

The MRC ConDuCT-II Hub for Trials Methodology Research

Final report

December 2018

**Collaboration and innovation in Difficult and Complex
randomised controlled Trials In Invasive procedures**

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Report overview

This is a summary of work carried out by the MRC ConDuCT-II (C-II) Hub since work started in 2014.

The last external advisory meeting took place in November 2016, including Professors Damian Griffin, Mark Sculpher and Shaun Treweek. Overall feedback from the committee was very positive (“The C-II Hub is a significant part of the landscape in the UK. A concentration of people doing excellent work”) and highlighted the broad publications and interests of the Hub. The committee specifically recognised the significant impact of the Quintet Recruitment Intervention (QRI) and studies with integrated methodological projects. Committee feedback emphasised that although all Hub members are not doing surgical trials methodology, it is a special part of the Hub that should be continued as a flagship theme.

In this report we summarise the Hub’s progress and describe the work achieved within each research theme, together with illustrative impact case studies. We also outline major successes and future plans.

A summary of training and capacity building work undertaken is outlined, including details of PhD, MD and MSc projects undertaken within and affiliated with the Hub, personal awards and fellowships gained by Hub members, the contribution of Hub members to short courses, and workshops and training courses delivered by Hub members. In addition, the external advisory functions of Hub members are detailed. Finally, key grants and publications are outlined, with a comprehensive list of grants and publications since the start of the C-II Hub included as appendices.

ConDuCT-II Hub overview, aims and objectives

The MRC ConDuCT-II (Collaboration and innovation for Difficult and Complex randomised Controlled Trials In Invasive procedures) HTMR aims to develop into a centre of excellence for high-quality, cutting-edge methodological research of relevance to pragmatic randomised controlled trials (RCTs) in general, but with a particular focus on the needs of RCTs in surgery. It is a multi-disciplinary team based in the Bristol Medical School, Population Health Sciences, University of Bristol, led by Director Jane Blazeby, Professor of Surgery, and supported by Deputy Director Professor Will Hollingworth, Professor of Health Economics. The Hub is supported by a grant of £1,921,689 over five years, which was activated in April 2014.

Overview of Hub research themes

The Hub has four research themes, underpinned by methodological expertise in medical statistics, social sciences and clinical expertise in surgery, primary care and public health. Additional relevant expertise is available from the local CTUs, the DECIPHer Centre and the NIHR Schools for Primary Care and Public Health Research. Although presented as separate themes, there is considerable overlap and continuity between the themes in terms of the development and application of the methodological work.

Theme 1 - Prioritisation and design of trials for cost effectiveness analysis. This theme considers the development of value of information and health economic methods to improve the selection and design of RCTs to optimise evidence on cost-effectiveness.

Theme 2 - Integrative and dynamic research methods to optimise recruitment to RCTs. The focus of theme 2 is the improvement and optimisation of trial recruitment by the development of integrative and dynamic research methods.

Theme 3 - Improving Feasibility study designs And Conduct to enhance Trial quality and results (FACT). Work in theme 3 centres around improving trial performance by defining feasibility study designs and developing methods for trial monitoring and conduct.

Theme 4 - Outcomes in RCTs: selection, reporting and integration in decision making. Theme 4 concentrates on methods for outcome selection and reporting, and the integration of outcomes into decision-making.

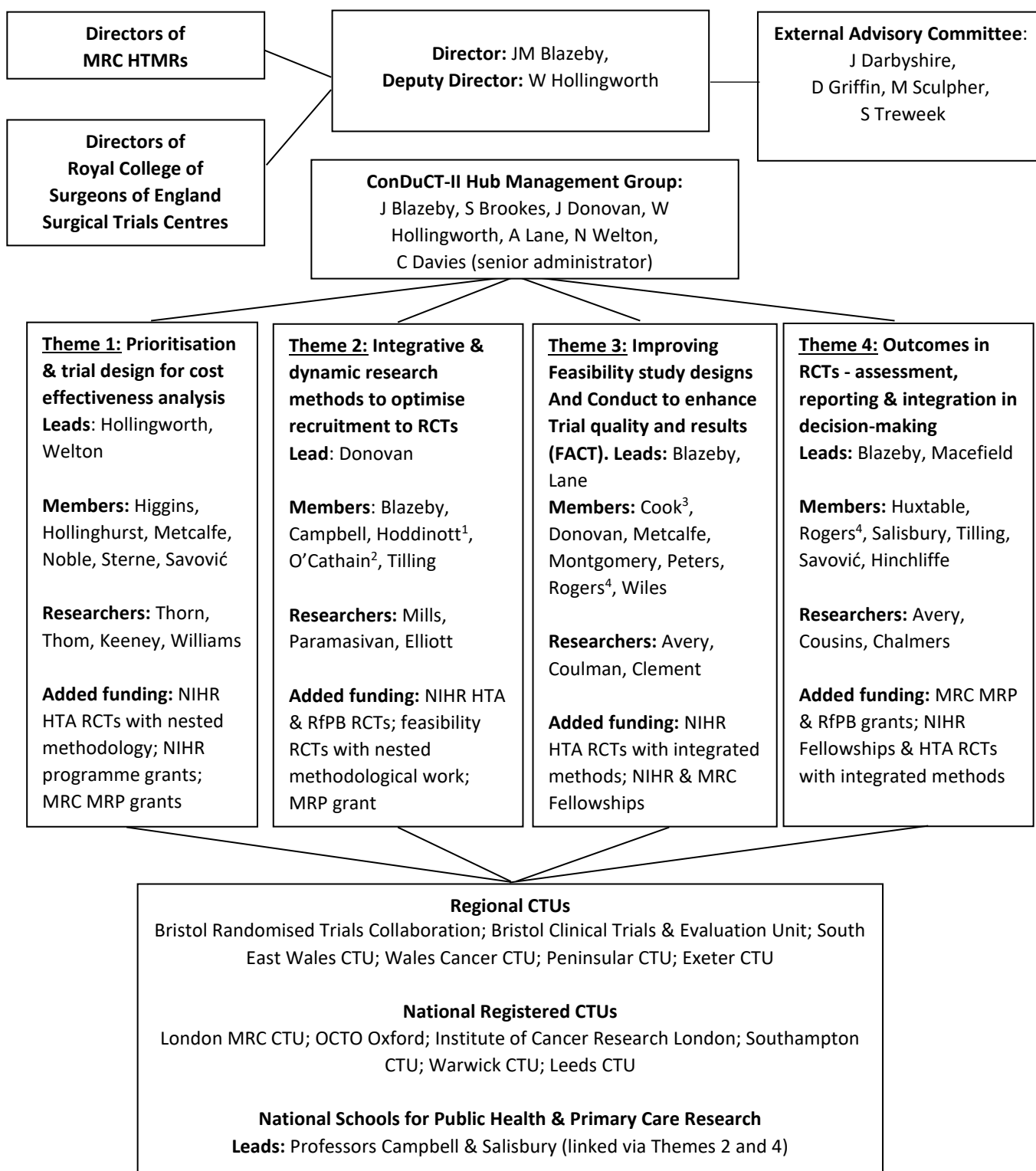
Aims and key objectives

The overall aim of the Hub is to develop and implement research methods that will lead to marked improvements in the successful prioritisation, design, conduct and completion of pragmatic RCTs in general, and surgery in particular.

The key objectives are:

- To focus on and extend the Hub's methodological research themes.
- To expand the Hub's national role in supporting the optimal design and conduct of 'difficult' trials of complex healthcare interventions.
- To continue and expand provision for methodological collaboration with CTUs, HTMRs, the NIHR Research Design Service (RDS) and Schools for Primary Care and Public Health Research in the South West.
- To develop future capacity for methodological research with provision of short courses, PhD studentships and clinical primer opportunities based on the Hub's methodological research themes.
- To develop international and national collaborations with organisations concerned with standards of surgery and invasive procedures.
- To provide a focal point for collaboration between research, surgery, policy and practice that will maximise the relevance, innovation, translation and impact of surgical RCTs in the UK and internationally.
- To establish a sustainable environment and infrastructure beyond the end of the funding for this Hub.

Hub structure



Theme members are all based within the School of Population Health Sciences, University of Bristol, except: ¹School of Midwifery, University of Stirling; ²Health Services Research, University of Sheffield; ³Centre for Statistics in Medicine, University of Oxford; ⁴School of Clinical Sciences, University of Bristol.

Appendix 1 provides a full list of the Hub theme leads, members, researchers and affiliates.

A message from the Hub Director, Jane Blazeby

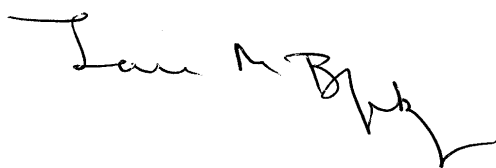
It has been my pleasure and privilege to direct the MRC ConDuCT Hub for Trials Methodology Research in Bristol for the past 10 years. Core funding has seeded, developed and contributed methodological expertise to help establish and/or expand these now substantive groups at the University of Bristol:

- Health Economics at Bristol (HEB)
- Multi-Parameter Evidence Synthesis (MPES)
- Bristol Appraisal and Review of Research (BARR)
- Qualitative Research Integrated within Trials (QuinteT)
- Royal College of Surgeons Centre for Surgical Research
- Surgical Innovation Theme of the Bristol Biomedical Research Centre

Novel methods developed in the Hub have been integrated into newly funded RCTS, pilot and feasibility studies. This has mutually benefitted trial conduct, and, the methodological research by allowing evaluation and testing in a real trial setting. Close liaison with registered clinical trials units in Bristol and nationally has made this possible. Novel methods developed by the Hub and trial conduct evidence have also been implemented in national guidelines and policy, e.g. NICE Clinical Guidelines, NICE Technology Appraisals, and the NIHR Clinical Trials toolkit.

Capacity building has been a major focus in the Hub. Over 20 doctoral studentships have been funded via the Hub, Hub for Trials Methodology Research Network, NIHR, Royal College of Surgeons and other schemes to undertake Hub related research. Clinical academic trainees including academic foundation doctors, academic clinical fellows and clinical lectureships have been linked to the Hub. University posts have been appointed (lecturerships, senior lectureships and chairs) in all the above substantive methodological areas. Three academic surgeons have successfully gained clinician scientist awards (NIHR and MRC).

I am very grateful for the support of the theme leads and Hub researchers, for the administrative staff, the university for hosting the Hub and the MRC for its funding.



Jane Blazeby

Theme 1: Prioritisation and trial design for cost-effectiveness analysis. Leads: Professor Will Hollingworth, Dr Nicky Welton

Overview and specific objectives

The broad aim of the theme is to develop methods to ensure that RCT funding is targeted at the questions where it is most needed and that RCTs, once funded, are designed to collect complete and unbiased evidence on the cost-effectiveness of the intervention.

