the thigh

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

For example: whether the area of the body that the skin is taken from for a skin graft becomes infected.	
C1.10 Whether a burn wound becomes infected. For example: Burn wounds may become infected because they have lost the outer layer of the skin. This will require treatment such as wound cleaning and/or antibiotics.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
C.1.11 Whether a patient has an infection elsewhere in the body, other than in the burn wound. For example: chest infection, urine infection.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
C1.12 Whether a burn infection results in bloodstream infection (sepsis). For example: severe infection in the blood with risk to life.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
C1.13 Whether patients experience <u>mild</u> complications relating to the burn or its treatment.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9

For example: a rash from the dressing requiring no treatment and not affecting a patient's recovery.										

C1.14 Whether patients experience <u>moderate complications</u> relating to the burn or its treatment, which will get better with treatment but may affect a patient's length of stay in hospital. For example: allergy to medication or bleeding under their skin graft.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

C1.15 Whether patients experience <u>serious complications</u> relating to the burn or its treatment which could result in death, or require considerable treatment and may considerably extend the hospital stay For example: Blood clots in the lungs or legs from lying in bed.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

C1.16 Death due directly to the burn injury soon after a patient is injured.

For example: death due to 'burn shock' or due to a burn wound infection or sepsis.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.17 Death of a patient from any cause soon after a patient is injured.

For example: death from a heart attack.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C.1.18 The effect of the burn on how well the body uses energy.

For example: the body may have a very high use of energy when trying to heal the wounds so that muscles become weak and there is weight loss.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.19 The effect of the burn on a patient's heart and blood circulation function.

Large burns can affect patients' heart function.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

For example: low blood pressure requiring intensive care and drugs which could be life-threatening or high blood pressure.

C1.20 Effect of the burn on a patient's kidney function that <u>does not require</u> dialysis.

Burns can affect the functioning of a patient's kidneys. The kidneys filter waste products out of your blood. <u>Dialysis</u> is a machine that does the work a patient's kidneys normally do.

For example: minor effects of the burn on the working of a patient's kidneys requiring drugs or more fluid.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.21 Kidney failure caused by the burn that <u>requires</u> dialysis.

For example: serious effect of the burn on the kidneys that mean a machine is needed that does the work of the kidneys (dialysis), which may or may not be permanent.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.22 The effect the burn has on a patient's liver function.

For example: Rarely, a burn injury can affect a patient's liver because of changes in the patient's blood pressure or infection. This would be serious and affect a patient's ability to clot their blood normally, increase their time in hospital and if very serious may be a risk to life.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.23 Whether a patient with a burn has any difficulty with breathing or their lung function.

For example: a small number of patients with burns have problems with their breathing or lungs due to inhaling smoke, or because the burn or fluid given to treat the burn can affect the lungs. This might mean that a patient needs to be helped to breathe with a ventilator or use oxygen.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.24 The effect of a burn on the function of a patient's stomach or bowel.

For example: diarrhoea, constipation, sickness, vomiting, nausea, inability to keep food down.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.25 Whether the burn causes several body organs to stop working well <u>at the same time</u> (multi-organ dysfunction).

After a burn a patient can develop problems with several organs at once (called multi-organ dysfunction), but with treatment the organs can recover.

For example: poor kidney function and poor liver function at the same time <u>that is likely to get better</u> <u>following treatment</u>**.**

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.26 Whether the burn causes several body organs to <u>fail</u> (not work at all) <u>at the same time</u> (multi-organ failure).

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

Rarely, a patient with a burn can develop organ failure in several organs at once (called multi-organ failure).

For example: kidney failure and liver failure at the same time, where it is unlikely to get better, or will need long-term care.

C1.27 The amount of fluid given to a patient, either into a patient's vein (through a 'drip') or as a drink.

When a patient loses skin due to a burn they will lose liquid through this area and if it is a large area, it may require replacement.

For example: how much extra fluid through a drip does a patient need to have to ensure their organs work well.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.28 The length of time a patient stays in hospital after a burn injury.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

For example: the number of days or weeks after the injury that a patient needs to stay in hospital.	

C1.29 The length of time a patient stays in an intensive care unit after a burn injury.

For example: number of days or weeks after the injury that a patient has to receive intensive care.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.30 The length of time a patient uses a breathing machine after a burn injury.

For example: the amount of time a patient needs to be on a 'ventilator'.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.31 Medical tests to find out how well the body is handling the stress of the burn injury (inflammatory markers).

For example: blood or urine tests to find out how well the body is coping with the stress placed on the body after burn injury.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C1.32 Whether a patient can maintain their body weight.