Specific objectives:

1. We aim to improve methods for evidence synthesis so that information generated by RCTs can be summarised accurately and rapidly incorporated into practice. These methods include:
 - a. Developing risk of bias assessment tools for use with RCTs and systematic reviews, applying methods for bias adjustment and capturing uncertainty induced by missing data in evidence synthesis.
2. To develop and apply value of information (VOI) and other methods to help prioritise which RCTs are most needed and optimise RCT design in the face of heterogeneity. For example:
 - a. Consideration of the relative value of further research in particular patient populations/sub-groups.
 - b. Application of recently developed methods for mapping between outcomes to inform trial design, such as which outcomes to measure.
 - c. Incorporating multiple treatment options (how many and which arms to include, and which types/components of interventions to include - in collaboration with theme 3).
3. We aim to improve the conduct of economic evaluations alongside RCTs so that research funder money invested in RCTs provides clinicians and policy makers with better evidence on the cost effectiveness of medical technologies. This includes:
 - a. Improving the accuracy of participant completed resource use measures (RUMs) by providing a repository of existing RUMs, including information on their validity; testing methods for minimising missing data; and developing a new generic, modular RUM for use in UK trials.
 - b. Developing broader measures of outcomes (i.e. capability measures) for use in trials of interventions where conventional measures (e.g. EQ-5D) are unlikely to capture important consequences for patients.

Major successes

Theme members (Savović, Higgins, Sterne) working with Cochrane and supported by MRC Network funding developed RoB 2 - a new tool for assessing the risk of bias in randomised trials included in systematic reviews. We expect this tool will be widely adopted by researchers and that it will be influential in helping policy makers interpret the findings of RCTs.

Theme members (Savović, Higgins) also worked with the Cochrane collaboration to publish ROBIS, a new tool for assessing the risk of bias in systematic reviews (see impact case study for further details).

Members of the theme (Welton, Lopez-Lopez) applied novel methods for network meta-analysis of complex interventions alongside an NIHR programme grant evaluating effectiveness and cost-effectiveness of integrated therapist and online CBT for depression in primary care, to be used to inform the development of the intervention to be used in the RCT. Theme members (Thom, Welton) have used ideas from financial mathematics to make value of information calculations more computationally efficient. The theme has also been involved in a variety of applications of value of information methods, which are important to contribute to changes in practice, in the acceptability and use of these methods. These include surgical wound dressings (Bluebelle, Welton, Williams, Blazeby, Reeves), low friction sheets for burns patients (Thom, Welton, Young), and the Ross procedure (Thom).

We (Welton, Dias, Phillippo, Ades) successfully obtained funding for three MRC Methodology Research grants: (1) in collaboration with Pfizer to develop methods for model-based NMA to account for dose and time relationships in synthesis of phase-II and phase-III trial evidence, (2) to develop population adjustment methods for indirect comparisons and network meta-analysis, and (3) inferring relative treatment effects from combined use of observational and randomised data in collaboration with Universities of Leicester and York. We (Ades, Welton, Dias, Phillippo) developed a method to assess sensitivity of recommendations based on network meta-analysis to potential bias and errors in the evidence, and successfully piloted the method on a NICE clinical guideline. Phillippo, Welton, and Dias have also produced a NICE Decision Support Unit Technical Support Document on methods for population-adjusted indirect comparisons which has already changed practice and been cited in submissions to NICE.

We (Thorn, Noble, Hollingworth) have been awarded funds by the European Horizon 2020 scheme to develop a resource-use questionnaire for patients with mental health conditions across Europe. Pecunia (Programme in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluations) is an ambitious project (involving ten partner institutions across six European countries) that aims to develop better understanding of the variations in costs and outcomes within and across countries and to increase the comparability (and therefore transferability) of economic evaluations in Europe.

We (Thorn, Noble, Hollingworth, Brookes (Theme 4)) secured Network funding to review existing RUMs to generate a 'long list' of items of resource use (such as GP appointments or outpatient visits) that are commonly included in resource-use questionnaires. We conducted two rounds of a Delphi survey with an expert panel of health economists to identify the key items that should be included in a standardised RUM. This work was presented at the Health Economists Study Group meeting and has been published in *Value in Health*.

We (Coast) have continued work on developing and validating the ICECAP questionnaires to measure how health and healthcare affects people's ability to enjoy life, have autonomy, sense of achievement, etc. These measures are being adopted in an increasing number of RCTs instead of, or as well as, conventional preference based health-related quality of life measures. We have recently developed an ICECAP measure suitable for use in economic evaluation that captures the benefits of end-of-life care to those close to the dying. Theme member Coast has also recently been awarded a five-year Wellcome Investigator Award, which started in January 2018. The research will focus on generating a life-course approach to capability measurement for use in

economic evaluation. This will include developing child ICECAP capability measures and exploring when and how to shift between capability measures at different stages of the life-course. Much of the work will be conducted using qualitative methods.

Training and capacity

Dr Thom successfully obtained a promotion/new position as Research Fellow in the NIHR funded Biomedical Research Centre Surgical Innovation theme, but remains affiliated to the Hub, working on a synthesis of interventions to prevent surgical site infections. Dr. Claire Williams replaced Howard in the Hub as Senior Research Associate in Health Economics Modelling, working on expected value of sample information methods with multiple treatment options. Theme 1 researchers (Dr Thom and Dr Joanna Thorn) have both been awarded HTMR network grants, allowing them to gain experience as principal investigators (PIs).

Patricia Guyot (supervised by Welton) was awarded her PhD on *'Expected survival time as a summary statistic in evidence synthesis and economic analysis'* in July 2014 and is now working for MAPI values research. Theodoros Mantopoulos (Welton & Dias) was awarded his PhD on *'Incorporating Covariates in Cost-Effectiveness Analysis'* in June 2018 and is now working as a Senior Analyst at PRMR Consulting. Theme 1 supports Hub-funded PhD students: Kirsty Garfield (Thorn, Noble, Hollingworth) *'Developing a modular resource-use questionnaire for use in economic evaluations alongside randomised controlled trials'*; Gemma Clayton (Jones & Higgins) *'Incorporating external evidence syntheses in the analysis of a clinical trial'*; and Ashma Krishan (Welton) *'The analysis and reporting of time to event data in randomised controlled trials: impact on evidence synthesis and cost effectiveness'*. Hub-affiliated student Mairead Murphy (Hollinghurst & Coast) was awarded her PhD on *'Developing a generic outcome measure for primary care'* in February 2017 and won the Faculty of Health Sciences award for Best Doctoral Research Thesis. She is currently working as a Senior Research Associate for the Centre for Academic Primary Care. A second Hub-affiliated student, David Phillippo (Dias, Welton & Ades) is currently working on *'Calibration of treatment effects in network meta-analysis using individual patient data'*. Welton is on the advisory group for several fellowships: Prof Tracey Sach (UEA) NIHR CDF on economic evaluation methodology alongside trials of eczema, Dr Sarah Donegan (Liverpool) MRC fellowship on incorporating covariates in network meta-analysis, Becky Boucher (Leicester) NIHR DRF on adjusting for treatment switching in health technology assessment, and Laura Flight (Sheffield) NIHR DRF on the economic evaluation of adaptive design trials.

We jointly organised (Welton with Mark Strong, Sheffield; Gianluca Baio & Anna Heath, UCL) the 3-day short course, "Statistical Methods for Value of Information" UCL June 2016, funded by the MRC HTMR. The course was attended by 33 delegates and was the first course of its kind providing hands-on training on how to do VOI calculations. The course has subsequently developed into a self-supporting 5-day short course on Bayesian Methods in Health Economics, which now runs annually. We (Thom, Dixon, Williams) also ran a workshop part-funded by the Hub network on "Using R for Cost-Effectiveness Analysis", which was attended by 51 delegates, and led to the development of a pilot short course (see below).

We also deliver training as part of the School's annual short course programme. We (Marques, Noble, Thom, Welton, Hollingworth, Hollinghurst & Thorn) developed and delivered training on *'Introduction to Economic Evaluation'*, *'Introduction to Network meta analysis'* (Welton, Dias, Phillippo), *'Introduction to Bayesian analysis using WinBUGS'* (Dias, Welton, Ades), *'Systematic reviews and meta-analysis'* (Higgins, Jones, Savovic). Two new short courses are being piloted

internally in 2019 before being offered externally: *'Introduction to Qualitative Methods for Health Economics'* (theme member Coast) and *'Economic Evaluation and Modelling Using R'* (theme members Thom, Dixon, Williams, Welton). Theme members Thorn and Noble have contributed sessions to the School short course on questionnaire design.

We deliver external training (Welton, Dias, Phillippo, Mawdsley, Pedder) including: a regular annual course in Mixed and Indirect treatment comparisons in collaboration with colleagues in Leicester; various courses for NICE Guidelines; Introduction to Network Meta-Analysis in Health Psychology in Galway 2018; courses and workshops at conferences (Society for Medical Decision Making; International Society of Clinical Biostatistics; G-I-N (Guidelines International); American Conference on Pharmacometrics; International Society for Pharmacoeconomics and Outcomes Research, International Society for Clinical Biostatistics); training to Industry: Model-Based Network Meta-Analysis for Pfizer Ltd; Inconsistency checking for ICON.

MRC HTMR Working Groups

Members of Theme 1 contributed to the Evidence Synthesis Working Group. Gemma Clayton conducted a survey on use of evidence synthesis in RCTs, as part of her PhD, in collaboration with the working group, published in *Trials*. Members of Theme 1 organise (Noble) and contribute to the Health Economics: Resource use and costs Working Group. This group has collaborated on the DIRUM initiative, related papers and several workshops including hosting workshops on the role of health economics analysis plans (Oct 2015) and cost-effectiveness alongside surgical trials (Nov 2017).

Update: Impact case study (year 1)

Value of information methods help research funders make the best use of public funds

Research team: Soares MO (York), Welton NJ (ConDuCT-I & II), Harrison DA (ICNARC), Peura P (York), Shankar-Hari M (ICNARC), Harvey SE (ICNARC), Madan J (ConDuCT-I), Ades AE (ConDuCT-I), Palmer SJ (York), Rowan KM (ICNARC), Lewis G (UCL), Dowrick C, Gilbody S (York), Peters T (Bristol), Wiles N (Bristol), Hollingworth W (ConDuCT-I & II), Kendrick T, Kessler D, Thom HHZ (ConDuCT-II)

Summary of initial impact

VOI methods to identify the net returns from future trials/research studies of a given design. These methods have been used to help funders identify the best use of public funds for future research studies through (i) an NIHR commissioned VOI analysis to help inform a funding decision on a trial of Intravenous Immunoglobulin (IVIg) for patients with severe sepsis; (ii) a VOI analysis conducted in the early phase of the PANDA NIHR programme grant on use of anti-depressants according to baseline severity of symptoms, to help inform the design of the subsequent RCT, and presented in a report to justify continued funding to the RCT phase of the project.

Recent impact

The RCT phase of PANDA was funded, has now finished recruitment and is about to report results. VOI analyses have been conducted alongside feasibility phases of RCTs: (i) a project evaluating the feasibility of an RCT of a physiotherapy intervention for patients with hypermobility, and (ii) to evaluate which type of surgical dressings are cost-effective, and to inform the design of an RCT comparing different surgical dressings.