For example: burn injuries can affect a patient's ability to eat normally and absorb their food. This can result in

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

weight loss, not being able to keep a normal weight.	
C1.33 The costs of burn treatment for the NHS. For example: how much the treatment for the burn costs the NHS/hospital through paying for staff, dressings and medications and equipment.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**

C2: Other outcomes that relate to a patient's experiences of having a burn injury during the process of healing

How <u>important is it to measure</u> the following outcomes in research about burns?

C2.1 The amount of dressing changes or cream applications needed to treat the burn. For example: How many times a patient needs to have their dressing changed, for how long and how frequently they have to apply creams.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**
C2.2 The number of outpatient appointments a patient needs to attend.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**

For example: How many times a patient needs to come to the hospital for follow-up appointments or dressing changes.	
C2.3 The number of surgical treatments/ operations a patient needs. For example: the number of times they need to have an operation or receive a treatment where they have a general anaesthetic (medicine to make you sleep during an operation).	**Not at all important** | **Important but not vital** | **Very important** | **No opinion** 1 2 3 4 5 6 7 8 9
C2.4 The smell of the burn wound. For example: does the burn wound smell unpleasant?	**Not at all important** | **Important but not vital** | **Very important** | **No opinion** 1 2 3 4 5 6 7 8 9
C2.5 How much medication a patient needs to treat a burn injury. For example: how many painkillers are needed or whether a patient needs medication for blood pressure?	**Not at all important** | **Important but not vital** | **Very important** | **No opinion** 1 2 3 4 5 6 7 8 9

C2.6 How well a patient sticks to their planned treatment. For example: do patients take medication, do they attend appointments and have blood tests as directed by their medical team?	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.7 The anxiety a patient experiences about their medical treatment. For example: worry about the pain of operations, dressing changes, blood tests.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.8 How comfortable wound dressings are for a patient. For example: do the dressings fall off, do they stop a patient moving normally, are they itchy?	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
C2.9 The dignity of a patient during and after treatment. For example: does the patient feel respected, are they given privacy?	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

C2.10 Itch in the burn wound during healing of the burn.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C2.11 Pain in the burn wound when treatment is <u>not</u> taking place.

For example: pain all the time, pain at night.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C2.12 The amount of pain caused by medical treatments and tests for a patient with a burn.

For example: pain when having dressing changes, blood tests.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

C2.13 Pain in the donor site

Donor site: is the place from which healthy skin is taken for a skin graft — usually top of the thigh.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

For example: how sore is the area where the skin for a graft is taken from?	
C2.14 A patient's anxiety about the future. For example: worries about appearance, worries about working or school, worries about relationships.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**
C2.15 The effect being treated for a burn has on a patient or their family in terms of money. For example: lost salary for a patient or their carer, costs of travel to appointments and parking for a patient or their family, buying food at the hospital, costs of painkillers and prescriptions.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**
C2.16 The effect of the burn and treatment on a patient's thirst. For example: feeling so thirsty that a drink of water does not make it better.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**

C2.17 How much a patient understands the treatment they receive for a burn injury. For example: whether a patient understands the need for surgery, how long scar treatment will take.	Not at all important			Important but not vital			Very important			No opinion
	1	2	3	4	5	6	7	8	9	

SECTION D: After wound healing- when a patient's wound has healed and they are at home

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This Section asks you about what outcomes are important <u>after wound healing</u>, when the wound is healed or has scarred.

D1: Medical outcomes affecting a patient's burn or body after the wound has healed

How <u>important is it to measure</u> the following outcomes in research about burns?

D1.1 The effect of a burn on the strength of a patient's bones after healing. For example: a burn injury can affect a patient's bones. This might	Not at all important			Important but not vital			Very important			No opinion
	1	2	3	4	5	6	7	8	9	

include a change in bone density, brittle bones with an increased risk of broken bones (osteoporosis).	
D1.2 The costs of burn treatment for the NHS. For example: how much the treatment for the burn and scar costs the NHS/hospital through paying for staff, dressings and medications and equipment.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
D1.3 Death of a patient from any cause. For example: death from a stroke or a heart attack after the burn has healed.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
D1.4 The effect of the burn on how well the body uses energy. For example: a patient's body may need to use a lot of energy during healing so that muscles become weak and there is weight loss.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
D1.5 The effect of the burn on a patient's heart and blood circulation function.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9

For example: a burn injury can affect a patients' heart functioning or circulation. A long-term effect after healing might include the need for blood pressure treatment.										
D1.6 Whether there are problems with the skin graft donor site <u>after healing</u>. Donor site: is the place from which healthy skin is taken for a skin graft — usually top of the thigh. For example: pain, colour change of the donor site after it has healed.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D1.7 How much the burn affects a patient's ability to walk and get about normally. For example: being able to walk to the shops, go on foot outside of the house, move around at home.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D1.8 The effect of the burn scar on a patient's movement (excluding walking). For example: inability to straighten arm, difficulty moving fingers normally.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

D1.9 The effect of the burn (and treatment) on a patient's fitness.