Update: Impact case study (year 1)

Database of instruments for Resource Use Measurement (DIRUM)

Research team: Hughes D, Ridyard C (Bangor), Hollingworth W, Noble S, Thorn J, Coast J (ConDuCT-II), Wordsworth S (Oxford), Cohen D (South Wales), Knapp M (LSE), Whitehurst D (Vancouver)

Summary of initial impact

Randomised controlled trials (RCTs) are commonly used to estimate the value (i.e. cost-effectiveness) of medical interventions. Despite advances in access to routine data, trialists frequently rely on patient-reported health care use questionnaires. However, resource-use measurement by patient recall in economic evaluations alongside RCTs is characterised by inconsistency and a lack of transparency or validation. To address this, three HTMRs applied for MRC network support to develop the Database of Instruments for Resource Use Measurement (DIRUM). DIRUM (www.dirum.org), established in 2011, is a repository of resource use measures and related methodological papers that allows economists to share questionnaires, identify best practice and collaborate on resource use methodology projects.

Recent impact

- Funders & research design: DIRUM is part of the 'improving health by improving trials' [guidance pack](#) issued by the MRC Hubs for Trials methodology research and is widely signposted on the NIHR Research Design Service [websites](#). It has been adopted by [UK](#) and [international](#) researchers as an essential resource for identifying existing questionnaires in the relevant clinical area. DIRUM is widely referenced in standard operating procedures for economic evaluation used by [Clinical Trials Units](#) and is cited in the [NIHR clinical trials toolkit](#).
- Academia: The DIRUM database is cited in four textbooks (UK and US) on methods for economic evaluation and health services research:
 - a. Drummond MF, et al. *Methods for the economic evaluation of health care programme*. Fourth edition. Oxford: Oxford University Press, 2015.
 - b. Glick HA, et al. *Economic Evaluation in Clinical Trials, Second Edition*. Oxford, Oxford University Press, 2015
 - c. Baio G. *Bayesian Methods In Health Economics*. Boca Raton: CRC Press, 2013
 - d. Richards D, Hallberg I, editors. *Complex Interventions in Health: An Overview of Research Methods*. New York: Routledge, 2015
- International: The database has had over 4000 visits in the last year with over 60% of these coming from overseas. To cater for these overseas visitors, the database now accepts RUMs from all over the world. The database now contains 86 instruments and has had over 7000 downloads.

Impact case study 1 (year 2)

ROBIS: a new tool to assess the risk of bias in systematic reviews

Research team: Savović J, Higgins JPT (ConDuCT-II)

ROBIS is a new tool for assessing the risk of bias in systematic reviews. Systematic reviews are generally considered to provide the most reliable form of evidence for the effects of a medical intervention, test, or marker. Because systematic reviews serve a vital role in clinical decision making and resource allocation, decision makers should expect consistent and unbiased standards across topics. Systematic flaws or limitations in the design or conduct of a review have the potential to bias results. Bias can arise at all stages of the review process; users need to consider these potential biases when interpreting the results and conclusions of a review. The potential of flaws in the design and conduct of systematic reviews are becoming better understood. Several tools exist for undertaking critical appraisal and quality assessment of systematic reviews, but none were specifically aimed to assess the risk of bias in systematic reviews; all previously available tools have a broader objective of critical appraisal or focus specifically on meta-analyses. We developed the ROBIS tool to fill this gap.

ROBIS has been developed using rigorous methodology and is aimed at four broad categories of reviews: interventions, diagnosis, prognosis and aetiology. The tool is completed in three phases: (1) assess relevance (optional), (2) identify concerns with the review process and (3) judge risk of bias. Phase 2 covers four domains through which bias may be introduced into a systematic review: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis of findings. Phase 3 assesses the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the Phase 2 domains. We hope that ROBIS will help improve the process of risk of bias assessment in overviews and guidelines, leading to robust recommendations for improvements in patient care.

ROBIS is being used by a broad range of international academic audiences. We are aware of the following organisations who are recommending or using ROBIS: NICE (UK), KSR evidence, Estonian Health Fund, Collaboration for Environmental Evidence, Cochrane organisations (e.g. Cochrane Argentina, Cochrane Australia, Cochrane Italy), Melbourne GRADE Center, NHS organisations, South African Medical Research Council, CADTH, and the Brazilian Ministry of Health. ROBIS has been translated into Italian, Portuguese and Spanish language. The journal "Environment International" has formally included ROBIS as part of the peer review process.

Impact case study 1 references:

Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R and the ROBIS group. ROBIS: a new tool to assess the risk of bias in systematic reviews was developed. Journal of Clinical Epidemiology. 2016; 69:225-345 (doi:10.1016/j.jclinepi.2015.06.005)

Impact case study 2 (year 2)

Model-Based Network Meta-Analysis; a framework for evidence synthesis of clinical trial data.

Research team: Nicky Welton, Sofia Dias, David Mawdsley, Hugo Pedder (ConDuCT-II). Meg Bennetts, Martin Boucher (Pfizer).

Model-based meta-analysis (MBMA) is increasingly used in drug development to inform decision making and future trial designs, through the use of complex dose and/or time course models.

Network Meta-Analysis (NMA) is increasingly being used by reimbursement agencies to estimate a set of coherent relative treatment effects for multiple treatments that respect the randomisation within the trials. However, NMAs typically either consider different doses completely independently or lump them together, with few examples of models for dose. We proposed a framework, Model Based Network Meta-Analysis (MBNMA), that combines both approaches, that respects randomisation, allows estimation and prediction for multiple agents and a range of doses, using plausible physiological dose-response models. The method is general for binary endpoints and other outcome types. We have also developed methodology to model time-course, and to check inconsistency and model fit. We have a pilot version of an R-package, to make the method accessible to analysts. We demonstrated this during a tutorial at the American Conference of Pharmacometrics, and also to Pfizer Ltd in La Jolla, US. We are also developing methods to assess model fit and inconsistency for dose-response models, which will also be available in the R-package.

Impact case study 2 references:

Mawdsley D, Bennetts M, Dias S, Boucher M, Welton NJ. Model-Based Network Meta-Analysis; a framework for evidence synthesis of clinical trial data. CPT: Pharmacometrics & Systems Pharmacology. 2016; 5:393-401 (doi:10.1002/psp4.12091)

Impact case study 3

Population adjustment methods for indirect comparisons

Research team: David Phillippo, Nicky Welton, Sofia Dias, Tony Ades

We developed a technical support document (TSD) for the NICE Decision Support Unit critiquing methods for population adjustment for indirect comparisons in Health Technology Assessment, when combining evidence from RCTs where individual patient data is available from one trial only. The research was also published in a paper for Medical Decision Making. The TSD has since been cited in manufacturer submissions to NICE where methodological practise has changed in light of the recommendations from the TSD.

Impact case study 3 references:

Phillippo DM, Ades AE, Dias S, Palmer S, Abrams K, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. Medical Decision Making. 2018. 38:200-211. <http://journals.sagepub.com/doi/10.1177/0272989X17725740>

Phillippo DM, Ades AE, Dias S, Palmer S, Abrams K, Welton NJ. Methods for population-adjusted indirect comparisons in submissions to NICE. NICE Decision Support Unit Technical Support Document 18. December 2016. <http://nicedsu.org.uk/technical-support-documents/population-adjusted-indirect-comparisons-maic-and-stc/>

Future plans

Theme members will continue work on developing capability measures for economic evaluation (ICECAP), improving risk of bias assessment (ROBIS) and network meta-analysis and value of information methods. In addition, we will focus on the following three projects in the next 30 months:

1. Developing a standardised resource use measure for economic evaluation (ISRUM)

A key research area within theme 1 has been to improve the methods by which resource use is identified and measured in economic evaluations conducted alongside randomised controlled trials, with a particular focus on patient self-report methodology. We successfully applied for Network funding to review resource-use questionnaires held in the Database of Instruments for Resource-Use Measurement (DIRUM), allowing us to build on work carried out under ConDuCT-I. The review generated a 'long list' of 60 items of resource use (such as GP appointments or outpatient visits) that are commonly included in resource-use questionnaires. We then conducted a Delphi survey with an expert panel of health economists to identify the key items that should be included in a standardised resource use instrument that is relevant across a wide range of conditions and interventions. The Delphi results suggested ten key items of NHS resource use that should be included in a core questionnaire, and a number of 'bolt-on' modules for use in particular circumstances.

Funding was obtained via the MRC HTMR for a PhD project to take forward the work from the Delphi study to develop and validate a standardised resource-use questionnaire (RUQ). The PhD project is currently underway. The initial task was to undertake a review of the methods used to develop existing resource-use questionnaires. The review identified that for the majority of RUQs, details on their development were not published or limited information was provided. While several RUQs did include detailed information on their development, these RUQs have either not been well utilised, or if they have been used frequently they have undergone a considerable amount of adaptation. A paper detailing this study was presented at the summer 2018 meeting of the Health Economists' Study Group and is currently being finalised for submission to a journal.

A draft version of the questionnaire is currently under construction. Development of the draft has been informed by a review of the structure, wording and formatting of existing RUQs stored in DIRUM, and by several research team meetings to discuss the optimal structure, wording and formatting of the initial draft. Once the draft is finalised, several studies will be undertaken to test and revise items, and to validate the questionnaire. Studies will include semi-structured interviews with patients to finalise the initial wording, semi-structured interviews with health economic experts to ensure the questionnaire is valid for costing purposes, "think-aloud" interviews with patients to assess content validity, a pilot study to assess acceptability and assessing criterion validity in a study comparing questionnaire results to data from GP records.

2. Improving indirect comparisons of treatment effects, allowing for differences in effect modifiers between RCT populations

In our NICE Decision Support Unit Technical Support Document we critique methods Population Adjustment for Indirect comparisons. We (Phillippo, Welton, Dias, Ades) have now developed a new approach (Multi-Level Network Meta-Regression) which overcomes some of the limitations of previous methods and has the advantage that it can be applied to general networks. We have submitted this work for publication, and are currently working on a simulation study to evaluate and compare the performance of the various methods. The work has been presented at various conferences, including invited speaker at focussed workshops.

3. Model-Based Network Meta-Analysis (MBNMA)

We (Pedder, Welton, Dias) have developed methods for time-course and dose-response MBNMA. We are currently working on evaluating the performance of these methods in a

simulation study. We are also finalising two R packages to be made available on CRAN or Github, to help make the methods easily accessible. We plan to work on a combined model for both dose and time course in the future, where the focus will be on interactions between the two functional relationships.

References

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Theme 2: Integrative and dynamic research methods to optimise recruitment to RCT's. Lead: Professor Jenny Donovan

Overview and specific objectives

We aim to extend the development of innovative, integrative and dynamic research methods developed during ConDuCT-I, with a view to optimising recruitment in trials in general and particularly those involving invasive procedures. Mostly, recruitment investigations will be integrated at the feasibility and/or pilot stage to allow sufficient opportunity to optimise recruitment/delivery of a main trial or promote rapid closure of RCTs deemed to be undeliverable.

Specific objectives:

1. Build a detailed understanding of the recruitment process in pragmatic trials, in order to identify discrete and integrated parts of the recruitment process that can form separate interventions or components of an improved dynamic integrative intervention to optimise recruitment.
2. Extend the development and application of the innovative, dynamic and integrative research methods developed in ConDuCT-I (e.g. targeted conversation analysis and quanti-qualitative techniques), in order to develop or refine separate interventions of aspects of a single dynamic intervention to optimise recruitment and informed consent.
3. Develop and apply robust methods to evaluate the effectiveness of the evolving recruitment interventions.
4. Critically appraise definitions of 'pilot' and 'feasibility' studies in collaboration with other HTMRs, and jointly write an expanded guide for designs of such studies for researchers.
5. Provide encouragement for the use of qualitative methods in RCTs more generally.