For example: ability to walk as far as normal, being able to do exercise.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.10 The effect the burn has on how well a patient's muscles work.

For example: how well a patient can move their face, arms or legs normally.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.11 The effect of the burn on the strength of a patient's muscles.

For example: poor muscle strength, difficulty with carrying children or shopping.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.12 Whether a patient can maintain their body weight after a burn injury after healing.

For example: weight loss, not able to keep a normal weight.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.13 The effect a burn has on a child's growth.

For example: A burn can rarely affect a child's growth. This might mean not achieving potential height, slowing of growth.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.14 The difference in colour of a burn scar compared to normal skin.

For example: whether a burn scar is very red or loss of colour in a scar.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.15 The size of a burn scar.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D1.16 How much medication a patient needs to manage the burn scar and other symptoms after the injury.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

For example: whether a patient requires medication for a long time after the injury, how many painkillers are needed.	

D2: Outcomes that relate to a patient's experiences of having a burn injury

How <u>important is it to measure</u> the following outcomes in research about burns?

D2.1 A patients' ability to carry out normal daily tasks. For example: dressing, washing, making food or drinks.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	
D2.2 How well a patient sticks to their planned treatment. For example: do patients take medication, do they attend appointments and have blood tests.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

D2.3 The anxiety patients experience about their medical treatment.

For example: worry about the pain of operations needed for treating scars.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.4 Patients' appearance after a burn injury.

For example: appearance of scar, facial appearance, body image.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.5 The difficulty patients have with body temperature management after a burn.

For example: sensitivity to heat, being unable to sweat.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.6 How much the burn results in a patient experiencing unwanted attention.

For example: people looking, judgement by others, name-calling.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.7 How much a patient understands the treatment they receive for a burn injury. For example: whether a patient understands the need for surgery, scar treatments.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**
D2.8 The amount of cream applications, or amount of time wearing pressure garments needed to treat the scar. For example: for how long and how frequently a patient has to apply creams or use pressure garments for their scars.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**
D2.9 The number of outpatient appointments a patient needs to attend. For example: How many times a patient needs to come to the hospital for follow-up appointments.	**Not at all important** 1 2 3 | **Important but not vital** 4 5 6 | **Very important** 7 8 9 | **No opinion**

D2.10 The number of surgical treatments or operations a patient needs.

For example: the number of times they need to have an operation or receive a treatment to help with scarring where they are put to sleep.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.11 How much treatment is required for a patient's burn scars.

For example: how many times their scar may need surgery, whether and how long they need pressure garments, whether creams are needed.

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.12 The dignity of a patient during scar treatment.

For example: does the patient feel respected, are they given privacy?

Not at all important			Important but not vital			Very important			No opinion
1	2	3	4	5	6	7	8	9	

D2.13 The loss of a patient's hair due to the burn injury.

Not at all important	Important but not vital	Very important	No opinion

	1	2	3	4	5	6	7	8	9	

D2.14 The amount of pain caused by a burn scar.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

D2.15 The texture or feel of a burn scar. For example: whether a scar is rough, lumpy or tight.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

D2.16 Whether the burn causes a patient to have problems with itch <u>after</u> healing. For example: some patients have itchy scars that can affect their ability to sleep, and take part in daily activities.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

D2.17 A patient's anxiety about the future.	**Not at all important**			**Important but not vital**			**Very important**			**No opinion**
	1	2	3	4	5	6	7	8	9	

For example: worries about appearance, worries about working or school, worries about relationships.										

	Not at all important			Important but not vital			Very important			No opinion
D2.18 The effect that being treated for a burn has on a patient or their family in terms of money For example: lost salary for a patient or their carer, costs of travel to appointments and parking for a patient or their family, buying food at the hospital, costs of painkillers and prescriptions.	1	2	3	4	5	6	7	8	9	

	Not at all important			Important but not vital			Very important			No opinion
D2.19 The effect of the burn on a patient's ability to think and remember clearly. For example: memory, concentration.	1	2	3	4	5	6	7	8	9	

	Not at all important			Important but not vital			Very important			No opinion
D2.20 The effect a burn has on general well-being. For example: don't feel right, general illness.	1	2	3	4	5	6	7	8	9	

D2.21 How much a burn affects the amount and quality of sleep a patient gets.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
D2.22 How the burn injury and treatment affect a patient's personal relationships. For example: effect of relationships with parents, brothers and sisters, boyfriend, girlfriend, partner, children, friends.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9
D2.23 How long a burn prevents a patient from returning to work or a child returning to school, University / College or work.	**Not at all important** / **Important but not vital** / **Very important** / **No opinion** 1 2 3 4 5 6 7 8 9

D2.24 Are there any other outcomes that you think are important to measure and report in trials? If yes, please write them below:

END OF QUESTIONNAIRE

THANK YOU VERY MUCH FOR YOUR PARTICIPATION

You will be contacted by email about the next survey in 6-12 weeks

Appendix K Outcomes extracted from semi-structured interviews.

Outcomes reported in interviews from patients, carers and HCPs n=149		
Activities of daily living	ICU treatment	Return to work
Analgesia	Impact on family	Relationships
Anxiety	Impact on friends	Scar and aging
Body image	Impact on relationships	Scar and gender
Bullying	Inconvenience	Scar camouflage
Burden of care	Infection	Scar colour
Burn smell	Itching	Scar discomfort
Children's worries	Judgement by others	Scar fragility
Clothes	Lack of empathy	Scar height
Communication	Laser treatment	Scar impact
Complications of drugs	Length of hospital stay	Scar improvement
Complications of medication	Look of burn wound	Scar management
Concentration	Look of scar	Scar permanency
Confidence	Mask for scarring	Scar problems
Constipation	Massage for scarring	Scar sensation
Contractures	Memories	Scar tightness
Coping	Memory of injury	Scarring
Cosmesis	Mental health issues	Sensation
Cough	Mobility	Silicon
creams for burn	Mood	Skin graft
Creams for scarring	Nasogastric feeding	Skin graft impact
Depression	Need for surgery	Skin graft loss
Digestion	Nexabrid pain	Skin graft pain
Dignity	Non-surgical scar treatment	Sleep quality
Discharge planning	Normality	Sleep quality
Distress	Nutrition	Stamina
Donor site pain	other people	Steroid complications
Dressing change pain	Outpatient visits	Suicide
Dressings	Outreach	Sun issues
Eating	Pain	Surgery for burn treatment

Effect of growth	pain general	Surgery for scars
Exercise issues	Pain immediately after injury	Survival
Extension of burn	Parent impact	Swimming
Exudate	Patient information	Temperature issues
Face burn problems	Patient knowledge of care	The future anxiety
Family roles	Patient self-help groups	Theatre trip
Finance	People looking	Thirst
Flashbacks	Physiotherapy	Time spent in hospital
Friends	Pressure garments for scarring	Tiredness
Functional impact general	Progress	Treatment by other people
Gabapentin use	Psychology	Treatment for itch
General anaesthesia	PTSD	Ventilator days
Getting dressed	Re-operation	Washing
Getting home	Reconstruction	Wearing shorts
Guilt	Recovery issues	Worries re scarring
hair loss	Rehabilitation	Worry re pain
Hallucinations	Relationships	Wound breakdown
Hand injury	Return to home	Wound infection
Healing process	Return to normal	
Honey treatment	Return to school	

Appendix LCOSB-i Consensus report

COSB-international

Core Outcomes for Burn Care Research

Consensus Meeting

9th October 2019, BMA House Conference & Events Venue, London

- FINAL REPORT -

University of BRISTOL

NIHR | National Institute for Health Research

1. Participants

28 participants attended the meeting, as well as 19 participants who joined the voting by telephone.

Participant locations and job roles are illustrated in table 1.

Table 1: Participant type, and country (n=47)

Country of participant	**N (%)**
UK	28 (59.6)
Australia	6 (12.8)
USA	4 (8.5)
Belgium	1 (2.1)
Indonesia	1 (2.1)
Japan	1 (2.1)
Netherlands	3 (6.4)
Norway	1 (2.1)
Sweden	1 (2.1)
Not reported	1 (2.1)
Participant group	
Health care professional incl. commissioners, researchers, charity sector staff	44(93.6)
Patient/ parent of patient	3 (6.4)
Participant group breakdown	
Researcher, academic or journal editor	11(23.4)
Consultant plastic surgeon involved in burn care	5 (10.6)
Registrar/junior doctor with at least 6 consecutive months' burn care experience	2(4.3)
Burn care research nurse or nurse	8(17.0)
Psychologist/ counsellor working with patients with burns	1(2.1)
Physiotherapist/ occupational therapist working with patients with burns	5(10.6)
Missing	15(31.9)

2. Initial discussion about items for consensus voting

30 items to be discussed and voted on were taken to the meeting. These are presented in tables 2 and 3.