Major successes

Optimising RCT recruitment and informed consent has continued to be a major focus of theme 2, with the continued development, refinement and application of the 'QuinteT Recruitment Intervention' (QRI). A protocol paper has been published which describes the QRI in detail for the first time, from its development, implementation and applicability to feasibility/pilot studies and main phase RCTs (Donovan et al, 2016). This paper is now part of the guidance pack on optimising recruitment on the HTMR network website. Consideration has since been given to how the QRI may be tailored to particular stages of an RCT, from integration at the outset, to involvement partway through RCTs encountering recruitment difficulties. Methodological advances have seen the development of a tool to measure the timing of aspects of recruitment discussions to flag equipoise issues (Paramasivan et al, 2015), a tool to measure informed consent in RCT recruitment discussions (Wade et al, 2017), and a framework to facilitate clearer recording of the recruitment process and the number of patients screened, eligible, approached and randomised to identify difficulties (Wilson et al, 2018). Activities have also focused on synthesising data from QRI studies to identify the clear obstacles and hidden challenges to

recruitment (Donovan et al, 2014a, Donovan et al, 2014b), as well as developing a richer understanding of specific hidden challenges and offering strategies to manage them (Mills et al, 2014, Rooshenas et al, 2015, Jepson et al, 2018). These QRI lessons have been applied more widely through development and dissemination of a range of training sessions targeted at clinical audiences to enhance their recruitment practice. Theme 2 members are beginning to broaden the clinical contexts in which the QRI can be applied, focusing beyond invasive procedures into contexts such as renal therapies for example. Links have also been established with international colleagues in Europe, India and USA to enable the QRI and its associated methodologies to reach an international market.

Theme 2's applied work has continued through a number of successful grants with integrated QRIs to optimise trial design and/or recruitment. Some of these are main RCTs that build on successfully completed feasibility/internal pilot studies that integrated the QRI – e.g. HTA-funded FASHIoN, Optima, ROMIO, VIOLET and By-Band-Sleeve studies. Other main RCT and feasibility studies that have been funded embedding a QRI include CRUK-funded COMPARE study, RfPB-funded VOCALIST study and RfPB-funded HAND-1 feasibility study – the latter of which has been successfully completed and a proposal for main RCT with integrated QRI submitted to the HTA. More recently funded and initiated QRIs include the HTA-funded Nairo, Prepare, MARS2, H4RT, TARVA, and Sunflower studies, spanning a range of contexts and interventions from surgery to renal care. A phase III randomised multicentre trial with embedded QRI addressing over-treatment of small, screen-detected breast cancer (SMALL) has recently had funding confirmed by the HTA, with two further studies being provisionally recommended for funding and two studies that have been invited to stage 2 of the funding process. In addition, Theme 2 members secured funding to apply aspects of the QRI to three ongoing RCTs nearing the end of their recruitment or funding period (BASIL-2, MASTER, PulMICC), as well as to a cohort study of effective treatments for thoracic aortic aneurysms that was experiencing recruitment difficulties (ETTAA). Key publications highlighting the integration of the QRI and its methods in RCTs (with anticipated recruitment difficulties) that successfully recruited to target include the in-press HTA report on the ProtecT study for treatment of localised prostate cancer (Hamdy et al, in press), and two studies recently published in the Lancet - the UK FASHIoN study for the treatment of femoroacetabular impingement syndrome (Griffin et al, 2018) and the CSAW study for treatment of sub-acromial shoulder pain (Beard et al, 2018).

A further key focus of Theme 2 is the integration of qualitative research into RCTs, to optimise trial design, conduct, and relevance to practice. Theme 2 members published a set of guidance on maximising the impact of qualitative research in feasibility studies. This paper has been cited on the HTMR network website as a practical resource for clinicians, trialists and researchers. A case study demonstrating the impact of qualitative research integrated at the pre-pilot stage of feasibility studies has been published and widely disseminated through various forums (Bluebelle Study Group, 2016; Blazeby et al, 2016). A variety of research has been published highlighting the integration of qualitative research in both feasibility and main stage RCTs to support trial design and conduct covering a range of different clinical contexts and health care settings including mental health in primary care, CFS in paediatric specialist care, and community health promotion. Qualitative research was also instrumental in exploring the role of teamwork in recruitment to RCTs in surgical oncology, resulting in a successfully defended Hub related PhD thesis that highlighted a number of aspects of team functioning that are important for recruitment (Strong et al, 2016). Theme member O'Cathain recently published a book offering a practical guide that covers the process of using qualitative research with RCTs targeting researchers who are leading, undertaking, or planning to undertake such research (O'Cathain et al, 2018).

Training and capacity building

Completed and ongoing theme 2 research has been presented at a number of national and international meetings, ranging from broad issues such as the value of qualitative research in RCTs and the clear obstacles and hidden challenges of recruitment, to training within individual trials to address specific issues. Members have been frequent presenters at the International Clinical Trials Methodology conferences and Society for Clinical Trials (SCT) Meetings in the USA, presenting on a wide range of topics including: strategies for maximising the impact of qualitative research in pilot and feasibility studies; intervention development and fidelity; the impact of pre-trial qualitative research on trial design; ethical aspects of clinical trials in India; examination of how equipoise and randomisation are conveyed by RCT recruiters; and optimising set up and recruitment of multi-centre complex RCTs. Theme members have been fortunate to lead another stimulating invited session to an international audience at the 2018 SCT Meeting in Portland, Oregon, on whether we can achieve the impossible in successfully recruiting to RCTs considered contentious or impossible.

Theme 2 members have developed and successfully delivered five national workshops to support surgeons and research nurses who recruit patients to RCTs, established a collaboration with the NIHR West of England Clinical Research Network delivering two workshops for their Network members, and are currently working with two local NHS Trusts to train their recruitment staff. Before-after evaluation of the first four national workshops showed that these workshops, with a focus on addressing the emotional and intellectual challenges of recruiting patients to surgical RCTs, increased confidence with recruitment, raised awareness of hidden challenges and impacted positively on self-assessed recruitment practice (Mills et al, 2018). Since then we have had several requests to provide this training within specific RCTs or clinical groups, both nationally and internationally, and we have used discrete elements of the training material to train medical students and surgical trainees in RCT recruitment through ongoing collaborations with the Universities of Birmingham (GRANULE), Oxford (BOSTiC) and Geneva (BOGOSTiC). We recently acquired Network funding to refine and expand our training, tailoring it to a wider audience and creating a sustainable annual short course on optimising RCT recruitment and informed consent. We are also in discussions with York clinical trials unit to evaluate our training intervention more robustly as part of a SWAT (Study Within A Trial), and in collaboration with the University of Birmingham and NIHR to develop an online training tool for recruiters to RCTs based on our training material. In addition to training tomorrow's recruiters, we are also invested in training tomorrow's academics. Theme 2 has two Hub-funded PhD students investigating treatment preferences in recruitment to paediatric RCTs (Beasant) and exploring patient perspectives in relation to recruitment in RCTs (Farrah).

MRC HTMR Working Groups

Theme 2 member, Alba Realpe, acts as co-lead facilitator for the MRC HTMR Trial Recruitment Working Group. This is a cross-institutional group attended by members of UoB and other universities and trials units around the country, which works to identify the most effective and efficient strategies for recruitment to trials. Theme members are regular attenders and contributors to this group.

Impact case study 1

Recruitment to a difficult surgical trial was transformed by the QuinteT Recruitment Intervention (QRI)

Research team: Paramasivan S, Realpe A, Wilson C, Whybrow P (qualitative researchers), Blazeby J (Chief investigator), Donovan JL (QRI lead), recruiters in the clinical centres.

A dynamic recruitment study (the Quintet Recruitment Intervention – QRI) aimed at investigating and improving recruitment, developed within the MRC ConDuCT-I/II Hub, was integrated into the By-Band-Sleeve randomised controlled trial (RCT) funded by the NIHR HTA Programme in January 2012. The RCT (ongoing) initially compared gastric bypass and gastric banding for complex obesity in the internal pilot phase and it adapted to a three-group trial to also compare sleeve gastrectomy in the main phase. The RCT was anticipated to face recruitment challenges – the QRI, which is currently ongoing, facilitated the process of optimising and subsequently sustaining recruitment in four key ways as outlined below.

Initial impact

The QRI was integrated into the By-Band-Sleeve RCT in the first clinical centre. This increased the centre's recruitment from 7% (2 recruited out of 30 eligible patients who were approached) in the first two months of recruitment to 41% (24/68) in the first five months following feedback. The findings from the first centre also helped the second centre to rapidly attain and maintain target recruitment and exceed expectations. The QRI, embedded into the internal pilot phase of the RCT, was a key contributor in the achievement of target recruitment in its two pilot centres. The RCT met recruitment and other progression criteria to proceed to the main trial.

Impact on transitioning to the main phase

The rapid emergence of a new but unproven procedure, sleeve gastrectomy, warranted its inclusion in the trial design, leading to the comparison of three procedures in the main trial, with a total of 11 centres at this stage.

Lessons learned during the internal pilot phase were incorporated in to the main trial and informed the pre-recruitment training provided during each site initiation visit. For instance, the value of integrating the RCT and its processes within clinical service provision were highlighted in the first centre. New centres were therefore requested to ensure their clinical set up facilitated RCT integration and recruitment. Similarly, drawing from the QRI findings in the first centre, it was realised that new centres with little or no research experience require additional support from the QRI team.

Concurrent to above, the QRI was initiated in each new centre to identify challenges unique to that centre. Audio-recordings and eligibility/recruitment logs were routinely analysed. Each centre experienced variations on the challenges reported in the first two centres. In addition, new challenges in relation to equipoise arose with the addition of the third procedure to the trial. These were consistently addressed in feedback sessions with centres and individual recruiters, in investigators' meetings and in tips documents to ensure that the transitional phase was smooth and that the new centres had a good start with recruitment.

Impact on sustaining recruitment

When the main phase was fully underway, the responsive nature of the QRI allowed the focus to remain on centres that require support, while still maintaining the momentum in centres that were recruiting well.

At this stage all centres required tailored support and feedback, with the exception of the second centre which continued to recruit at or above target. The first centre stabilised at a recruitment rate of around 36% for an extended period of time, but this later dropped, necessitating an increase in the intensity of the QRI. Of the nine new centres, five were recruiting to target or progressing satisfactorily following feedback sessions. These centres were followed up to monitor the implementation of changes suggested by the QRI and to ensure recruitment was sustained. Most crucially, the responsive nature of the QRI allowed the focus to shift to the four remaining centres with ongoing recruitment issues following feedback. The QRI team redirected attention towards these centres with the aim of converting them to recruiting centres or understanding the reasons for sustained poor recruitment that could mean they were unable to continue as a By-Band-Sleeve centre. A further centre was added to the RCT, making a total of 12 centres. Overall recruitment in By-Band-Sleeve had stabilised at around 30% by this period. However, by the end of the originally intended study period, the study was short of approximately 250 patients of the required 1341. A 15-month costed application to extend the recruitment period to September 2019 was accepted by the funder, with the QRI currently continuing to work with centres and individual recruiters to achieve the final recruitment target as below.