Items in Table 2 were those rated them as important (8-9) by both patients and professionals working with patients with burn injuries. Items presented in Table 3 were those where either clinicians or patients had rated it as being important (>70% rating it as 8-9), but not both groups.

Table 2: Outcomes rated as important (8-9) by at least 70% of both patients and professionals

Outcome	**% rating**	**Outcome**	**% rating**
Death due to burn injury	96.8	Scar pain	83.9
Serious complications (e.g.	96.3	Time to heal a (grafted) wound	83.6
Sepsis (bloodstream infection)	95.3	Breathing and lung function	79.5
Multi-organ failure	92.9	Pain during procedures (dressing	79.3
Scar contractures	92.2	Kidney function	77.5
Daily tasks	91.9	Appearance	75.3
Wound infection	90.1	Pain in the burn wound	74.6
Multi-organ dysfunction	89.9	Patient psychology	74.6
Death from any cause	87.9	Growth (achieving expected height)	73.5
Time to healing	85.8	Walking	72.8

Table 3: Outcomes voted important (8-9) by at ≥70% of clinicians **or** patients

Outcome	**% Patients rating outcome as important (8-9)**	**% Clinicians rating outcome as important (8-9)**
Infection in donor site	81.6	66.1
Understanding of treatment received	80.9	57.3
Well-being	76.1	67.1
Donor site healing	73.5	64.0
Anxiety	71.7	66.1
Number of surgeries needed	70.2	60.9
Anxiety about the future	70.2	65.8
Length of stay in ICU	69.4	70.0

Time to return to work/school/ previous occupation	67.4	74.3
Length of time on ventilator	65.3	74.9
Immune response to fighting infection	76.5	60.2

Discussion points

1. **Intensive care:** There was discussion about length of stay on ICU and ventilator days. It was discussed that as most studies would not be conducted with an ICU patient population, these items relating to ICU would be unlikely to be core to burn care.
2. **Quality of life:** it was raised that quality of life should be included in the voting set. Discussion indicated that this could be covered under patient psychology, and the specific measures of psychology would be further delineated during the measure development phase of the COS.
3. **Serious complications:** Definition of serious complications should be expanded to include pulmonary embolism, sepsis, wound infection, deep vein thrombosis. This would be assessed in most trials as adverse events and specific events would be noted under this outcome. This would reduce items to be voted on. Serious complications could be used as the main heading, and within this outcome authors must report 3-4 items. There was discussion about whether death should be considered under serious complications, however there was a decision that this outcome should be separated. Organ failure is also not included under this heading.
4. **Death:** AY put forward that cause of death relating to burn or other causes could be merged under one item. It was agreed that this should be done.
5. **Multi-organ failure/dysfunction:** it was discussed that these items are used interchangeably so combine to one field. It was further discussed that dysfunction of individual organs (e.g. kidney, heart and lungs, liver) could be combined under this heading if needed.
6. **Burn wound healing, healing of grafted wounds**: It was agreeded that these items represented 'healing of the burn wound' and so could be combined.
7. **Scar pain and wound pain** – Scar pain should be combined with itch to represent chronic neuropathic pain and itch. Discussed that these need to be kept separate from acute pain in the non-healed wound.
8. **Procedural and background pain** – Combine have main heading of acute pain with sub categories.
9. **Walking**: This could be covered under physical well-being or daily tasks
10. **General points:**

- If adding sub-categories under a main heading it is important that outcomes already voted on in the Delphi survey and not selected to bring to the consensus meeting do not end up being added back into the core set by virtue of being added under another headline outcome.
- If add too many sub-categories under main heading will become too difficult to deliver.

ACTIONS resulting from discussion

The following actions were taken after the above discussion:

- Combine outcome death relating to burn, death from other causes
- Combine multi organ failure and multiorgan dysfunction as often used interchangeably. Move kidney and lung function into organ dysfunction outcome.
- Burn wound healing: should incorporate burn wound and grafted wound- healing of the wound is important.
- Combine procedural and background pain under one heading- 'Acute pain'.
- Scar pain combined with itch- both to address long-term neuropathic pain, differentiated from acute pain.
- Merge complications under one heading 'complications' to formally include PE, DVT, sepsis and wound infection

The above decisions reduced the outcome list to be voted on to 11 items.

- Death (combined 2)
- Serious complications (to include sepsis, wound infection as above)
- Multi-organ failure (combined with dysfunction, lung and kidney function)
- Scar contractures
- Daily tasks (to include walking)
- Time to heal (combined healing of burn wound and healing of grafted wound)
- Long-term pain (to include itch)
- Acute pain (include background and procedural)
- Appearance
- Psychology
- Growth

Therefore, it was agreed that any outcomes that were voted as being important by either patients or professionals should be added to the voting (see table 3). Further discussion resulted in some of the items being merged under existing items from the above set.

- Wound infection- this was merged under serious complications

- Understanding of treatment received
- Physical wellbeing to include walking
- Number of surgeries needed
- Length of stay in ICU – this was merged with Length of time on ventilator
- Immune response to fighting infection
- Time to return to work/school/previous occupation
- Anxiety about future, anxiety – these were merged under 'Psychology'.
- Donor site healing- this was merged under 'wound healing'

3. International Consensus voting

Voting slides were developed with changes of definitions of outcomes to reflect the decisions about item merging above. Seventeen outcomes were included in the first round of voting. Table 4 shows the final outcomes and their revised definitions, as well as the results of the round 1 vote.

In the first round of voting up to 44 participants voted (range 39-44 votes per item). Please note that total voter numbers increased between rounds 1 and 2 due to additional voters joining the online voting.

Table 4: Round 1 Outcomes, definitions presented and percentage voting to be included in COS

Outcome	**Definition**	**N Voting**	**N(%) voting included in COS**
Death	**Death of a patient from any cause soon after the patient is injured. Death due directly to the burn injury soon after the patient is injured.** For example: death due to 'burn shock' or due to a burn wound infection or sepsis or death from a heart attack.	41	36 (87.8)
Organ failure/ dysfunction	**Whether the burn causes several of the patient's organs to fail/not work at all or stop working well (dysfunction).**	39	28 (71.9)

	For example: kidney failure alongside liver failure, where it is unlikely to get better, or will need long-term care or poor kidney function and poor liver function at the same time that is likely to get better following treatment.		
Serious complications	**Includes: blood clot, sepsis, wound infection but <u>not</u> organ dysfunction/failure.**	39	36(92.3)
Scar contractures	**The effect of the burn scar on a patient's ability to move joints (contractures).** For example: inability to straighten arm, difficulty moving fingers normally, limited range of motion of joints.	41	28 (68.3)
Daily tasks	**A patient's ability to carry out normal daily tasks. This includes walking.** For example: dressing, washing, making food or drinks.	41	36 (87.8)
Time to heal (incl. wound graft)	**How quickly a patient's burn wounds heal. This includes wounds after receiving a skin graft (A skin graft is when healthy skin is taken from another party of the body and placed over the burn wound to help it heal).** For example: how many days or weeks does it take for the burn to heal completely or how well a burn that has needed a skin graft heals.	41	29(70.7)
Pain acute	**Pain in the burn wound. This includes background and procedural pain.** For example: pain all the time, pain at night.	39	23(59.0)
Pain long-term	**The amount of pain caused by a burn scar. This includes itch.**	41	31 (75.6)
Appearance	**Patients' appearance after a burn injury.** For example: appearance of the scar, facial appearance, body image.	44	27(61.5)
Patient psychology	**The psycho-emotional effect a burn has on a patients. Distress and anxiety can often be consequences of a burn and affect patient well-being.**	43	32(74.4)

	For example: anxiety triggered by reminders of how the burn happened or low self-esteem in case of a visible scar.		
Growth	**The effect a burn has on a child's growth.** For example: not achieving potential height, slowing of growth.	43	4(9.3) ≠
Understanding treatment	**How much a patient understands of the treatment.**	43	8(18.6) ≠
Physical wellbeing	**General Physical well-being**	42	20(47.6) ≠
Immune response	**Ability to fight infections**	42	6(14.3) ≠
Number of surgeries	**Number of surgeries**	43	16(37.2) ≠
Time to return to work/school/previous occupation	**Time to return to work/school/previous occupation**	43	34(79.1)
Length of stay in ICU	**This includes length of time on a ventilator.**	44	19(43.2) ≠

≠indicates items not meeting the 50% cut off for inclusion in second voting round.

Selection of items to carry through to round 2 vote

Outcomes where at least 50% of the participants stated that they should be included in the COS were carried through to the second round. On this basis, 5 outcomes were removed prior to the second round vote (indicated using * in table 4).

Table 5 illustrates the items that were voted upon in the second round of voting, the number of participants for each outcome and the % voting to include them in the COS. In round 2 45 people joined the voting (range 43-45 votes per item).