Impact on the final phase of recruitment (ongoing)

The QRI team has been intensely scrutinising the screening logs to identify centres and individual recruiters who have had recent reductions in the number of patients being screened, eligible, approached and randomised. Of these, centres/recruiters that have sufficient numbers of audio-recordings have been provided tailored feedback, with further monitoring of the logs to ensure the list of centres/recruiters requiring feedback is up to date. The QRI team has also been actively engaging with the centres that do not make or upload sufficient audio-recordings to ensure that feedback sessions can be arranged in the near future. The QRI team has been carrying out a series of research nurse (RN) refresher training teleconferences with centres to a) engage with the RNs who have continued to have an important role in recruitment and retention in By-Band-Sleeve b) enable new research nurses to understand the RCT and the QRI and c) develop a greater understanding of the issues around the recruitment pathway (organisational issues). The RCT is currently moving forward to achieve its recruitment target by the new study end date (September 2019).

In summary, the QRI has been an ongoing process of monitoring recruitment information, analysing audio recordings, and providing regular feedback to each of the sites in order to support surgeons and research nurses in discussing trial concepts and providing balanced, patient-focused information. The continuing integration of the QRI into the entire recruitment period of the By-Band-Sleeve RCT has helped with the cascading of the initial recruitment impact from the first centre to subsequent centres. However, while the RCT recruited more than 1000 patients in its original study period, this was still short of the target and an extension was required for the recruitment period. Nonetheless, the value of the QRI in the By-Band-Sleeve RCT has been in transforming recruitment in a difficult surgical RCT, but more importantly in sustaining recruitment by being flexible, iterative and responsive in its approach to addressing recruitment challenges.

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Impact case study 2 (year 2)

Qualitative research integrated at the pre-pilot stage transformed the design of a surgical RCT: The Bluebelle feasibility study

Research team: Rooshenas L, Elliot D (lead qualitative researchers), Donovan JL (ConDuCT-II) and Christel McMullan and Jonathan Mathers (University of Birmingham) and the Bluebelle study group.

Qualitative research at the pre-pilot stage of a feasibility study informed changes to the design of a surgical pilot RCT, enhancing its relevance to current practice and key stakeholders. The potential of integrated qualitative research was realised through dynamic reporting of emerging findings and close collaboration amongst a multi-disciplinary team.

Qualitative research was integrated throughout the pre-pilot stage of the NIHR HTA-funded 'Bluebelle' study: a feasibility study that sought to determine if an RCT of post-surgical wound dressing strategies could be delivered (Chief Investigator Blazeby). Bluebelle consisted of an exploratory mixed-methods phase (Phase A), followed by an external pilot RCT of wound dressing strategies (Phase B). Qualitative research conducted in Phase A aimed to fine-tune the protocol for the pilot RCT (details below). Semi-structured interviews with patients (n=51) and clinical professionals (n=92) explored current dressing practices, perceptions of equipoise, and acceptability of the proposed pilot. Interviews were conducted across clinical specialities that were anticipated to feature in the pilot RCT in a mix of district and university teaching hospitals. Emerging findings were regularly reported to the study management group, allowing sufficient time for planning and execution of additional sub-studies that were not planned at the outset of the feasibility study.

The Bluebelle feasibility study was funded in response to an NIHR HTA commissioned brief issued in 2012 calling for research proposals to investigate the feasibility of an RCT comparing 'simple', 'complex' and 'absent' dressings on primary (i.e. surgically closed) wounds. The brief arose in response to the lack of evidence around dressing use and development of surgical site infection (SSI), and uncertainty about whether an RCT of dressing strategies (including 'no dressing') could be delivered (Blazeby, 2016; Dumville et al, 2014).

The Bluebelle study opened in May 2014, with the qualitative research initiating shortly after (June 2014). Patients and health care professionals reported theoretical advantages and disadvantages of dressing use, and engaged with the idea that there was clinical uncertainty about the optimal approach to wound management. Whilst SSI prevention was deemed important, dressings were perceived to potentially carry other functions. Concerns about the possibility of foregoing a dressing were often based on considerations of how one might manage wound exudate, and the possibility of discomfort if exposed wounds rubbed against clothing. There were, however, also suggestions that foregoing a dressing could be preferable on a number of practical fronts (e.g. freedom to shower/bathe, avoidance of dressing changes, etc.).

Overall, interviews indicated that any future policies about dressing use needed to take account of the practical aspects of wound management.

Health care professionals showed enthusiasm for addressing the scientific questions underpinning Bluebelle but queried the relevance of the specified comparison groups. There was widespread support for randomising patients to 'dressing' or 'no dressing', although questions arose about the type of dressings that should feature in a future RCT. Professionals did not refer to dressings as 'simple' or 'complex' in their routine clinical practice; instead, they tended to dress primary wounds with a single default dressing, often referred to by trade name (or simply as 'dressing'). These default dressings reportedly varied over time and across hospitals but had similar characteristics. Professionals intuitively categorised these as 'simple dressings', on the basis that they were conceptualised as adherent coverings that did not interact with the wound. 'Complex' dressings, by contrast, were assumed to have specialised properties that actively facilitated healing, although these products were reportedly rarely applied to primary wounds.

In addition to questions of relevance, interviews also highlighted the possibility for inconsistent interpretations of the specified comparison groups. Health care professionals' definitions of what constituted a 'dressing' were variable – especially with respect to tissue-adhesive ('glue'). Glue was routinely used to close some surgical wounds, though some professionals reported that it could also be applied as a covering over primary wounds, thus functioning as a dressing. Questions also arose around whether a wound needed to be completely covered to be deemed 'dressed', and whether a product needed to be adhered to the skin to constitute a 'dressing'.

The above qualitative insights were fed back to the study management group through preliminary reports and a presentation at a study management group meeting in September 2014. This prompted the decision to design a prospective survey to capture dressing use across 25 NHS hospitals in the Midlands and South West regions of England. Pragmatic definitions of 'dressing', 'no dressing', 'simple dressing', and 'complex dressing' were also produced, informed by issues that provoked ambiguity in the qualitative interviews. These definitions were adopted throughout the remainder of the Bluebelle study and informed the design and interpretation of the survey. The survey collected data on 1794 wounds over a two-week period in January 2015. 1733 (97%) wounds were considered to have received a 'dressing'. Of the dressed wounds, most were covered with 'simple dressings' (n=1248; 72%), with the remainder covered with glue (n=485; 28%). This confirmed that 'complex' dressings were not routinely used in NHS practice. The unanticipated frequent use of glue as a dressing prompted an update to a Cochrane review, which in turn revealed the need for further evidence to assess glue's effectiveness at SSI prevention. The pilot RCT design thus evolved by replacing 'complex' dressings with 'glue-as-a-dressing'. Furthermore, patient and professionals' reported priorities about wound management informed development of additional outcome measures to assess the practical and comfort-related aspect of wound care.

The pilot RCT of 'simple dressings', 'glue-as-a-dressing', and 'no dressing' opened to recruitment in March 2016, with integrated qualitative research (interviews) to explore potential adherence issues and the acceptability of the dressing strategies from patients' and health care professionals' perspectives. Recruitment successfully completed in November 2016. The numbers recruited exceeded the target sample size within the scheduled recruitment period (nine months), and there was overall good adherence to allocation. The qualitative interviews indicated that all dressing strategies were acceptable to patients and health care professionals, and in alignment with the trial figures, suggested there were no major concerns pertaining to adherence. The integrated qualitative research and study team's experiences led to a series of

recommendations to optimise the design and delivery of a future RCT (reported in Reeves et al., in press).

In summary, integrating qualitative research at the pre-pilot stage enhanced the relevance of the Bluebelle pilot RCT, which subsequently ran smoothly, with no major issues pertaining to recruitment, adherence, or acceptability. The pilot RCT met or exceeded all of its feasibility targets, and led to recommendations for the design of a future definitive RCT comparing different wound dressing strategies (including 'no dressing'). A more detailed account of how the pre-trial (Phase A) qualitative research informed the pilot RCT (Phase B) has been published, serving as a case study of the potential impact of applied qualitative methods in feasibility studies (Bluebelle Study Group, 2016). A detailed report of the overall Bluebelle feasibility study has been accepted for publication in the NIHR Journal Health Technology Assessment (Reeves et al., in press), and specific qualitative and quantitative findings relating to the pilot RCT have also been submitted for publication in the Journal of Wound Care (qualitative findings reporting the acceptability of different wound dressing strategies) and the British Journal of Surgery (overall pilot RCT findings).

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Future plans

Theme 2 members will continue to extend the development of innovative, dynamic and integrative research methods, furthering existing partnerships as well as new collaborations with clinical trial units, trialists and clinicians to optimise recruitment to challenging RCTs. Of emerging significance, are the early-stage links made with international colleagues in the USA, India, Ireland, Sweden and the Netherlands. Links have been established with the Ireland-based QUESTS initiative (<http://quests.ie/>) to maximise the value of qualitative research in trials, with Theme 2 lead, Professor Jenny Donovan, on the executive committee in the capacity of an international expert and theme member Dr Nicola Mills on the steering committee to offer guidance and advice on their initiative to develop and evaluate an educational intervention for

RCT recruiters. Plans are underway to meet with key members of the Dutch HTA equivalent body (ZonMw) to explore routine use of QRI methods for monitoring processes in clinical trials, and collaborations have been secured with US colleagues to integrate the QRI and associated methods in their trials that are expected to face recruitment difficulties. Research has been initiated and contacts secured with Indian colleagues to explore recruitment and informed consent processes in clinical trials in India to gain an overview of the issues and identify gaps to address, and theme members are liaising with Swedish clinicians to offer training in their trials that are struggling to recruit. In addition, strategies for implementing the QRI in feasibility and ongoing trials will continue to be honed, with further exploration of methods to improve QRI delivery and integration. Theme 2 members will also continue to explore the feasibility of applying aspects of the QRI to ongoing trials that are approaching the end of their recruitment or funding period and intend to collaborate with theme 3 Hub members to investigate how the QRI can be adapted for use in trial retention.

Optimising secondary data analysis protocols will be a key priority in future work. We will continue to accumulate data to understand recruitment difficulties in challenging RCTs, contributing audio appointments and interviews to a useful resource of pooled data. This will enable cross-trial analyses of commonly-recurring challenges to inform publications, areas for further research, and training. We plan to regularly monitor and refine data collection protocols for newly-funded QRIs in light of our secondary data analysis agenda. This will include the examination of consent processes and prospective planning to ensure topic guides include in-depth investigation of concepts we wish to broadly examine across RCTs as our understanding of the gaps develops.

Recruitment training programmes will continue to be honed for different audiences and in the context of a new short course that we are developing, and we will continue to fine-tune approaches to optimising recruitment in different RCTs and clinical contexts. We intend to draw up longer term plans to develop an online training video to further expand training accessibility, reach and impact in the future. Initial discussions have already been undertaken with the NIHR CRN who are keen to pursue this. We will also consider an independent randomised evaluation of the effectiveness of the Hub-developed training. Informal discussions have already been initiated with proposed collaborators from York Clinical Trials Unit to evaluate the training intervention as a SWAT in host RCTs. As our secondary data analysis of QRI generated data develops, we will continue to refine and expand our training material to improve its evidence base and delivery.