Table 5: Round outcomes and voting results

Outcome	**N voting**	**N (%) voting to include in COS**

Death	43	34 (79.1)*
Organ failure/ dysfunction	44	20 (45.5)
Serious complications	45	41 (91.1)*
Scar contractures	44	23 (52.3)
Daily tasks	44	36 (82.0)*
Time to heal (incl. wound graft)	44	27 (61.4)*
Pain acute	45	21 (46.7)
Pain long-term	45	30 (66.7)*
Patient psychology	45	37 (82.2)*
Physical wellbeing	45	15 (33.3)
Time to return to work/school/previous occupation	44	37(84.1)*
Appearance	44	24(54.6)

*indicates final COS outcomes

4. Final Core Outcome Set

It was anticipated that between 5 and 7 items would be an appropriate number of outcomes to include in a COS. Following analysis seven outcomes were selected to be included in the burns core outcome set, using a cut-off of >60% of participants rating it as important to be included.

1. Death: to include death from any cause and death from the burn
2. Serious complications: to include Sepsis, wound infection, DVT, PE
3. Daily tasks: to include walking
4. Time to heal: to include wound healing, grated wound healing and donor site wounds
5. Long-term pain and itch
6. Patient psychology: to include anxiety and anxiety about the future
7. Time to return to work/school/ previous occupation

Further discussion

There was further discussion about including organ failure/dysfunction to the COS under serious complications because it can be considered to be a complication of burn care. It was agreed that this

should not be included due to the cut-off % would be an outcome that people may wish to include in their reporting as it would be reported as a Serious Adverse Event (SAE) in research trials.

Next steps

- Disseminate meeting report to all collaborators and attendees for comment
- Finalise the meeting report
- Write main COS paper – co-authors will be agreed
- Agree a dissemination plan

Agree next steps to look at outcome measures and when outcomes should be measured (outcome timing; short and long-term outcomes as separate

Appendix M COSB-I collaborator list

Collaborator name	Organisation	Country
Mr Jeremy Rodrigues / Matt Gardiner	RSTN	UK
Barnaby Scholefield	PICS	UK
Sharmila Dissanaike	Chair, Texas Tech University Health Sciences Center	USA
Christos Giannou	1. Honorary Lecturer at the Blizard Institute, Queen Mary & Barts, University of London; 2. International Health & Management of Health Crises. National and Kapodistrian University of Athens	UK / Greece
Albert Law	Chairman, Hong Kong Burns Assocation	China (Hong Kong)
Tom Potokar	1. Interburns; 2. Centre for Global Burn Injury Policy & Research; 3. NIHR Global Health Research Group on Burn Trauma	UK
Federica D'Asta	Consultant Burns Surgeon UK	UK / Italy
Duncan Nickerson	Medical Director, Plastic Surgeon, Calgary Firefighters' Burn Treatment Centre Foothills Medical Centre	Canada
Peter Moortgat	1. Physiotherapy coordinator; 2. Research & innovation manager; 3. Scar Academy coordinator; 4. OSCARE	Belgium
Anna Cutler	HTA Senior Research Fellow/Scientific Advisor NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)	UK
Jo Dumville	Cochrane Wounds	UK
dr. Michela Venturi	1. Cesena Burn Center; 2. University of Bologna	Italy
Rajeev Ahuja	Retired plastic surgeon New Delhi; Past president ISBI	India
Mohsen Rezaeian	**Professor** of Epidemiology; 2. Head of Epidemiology and Biostatistics Department, Rafsanjan medical School IRan	Iran
Rochelle Kurmis	Allied Health Project Manager, Adult Burns Service Royal Adelaide Hospital	Australia
Alison Tweddle	Children's Burns Trust	UK
Catrin Pugh	Patient	UK
Martin Risom Vestergaard	Anaesthesia	Denmark

Nicola Clayton	Clinical Specialist Speech Pathologist | B.App.Sc. (Sp.Path.), M.Sc.Med., PhD; Speech Pathology Department, Intensive Care & Burns Unit | Voice & Swallow Clinic | NSW Dysphagia Interest Group Coordinator; Honorary Affiliate, University of Sydney & University of Queensland	Australia
Jonathan Bayuo	Presbyterian University College, Ghana, Nursing Department; University of Ghana	Ghana
Belinda Gabbe / Yvonne Singer	Head of Pre-hospital Emergency and Trauma Research; Department of Epidemiology and Preventive Medicine; School of Public Health nad Preventive Medicine; Monash University	Australia
Leila Cuttle	Principal Research Fellow; Faculty of Health, School- Biomedical Sciences; Research- Biomedical Sciences IHBI Membership; Institute of Health Biomedical Innovation; IHBI Health Proejcts; IHBI Biomedical Sciences-IPTM University of Queensland	Australia
Susan Hendrickson	Plastic surgery STR	UK
Kamal Phuyal		Nepal
Cecilia Li	The Hong Kong Polytechnic University Hung Hom, Hong Kong.	China (Hong Kong)
David Kulber	Professor of Surgery, Cedars Sinai Medical Centre AND USC Keck School of Medicine	USA
As/prof. Nguyen Nhu Lam	Deputy director, National Burn Hospital 2. Vice President Vietnam Burn Association; Hanoi Vietnam	Vietnam
Tahir Mehmood Khan	Assoc **Prof**, Dr, School of Pharmacy, Monash University Malaysia Asian Centre for Evidence Synthesis in Population, Implementation and Clinical Outcomes (PICO),	Malaysia
Jonathan Oliver White	Head of education for many years in the ICU, accredited in simulation training and have responsibility for simulation in the intensive care ward; Trauma interested and am international faculty member for DATC / DSTC courses	Denmark
Pedro Santos	Plastic surgeon	Mozambique
Jim Gallagher.	I am burn director from the USA at Cornell, in NYC.	USA
Anthony Charles MD,MPH, FRCSEd, FACS	Professor of Surgery; Chief, Division of Trauma/Critical Care and Acute Care Surgery; Director, UNC ECMO Program; Director of Global Surgery, UNC Institute of Global Health; Adjunct Professor of Public Health, UNC School of Medicine, Gillings School of Global Public Health 4008 Burnett Womack Building.	USA
Tsjitske Haanstra	BORN coordinator, Beverwijk	Netherlands

Teruichi Harada	Trauma surgeon and critical care physician, professor of reconstructive surgery	Japan
Chuka Ahachi	Professor	Nigeria
AA Gde Putra Semara **Jaya**	man- contacted via researchgate; Surname is JAYA	Indonesia
Belson Rugwizangoga	Department of Pathology, University teaching hospital of Kigali, Rwanda	Rwanda
Mohsen Rezaeian		Iran
G Gerelmaa (Dr Gimaa)	Graduate student	Mongolia
Carisa Perry-Parrish	Assistant professor Psychiatry and Behavioral Sciences, Johns Hopkins, Baltimore	USA
Joanne Potterton		South Africa
Axel Pavez		Chile
Guillaume Monneret	Professor, Cellular immunology, E Herriot Hospital, Lyon	France
Marko Zdravkovic	Maribor, Slovenia	Slovenia
Zakiyeh Jafaryparvar	Iran. Master of science in critical care nursing	Iran
Murat Ali Cinar	Turkey	Turkey
Keng Siang Lee	Singapore UK	Singapore
Jennifer Zuccaro	Canada Sick Kids	Canada
Linda Yoder	Past predisdent academy of medical surgical nurses, Texas	USA
Andrea McKittrick	Occupational Therapist Brisbane	Australia
Randeep Mullhi	Anaesthesia Consultant	UK
Ioannis Goutos	Plastic Surgery Consultant, Barts Health	UK
Sarvesh Logsetty	Not known	Canada
Hairil rizal abdullah	Clinical director, perioperative services and senior consultant, dept of anesthesiology	Singapore
Sonia Gaucher	Plastic Surgeon	France
Tan Jin Huei		
Esteban Ortiz	Ecuador	Ecuador
Fikri Abu-zidan		UAE
Vivian Carvalho		Brazil
Mary Kennedy	Service improvement nurse	UK
Laura Shepherd	Clin psych	UK
Rachel Wiltshire	Mid essex	UK
Vladamir Berezutsky		Ukraine
Meltem Yildirim		Spain
Rei Ogawa		Japan
Tomasz Torlinski		UK

Laura Godat		USA
Ludovic Maudet		Switzerland
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Andrew Lindford		Finland
Linzette Morris		South Africa
Claire Jennings		UK
Mohammed Al Marjani		Iraq
Fredrik Huss		Sweden
David Rothstein		USA
Beth Sheilds		USA
Alexandra de Young		Australia
Bronwyn Griffin		Australia
Abdul Bachani		USA
A Cochran		
Syed Omair Adil	Lecturer Biostatistics Dow University of Health sciences	Pakistan
Corine Benjet		Mexico
Stijn Blot		Belgium
Guido Ciprandi		Czech Republic
D Azovskiy		Russia
Eduardo Herrera Reyes	Nuclear Medicine Physician	Austria
Ola Elsherbiny		Egypt
James Gollogly		cambodia
Josef Haik		Israel/ Australia??
Taous Khan		Pakistan
Markus Landolt		Switzerland
Lalit Makhija		India
Matt Mauck	Anaesthesia, UNC School of Medicine	USA
Asgjerd Litlere Moi		Norway
B Nega		ethiopia
Jennifer Newberry		USA
Jennifer Paratz		Australia
Petra Brysiewicz		South Africa
Pammla Petrucka		Canada
Joel Fish	Sick Kids	Canada
Julian Textoris		
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Denise Kendrick		UK
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