Upcoming outputs

A paper evaluating the impact of the QRI on RCT recruitment within five RCTs across diverse settings that showed convincing evidence of a positive effect has been submitted for publication. This paper will be an important building block in the evidence base of the QRI. The highly acclaimed ProtecT study, the largest and most successful RCT of treatments for localised prostate cancer of which theme 2 lead Professor Jenny Donovan is co-CI, has published its main findings and the HTA report detailing its progress is currently in-press. The report details the story, for the first time, of how the QRI emerged in reaction to difficulties in a trial that was considered 'impossible'. It will be an important foundation publication and case study for detailing the development of an intervention that provides compelling evidence of positively impacting recruitment. Publications of similar case studies in different RCTs are planned, as are cross-trial papers on good practice post-training in areas such as patient treatment preferences and explaining the rationale for randomisation. A systematic review of informed consent in clinical trials in India will soon be nearing submission in preparation for related empirical research.

Future training workshops are upcoming and discrete elements of this will be disseminated through an online e-training tool in collaboration with the NIHR and University of Birmingham.

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Theme 3: Improving Feasibility study designs And Conduct to enhance Trial quality and results (FACT). Leads: Dr Athene Lane and Professor Jane Blazeby

Overview and specific objectives

To enhance the design and effective conduct of RCTs through optimising feasibility and pilot study designs and evaluating methods to improve trial conduct.

Specific objectives:

1. Explore current practice and develop methods to standardise invasive interventions and co-interventions in surgical trials between trial sites and measure protocol fidelity.
2. Develop methods to assess operator and team expertise in surgical trials.
3. Maximise participant retention and clinical outcome data collection, including adapting and evaluating these methods for surgical trials.
4. Enhance site monitoring and staff training in non-investigational medicinal product trials.
5. Optimise trial oversight processes by extending ongoing research on the role and function of Trial Steering Committees.

Major successes

Interventions in surgical trials

One of the major challenges in RCTs in surgery is achieving standardisation of surgical interventions across surgeons and centres. Unlike medical RCTs, where tablets can be manufactured to exacting standards, surgical operations given the same 'label' can be performed in lots of different ways. There are several guidance documents that provide recommendations about standardising interventions within RCTs. Despite this, standardisation has remained poor in surgery, perhaps because the guidance is difficult to apply in this setting. It is also because surgical interventions are complex, comprising many components that are delivered along with other interventions. Strict standardisation of all these components may be impractical, and unreflective of the variety found in routine clinical practice. Conversely, a lack of standardisation can make it difficult to make sense of the results because it is hard to establish how interventions were actually delivered within a trial. We undertook research in the operating theatre using digital video recordings of operations and non-participant observation, which provided first-hand experience about how the same operation was performed differently by different surgeons and teams, as well as reasons for these differences. Differences between surgeons were explored in interviews after the operations. This research informed a typology to use in trial design to describe the surgical intervention and the agreed standardisation required for the specific trial (Blencowe 2015a; 2015b; 2016). The typology enables surgical procedures to be deconstructed into their component parts and then a 'traffic light system' of standardisation - prohibited (red), optional (amber) and mandatory (green) – is applied to each component to establish how it should be delivered within a trial. The typology has been used in several RCTs in surgery (By-Band-Sleeve, ROMIO, CIPHER and ones working with other CTUs).

Pilot and feasibility study design

Key to the success of main trials in surgery is high quality pre-trial work, including pilot and feasibility studies. In the Hub we have led an HTMR Network grant to examine how main trials are designed with an internal pilot phase (Avery et al). This gave us the opportunity to bring together key stakeholders to discuss key issues to consider in the optimal development and review of operational progression criteria for RCTs with an internal pilot phase (Avery et al, 2017). The publication from this workshop has been included in the NIHR Clinical Trials Toolkit. We also gained HTMR Network funding for a clinical PhD student to examine how pilot work may optimally inform RCTs in surgery, and we have successfully gained HTA trial funding in surgical trials in lung and oesophageal cancer surgery which include an internal pilot design. A HTMR Network grant has funded work to now focus on 'methods to establish when to do an external pilot study'. The NIHR clinical trials toolkit where the paper is referenced can be found here: <http://www.ct-toolkit.ac.uk/routemap/trial-planning-and-design/>.

Training of site staff

A systematic review of training for site staff in clinical trials was conducted by the ConDuCT-II PhD student Athanasia Gravani, in conjunction with the theme researcher Alex Nicholson. This revealed that there was little standardised practice and a poor evidence base for methods utilised at sites. The subsequent ATLAS (Analysis of Trial-specific Training during the Site Initiation phase) qualitative study used interviews and observations of site training in six trials (including some at CTEU) to investigate clinicians' attitudes towards training, including modes of delivery (e.g. face to face vs online video vs telephone). A feedback survey of the staff present at the site training gave broader views on the optimal methods. A site staff training checklist/toolkit has been developed based on the ATLAS research and systematic review and was reviewed by trial managers at the Bristol Randomised Trials Collaboration (BRTC) and Clinical Trials and Evaluation Unit (CTEU) trials units with positive feedback.

Retention

Research in the theme has also focused on maximising participant retention and clinical outcome data collection. The reasons for attrition in randomised trials to develop the evidence base has been investigated in an MRP programme led by Professor Gamble (North West and ConDuCT-II Hubs). The qualitative component led by Athene Lane, Jane Blazeby and Ali Heawood was based on conducting interviews with trial staff from five NIHR HTA-funded trials. Interviewees shed light on potential reasons for losses and described a range of strategies which were used to increase follow-up. A paper was published in *Trials* and presentations made at conferences, including Society of Clinical Trials, May 2018.

Recently, Athene Lane became co-applicant in an HTMR grant led by North West Hub (Anna Kearney) on the ORRCA2 project which aims to collate retention literature in a searchable database and has commenced with a scoping review. Athene Lane is also co-applicant on a study of the use of digital tools in recruitment and retention research led by Jeremy Wyatt at the Wessex Institute and Gareth Griffiths at Southampton CTU with funding from the NIHR CTU support funding efficient studies programme. A scoping review and a survey of CTUs have been undertaken alongside qualitative interviews with trialists.

Trial conduct advice

In more applied research from this theme, methodological and leadership support for many aspects of trial design and conduct has been given to several challenging surgical trials and intervention trials (e.g. HTA UNBLOCS, PGfAR INFORM) including those with internal pilot phases (HTA UPSTREAM) and HTA Prepare-ME trial with an internal pilot phase.

Training and capacity building

FACT theme research has been presented at the International Clinical Trials Methodology Conference (Glasgow, November 2015) and the Society for Clinical Trials (Montreal, May 2016) on the Qualitative Analysis of Trial Oversight Committees (QuAnTOC) study and the training of site staff including a systematic review of current practices. Presentations were also made at the Society of Clinical Trials meeting on retention research (Portland, May 2018) and surgical trainee collaborative research.

Members of the theme (Lane, Avery, Clement, Coulman, Metcalfe, Peters) have also delivered training on the Questionnaire Design, Application and Interpretation and the Randomised Controlled Trials courses as part of the annual School of Population Health Sciences short course programme. Athene Lane and Chris Metcalfe took over the leadership of the RCT course in 2018.

MRC HTMR Working Groups

Theme 3 member, Chris Rogers, currently co-chairs the Trial Conduct Working Group which includes other theme members (Lane, Coulman, Clement). This is a cross-institutional group attended by members of University of Bristol and other universities and trials units around the country, which focuses on enhancing trial conduct through research including nested studies. Chris Rogers recently gave a webinar entitled 'Audio-recording recruitment consultations – an exploratory study in two RCTs to investigate the impact on randomisation rates' in May 2018 as part of the working group. We have recently had a prioritisation exercise for working group research themes and agreed forthcoming webinars, including one on the surgical trainee network research.

Impact case study (year 1)

Improving trial conduct through site monitoring research to inform the NIHR Clinical Trials Toolkit

Research team: Lane JA, Macefield R (ConDuCT-II), Holding P (ProtecT trial nurse) and Bonnington S (ProtecT trial nurse), Beswick A (systematic review advice), PRIME: on site monitoring system

Summary of impact

The Clinical Trials Toolkit provides practical advice to researchers in designing and conducting publicly funded clinical trials in the UK. Through the use of an interactive route map, this site provides information on best practice and outlines the current legal and practical requirements for conducting clinical trials. (<http://www.ct-toolkit.ac.uk/routemap/>). A key section is the Trial Management and Monitoring section, which is underpinned by research, advice and review provided by ConDuCT-II Hub members. Athene Lane and Rhiannon Macefield provided advice and reviewed content of the Trial Monitoring section of the toolkit, using research evidence from

their systematic review of site monitoring and related PRIME research based on the ProtecT trial (cited at <http://www.ct-toolkit.ac.uk/about-this-site.htm>).

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Impact case study (year 2)

Updating Trial Oversight Committees Charters

Research team: Anne Daykin (CONDuCT Hub Affiliate), Lucy Selman, Helen Cramer, Alison Heawood, Rhiannon Macefield & Athene Lane (MRC Hub Members), Sharon McCann, Gillian Shorter (MRC All-Ireland Hub), Matthew Sydes (MRC London Hub) and Carrol Gamble (MRC North West Hub)

The Terms of Reference (TOR) or charter for Trial Steering Committees is widely used by CTUs but it is dated having been developed over 20 years ago by the MRC. This research underpins the updating of the charter which is anticipated to be adopted as NIHR guidance and used by all CTUs.

The QUANTOC (Qualitative Analysis of Trial Oversight Committees) study (funded through a MRC HTMR network grant led by Athene Lane and Ali Heawood) aimed to explore the role and valued attributes of Trial Oversight Committees (TOCs), with a view to informing future national guidance for TOCs. An ethnographic study design was used, consisting of non-participant observation of TOC meetings, and interviews with TOC members, study funders, and sponsors. A first paper was published in 2016 in *Trials* (Daykin et al, 2016) and was a featured article in *Trials* and a second was published in *Trials* in 2017 (Daykin et al, 2017).

The QUANTOC research study was linked to a parallel HTMR grant led by Professor Carrol Gamble (North West Hub, Lane co-applicant) which conducted a survey of registered CTUs (Conroy et al, 2015) and an expert panel meeting of trialists. The expert panel used results from both projects to revise the existing MRC TOR for TSC developed in 1998 which were out of date in some aspects, e.g. PPI involvement was a minimal aspect. These results have also been published in *Trials* (Daykin et al, 2018). There was also an analysis of trials published in the top medical journals which revealed wide international variation in the use of TSCs (Conroy, *Trials*, 2017).

A commentary summarising the challenges and issues to be resolved before a revised TOR for TSCs can be written which is the primary translation of these two research projects. The commentary points were included in a presentation about the TSC projects by Carrol Gamble and Athene Lane at the Annual HTMR meeting in London on September 25th 2018. NETSCC (NIHR) are interested to contribute to a specialist meeting to review these findings and to include NETSCC-commissioned research regarding PPI and TOCs. The pathway to impact for these projects will be clear if the revised TOR become mandatory for trials funded by the NIHR.

Internationally, the Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) Network (a pan-Canadian, patient-oriented, community development programme centred on venous thromboembolism related research, training, and knowledge translation) are developing guidelines and tools to aid standardisation of trial conduct. This team have requested

assistance regarding their oversight committee TOR from the QUANTOC team based on our research findings.

Future plans

We have completed the qualitative study data collection and analysis for the MRC HTMR study 'Developing a medical work force that designs, participates in, and implements findings of trials to improve evidence based practice: a case study in surgery' PI: Lane; Co-app(s): Coulman K, Blencowe N, Blazeby JM, Daykin A, Cook J, Pinkney T, Bulbulia R, Marson T, Arenas-Pinto A. £49,969. (April 2017 – October 2018). This study investigated surgical trainees' and surgeons' experiences of participating in clinical trials, including barriers and facilitators to successful trial conduct, using observations of key surgical trial meetings, and qualitative semi-structured interviews. Findings will be used to develop training methods to enhance clinician engagement in trials and inform the medical curriculum in training clinicians of the future in research methods. This work will also form the basis of a continued research programme addressing clinician engagement in trials. We will be holding an expert workshop in October for academic surgeons and trial methodologists to review the findings prior to publication.

We have also formed a collaboration with Nick Heywood, Chair of the North West TRC who conducted a survey of trainees about their experiences, and positive and negative aspects to TRCs. Natalie Blencowe, Karen Coulman and Athene Lane advised on the survey design and question content. Karen Coulman also contributed to the thematic analysis of results. The survey results were presented at the national TRC meeting in Birmingham, November 2017.

We are also interested in developing a programme of research related to Patient and Public Involvement (PPI), inspired by findings from the QUANTOC study, which is in the early stages of development. A paper describing the benefits and difficulties of incorporating PPI successfully in TMG and TSC based on the QUANTOC study is currently in preparation. Good links have also been made with complimentary research funded by the HTMR and led by Mr Richard Bulbulia (Oxford Hub) and Dr Jo Crocker (also Affiliate, ConDuCT II, University of Oxford), 'Developing a patient and public involvement intervention to enhance recruitment in surgical trials (PIRRIST)', which aims to address slow recruitment and poor retention in surgical trials. PIRRIST also forms part of the Trial Forge Initiative to improve trial efficiency involving Athene Lane (a co-applicant, Hub Member) and Kerry Hood (Hub Affiliate, Cardiff Centre for Trials Research).

Surgical interventions, co-interventions and context

We will develop the typology developed by Blencowe (described above) to ensure it can be applied to other trials and intervention types (e.g. placebos for invasive interventions). We hope to develop a web-based tool to achieve this as part of Blencowe's MRC Clinician Scientist Fellowship (starts April 2019). We are also just starting a review of methods for assessing adherence to interventions where patient choice may have an influence. We are doing this within a case study of Mallet finger injury. It is intended to use the work to develop new methods to optimise measurement and reporting of adherence. We are also collaborating with members of the University of Sterling to consider how contextual factors influence trial design to optimise implementation of trial results and specific work will be undertaken to establish how to identify co-interventions and contextual factors that are critical in trial design and conduct to successful implementation of an intervention.

We have also published how we adapted the By-Band-Sleeve study in bariatric surgery to include a novel intervention (Sleeve gastrectomy) to illustrate how to keep RCTs in surgery relevant to current practice (Rogers et al, 2017).

Upcoming outputs

Planned topics for further papers include a training checklist of optimal practices for site staff, a systematic review of site staff training, a paper on reasons for attrition in randomised trials, a paper related to PPI in TSCs (QUANTOC study), and two papers from our study on surgeon engagement in trials – one focusing on practical recommendations to improve trainee engagement in trials, and one on relationships key to the success of trainee research collaboratives.

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Theme 4: Outcomes in RCT's – assessment, reporting and integration in decision-making. Leads: Rhiannon Macefield and Professor Jane Blazeby

Overview and specific objectives

Previous work carried out in the outcomes theme within the first ConDuCT Hub focused on measurement, selection and reporting of patient-reported outcomes (PROs) and communication of PROs from RCTs in clinical decision-making. Key findings from this work emphasised the importance of not isolating PRO assessment and reporting in trials and the need for PROs and clinical outcomes to be integrated in trial hypotheses, design and reporting to inform clinical practice. Taken forward in ConDuCT-II, the focus of Theme 4 has been on continuing to improve both clinical and patient-reported outcome assessment, reporting and integration in RCTs.

Specific objectives:

1. Facilitate the ongoing development of Core Outcome Sets (COSs), identification of optimal measurement instruments (Core Measurement Sets) and methods for their integration and reporting in trials.
2. Incorporate patient views into the development of COSs and CISs (Core Information Sets).
3. Establish methods to better integrate clinical and patient-reported outcomes into clinical consultations and decision making.
4. Explore the use of composite / dual primary endpoints in trials.
5. Develop innovative methods to ensure blinding of outcome assessors and patients in RCTs in surgery.
6. Provide expertise to others developing and validating new patient-reported outcome measures (PROMs).

Major successes

Development of new core outcome sets and core information sets

A focus throughout ConDuCT-II and major success of Theme 4 has been the development of core outcome sets (COSs); agreed minimum sets of outcomes to be measured and reported in all clinical effectiveness trials of a particular condition or intervention, to facilitate evidence synthesis and better inform clinical practice. Members of Theme 4 have developed COSs for breast reconstruction surgery (Potter et al, 2015), bariatric surgery (Coulman et al, 2016) colorectal cancer surgery (McNair et al, 2016) and oesophageal cancer surgery (Avery et al, 2018). Ongoing work includes developing a COS in burn care research (Young et al, 2017), a generic COS for early-phase studies of surgical innovation, as part of the work being conducted within the surgical innovation theme of the new NIHR Bristol BRC (Biomedical Research Centre), a specific COS for rectal cancer surgical innovation studies (led by McNair, NIHR Clinician Scientist Award 2018) and a COS for diabetic foot ulceration. Work has included collaborations outside of the Hub providing expertise and advice to groups developing core sets in other diseases and health conditions, including ophthalmology and paediatrics (Tallouzi et al, 2017; Sherratt et al, 2017).

Moving forward, Theme 4 has progressed to think about *how* to measure a COS. Funding to develop a Core Measurement Set (CMS) for reconstructive breast surgery has been received (Potter, NIHR Clinician Scientist Award). Collaborations developing CMSs with external groups to the Hub have also been published (de Vries et al, 2018).

Alongside COS development, Theme 4 work has included the development of core information sets (CISs); a minimum set of information to be disclosed to patients in treatment decision consultations. A CIS for head and neck cancer surgery (Main et al, 2018) and oesophageal cancer surgery (Blazeby et al, 2015) have been developed and published, and a CIS for colorectal cancer is under review for publication (McNair et al). The development of each core outcome and information set has involved a substantial amount of work, including systematic reviews, qualitative interviews, Delphi surveys and face-to-face consensus meetings. Dissemination of the research has been widespread, with many oral presentations at national and international conferences including the Society for Clinical Trials (SCT) annual meetings and the International Clinical Trials Methodology Conference (ICTMC). More recently, funding has been received to explore how to implement core sets into clinical practice. This will be examined within a case study core information set for head and neck cancer surgery (Main, AMS grant).

Methods for developing core sets

A further success of theme 4's work has been improving methodology for the development of COSs and CISs. The majority of core sets developed by the theme have included embedded methodological studies to work towards an optimal approach to their development and provide guidance others in the field. A number of methodological papers have been published, including a comparison of how professionals and patients prioritise outcomes of bariatric surgery, recommending that the views of all relevant health professionals and patients should be considered (Coulman et al, 2016). The breast reconstruction study looked in more detail at methods for selection and integration of stakeholder views, considering not just broad patient and professional groups but also a number of subgroups and the impact this might have on the resultant core set (Potter et al, 2016). Three of the surgical core sets included nested randomised studies to examine the impact of feedback in the Delphi consensus process. Groups were randomised to receive feedback from their own stakeholder group only or multiple stakeholder groups. Subsequent prioritisation of outcomes and levels of agreement between stakeholder groups was examined, with recommendations to future core set developers (Brookes et al, 2016). Additional methodological work included an investigation of the effect of the ordering of patient-reported and clinical outcomes in a Delphi questionnaire on prioritisation of outcomes (Brookes et al, 2018), and a comparison of clinicians' views of important outcomes to include in a COS for colorectal cancer surgery compared with what clinicians considered important information for clinical practice (CIS) (McNair et al, 2016).

Throughout this work we have collaborated closely with the COMET (Core Outcome Measures in Effectiveness Trials) Initiative. Members of the theme have been invited speakers at annual COMET conferences and have contributed heavily to the production of an International COMET handbook, bringing together current thinking and methodological guidance for core set development (Williamson et al, 2017). Theme 4 members have been involved with the COMET group to develop standards for the design of COS studies (COS-STAD; Kirkham et al, 2017) and standards for reporting COSs studies (COS-STAR; Kirkham et al, 2016).

Other key successes

Further successes of the work of Theme 4 have included:

- development of new outcome measures for wound healing (Macefield et al, 2017); Bluebelle wound healing questionnaire (WHQ)), wound management and patient experience (Elliott, The Bluebelle study group, 2017) and several disease-specific modules to measure quality of life in cancer (EORTC modules).
- development of methods for incorporating patient reported outcomes in trial design and reporting (SPIRIT-PRO, CONSORT-PRO).
- development of systems for electronic data capture of patient reported outcomes after surgery (eRAPID feasibility study)

These successes are described in more detail under 'impact case studies' below.

Impact case study 1: The CONSORT-PRO statement

Research team: Calvert M (PI, Birmingham University, ConDuCT-II affiliate), Blazeby JM (ConDuCT-II theme 4 joint-lead), Macefield R (ConDuCT-II theme 4 joint-lead), McNair A (ConDuCT-II member), Brookes ST (ConDuCT-II member), other national and international team members (Brundage, Canada; Moher, Canada; Revicki, USA; Scott, England; Efficace, Italy; de Vet, Netherlands; Yount, USA; Snyder, USA; King, Australia; Lam, Hong Kong; Duffy, England; Bass, Canada)

Summary

Patient-reported outcomes (PROs), such as health-related quality of life (HRQL), are increasingly measured in trials. The rationale for their use, measurement and analyses should be robust and well reported, just as for any clinical outcome; but this is often not the case. In the first Hub, we developed an evidence-based extension of the CONSORT statement for reporting PROs in trials.

PROs are increasingly measured and reported as primary or secondary outcomes in RCTs of health interventions. Research suggests that PROs are highly valued and readily understood by patients compared to some clinical outcomes. However, the reporting of such outcomes in trials is often poor. The CONSORT (Consolidated Standards of Reporting Trials) Statement, provides recommendations on how to report evidence from RCTs and is endorsed by many major journals and editorial groups, yet it does not provide guidance for PROs. A systematic review identified existing guidelines for reporting HRQL outcomes. An on-line survey of stakeholders (membership of ISOQOL and others) asked participants to rate the importance of different reporting items identified in the systematic review. The results were debated at the 2011 annual ISOQOL conference in Denver, at which the decision was made to extend the study from just considering HRQLs to all PROs. 29 participants, including journal editors, methodologists, trialists, policy makers, clinicians, representatives of funding bodies, industry and patients, then attended a consensus meeting at which items to be included in the CONSORT PRO extension were agreed. The CONSORT PRO checklist items include the recommendations that: PROs are identified as primary or secondary outcomes; hypotheses for PROs are reported; evidence of PROs reliability and validity cited; approaches for dealing with missing data reported; PRO-specific limitations and generalizability of findings be discussed; findings are interpreted in relation to clinical outcomes.

The main CONSORT PRO paper was published in the Journal of the American Medical Association (Calvert et al, 2013) and the CONSORT PRO extension has been widely endorsed by journal editors and has now been cited over 300 times since its publication. An improvement in PRO reporting in trials since the CONSORT PRO extension has been shown (Mercieca_Bebber et al, 2017).

Further impact

The successful implementation of the CONSORT-PRO extension and reporting of PROs in trial reports has led on to work to improve the PRO content of trial protocols. Members of theme 4 have been involved in this work, publishing guidelines for including PROs in trial protocols: the SPIRIT-PRO extension (Calvert et al, 2018).

Impact case study 2

Development and validation of EORTC quality of life questionnaires and their widespread implementation in multinational RCTs

Research team: Blazeby J (ConDuCT-II theme 4 joint-lead), Avery K (ConDuCT-II member) and national and international clinicians and members of the EORTC Quality of Life Group

Summary

In 1986, the European Organization for Research and Treatment of Cancer (EORTC) embarked on a research program to develop a modular approach to evaluate the quality of life (QOL) of patients taking part in international clinical trials (Aaronson et al, 1993). Since its publication in 1993 (Aaronson et al, 1993) the first questionnaire to be developed, the EORTC QLQ-C30, has established itself as a standard tool to use in clinical trials in cancer. The QLQ-C30 assesses generic aspects of QOL. It has been translated into over 90 languages and used in more than 30,000 studies worldwide. Thirty disease-specific modules have been validated subsequently, with a further 25 currently under development. These are intended to supplement the core C30 questionnaire to evaluate QOL in groups of patients with specific cancers.

The ConDuCT-II Hub, in collaboration with the EORTC Quality of Life Group, have led the development and validation of nine disease-specific modules and contributed to three others. The QLQ-HCC18 module, for example, was developed to measure QOL in hepatocellular carcinoma (HCC), the second leading cause of cancer-related death worldwide. The module, comprising 18 items conceptualised as six scales and two single items, is designed to assess factors related to chronic liver disease, as well as issues related to the primary tumour and its treatment. A study to develop the module was conducted according to the EORTC QOL Group guidelines (Sprangers et al, 1998), involving a literature review and semi-structured interviews with patients and health-care professionals to identify QOL domains and psychometric testing of the questionnaire in patients from Europe, Taiwan and Hong Kong. A publication reporting on the development and validation process has since been cited 36 times (Blazeby et al, 2004), and the module has been rigorously translated into numerous languages (Yang et al, 2015; Chie et al 2012; Mikoshiba et al, 2012). The QLQ-HCC18 questionnaire has also been used in various international studies, including a cross-sectional exploration of the possible effects of clinical and cultural characteristics of HCC on patients' QOL (Chie et al, 2016) and a multicentre longitudinal study to assess the association between QOL changes and different treatments in HCC patients (Chie et al, 2015).

In addition, the Hub has collaborated on a study to test and adapt the scale structure and further explore the psychometric properties of the EORTC QLQ-NMIBC24 for non-muscle-invasive bladder cancer (NMIBC). Though this module had been used in clinical studies, formal validation

data were previously lacking. A further validation study was therefore undertaken to examine the scale structure, reliability and clinical validity of the QLQ-BLS24 in patients with NMIBC as part of the Bladder COX-2 Inhibition placebo-controlled Trial (BOXIT) in the UK (Blazeby et al, 2014). Comprising six scales and five single items and with a total of 24 items, the QLQ-NMIBC24 module has subsequently undergone further clinical and psychometric testing in new settings and has been translated into several languages, including Danish (Morgensen et al, 2016) and Spanish (Abáigar-Pedraza et al, 2016). The module is suitable for use in clinical trials of patients with high- or intermediate-risk bladder cancer and has also been used in various studies to evaluate QOL in patients with bladder cancer (Morgensen et al, 2016; Sanchez & Wzsolek, 2015).

Members of the Hub also led the development and validation of the module to assess QOL in patients with oesophageal cancer (Blazeby et al, 1996; Blazeby et al, 2003). This was subsequently merged with the gastric cancer questionnaire (also Hub led) to form a new measure for patients with gastro-oesophageal cancers (Largergren et al, 2007). All are widely used in trials in the UK led by Cancer Research UK, in continental Europe led by the EORTC and in North America and the Far East. In oesophageal cancer surgery, the measures have been used in trials of minimal access versus open surgery (ROMIO study and TIME and MIRO trials). The uniformity of outcome measurement will facilitate data synthesis, and the Hub has contributed to a meta-analysis (Jacobs et al, 2014). In the ROMIO study (a pilot RCT) the measure has been used as the primary endpoint and the main trial is now funded in the UK (Avery et al, 2014).

Recent collaborations include further development of the EORTC QLQ-STO22, a module to assess QOL in patients with gastric cancer (Blazeby et al, 2004).

Impact case study 3

Development of new outcome measures for surgical RCTs as part of the Bluebelle study: a feasibility study of three wound dressing strategies in elective and unplanned surgery

Research team: Avery K (ConDuCT-II member), Blazeby J (ConDuCT-II theme 4 joint-lead), Brookes S (ConDuCT-II theme 4 joint-lead), Calvert M (ConDuCT-II affiliate), Elliott D (ConDuCT-II member), Macefield R (ConDuCT-II theme 4 joint-lead) and members the Bluebelle study group

Summary

A major success of the work from theme 4 has been the development of three new outcome measures for patients undergoing surgery. This work was embedded within the NIHR-funded Bluebelle study, a feasibility study to explore whether a large randomised trial of different types of wound dressing, including no dressing, was possible. To address the lack of well-designed, robust measures for post-discharge assessment of surgical site infection, a single 'universal' outcome measure, designed for patient and/or healthcare completion, was developed (Macefield et al, 2017). Data from the Bluebelle study found the measure to be acceptable, reliable, and valid for use after abdominal surgery with high sensitivity and specificity for distinguishing between patients who had SSI/no SSI (publication accepted in BJS). Additionally, the Bluebelle study identified the need to measure outcomes relevant to assessing wound management and patient experience of dressings. To address the lack of existing tools to assess these relevant and important outcomes in a future large RCT, mixed methods including qualitative interviews and data extraction from published RCTs were used to develop two new measures. Initial work has demonstrated the measures are acceptable to patients and healthcare professionals with good face validity (Elliott, The Bluebelle study group, 2017).

Dissemination of the development and validation of the new outcome measures has been presented at national and international conferences, including the Infection Prevention Society conference (2015), the International Clinical Trials Methodology conference (2015, 2017) and the Society for Clinical Trials Annual meeting (2018). Interest in using the measure to assess wounds for surgical site infection (now called the Bluebelle Wound Healing Questionnaire; WHQ), has been high, with several funded studies including it to collect outcome data in other surgical specialties (e.g. Smart N, NIHR-HTA; Chetter I, NIHR-HTA)

Impact case study 4

Developing methods for monitoring symptoms and adverse events after cancer surgery: the electronic patient-reporting of adverse events (eRAPID) feasibility study

Research team: Avery K (ConDuCT-II member), Blazeby J (ConDuCT-II theme 4 joint-lead), Richards H (ConDuCT-II affiliate) and the eRAPID study group.

Summary

Surgery for upper gastrointestinal (UGI) cancer can result in adverse effects (AEs), many of which can occur once the patient has left hospital. When post-operative complications occur at home, late detection can lead to increased morbidity. The prompt identification of AEs is important to improve patient safety and outcomes. The NIHR-funded eRAPID study (Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice; led by Velikova in Leeds) has a workstream that has been led by theme 4 members; for patients to report symptoms during early recovery following UGI surgery in an online platform integrated into hospital electronic patient records (EPR). Tailored self-management feedback, advice to contact a clinician or an alert email to a clinician is generated dependant on the relative severity of the symptoms reported.

The eRAPID Surgery system was developed in three phases. The first phase involved the development of a 37-item questionnaire from a validated EORTC measure, and in close consultation with patients and clinicians. This questionnaire was then integrated into a web-based platform which linked with hospital systems, enabling clinicians to access patient's symptom severity reports. In the second phase, algorithms were established to determine which levels of symptom severity would generate tailored self-management feedback, advice to contact a clinician or an alert email to a clinician. In the third phase, questionnaire and qualitative data was collected from 33 patients to determine the feasibility of the eRAPID Surgery system.

The eRAPID system has shown to be a beneficial adjunct to patient self-management during recovery following UGI surgery, providing reassurance about symptoms and useful advice for symptom management. Dissemination of the project and results have been presented by theme 4 members at national and international conferences.

Future plans

Core outcome and core information sets

Theme 4's work to date to develop core outcome sets, and best methods to do, this will be extended into early phase studies through the work of the Bristol BRC. Development of a generic COSs for evaluating and reporting innovative surgical procedures and devices is currently underway. A recent HTMR-funded key stakeholder workshop for industry, innovators, clinicians,

trialists, journal editors and health policy makers was held in September 2018 for the innovation of new surgical devices (Hinchcliffe, 2018).

Continued development of COS and CISs in areas where they are lacking, and the move forward to developing *how* to measure and implement core sets will continue beyond ConDuCT-II through clinical academic members of the theme (McNair, Main, Potter) leading grants in their areas of specialties of colorectal cancer, head and neck cancer and breast reconstruction.

Patient-reported outcomes and electronic data collection

Plans to continue to develop and improve patient-reported outcomes for trials with a focus on electronic systems and methodology that were conceived as part of ConCuCT-II will continue. Work to evaluate real-time patient-reported symptoms and adverse events after surgery as part of the eRAPID project (Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice") will be published. A feasibility study exploring whether it is possible for patients or their carers to capture self-taken images of surgical wounds after hospital discharge is currently underway and will continue as part of Macefield's PhD work. The aim of this study is to explore the method to allow blinded assessment of wounds for use in RCTs, as well as supplementing the patient-reported WHQ data.

Further validation of Hub-developed new outcome measures

Work to further validate the Bluebelle Wound Healing Questionnaire (WHQ) in other surgical wound types (e.g. wounds healing with secondary intention) and to explore a cut-off value for SSI is underway, with external collaborations and co-app involvement of theme 4 members in funded trials including abdominal surgery, parastomal hernia and wounds healing with secondary intention. We have developed a provisional metric for assessing the quality of wound closure, a need that became apparent as part of the Bluebelle study, and further development and validation of this new tool is now required.

Optimising blinding in trials of invasive procedures

Work centred on optimising the design and conduct of placebo-controlled trials of invasive procedures is currently on-going. This work will inform a funded MRC workshop (Led by the Oxford Hub) taking place in December 2019 - MRC-NIHR methodology state-of-the-art workshop on methods for placebo comparator group selection and use in surgical trials.

Work includes an update of a systematic review conducted by Wartolowska (2016), which will identify new studies and key literature on invasive placebo procedures and review the rationale for placebo use, the type of placebo controls used, and any methodological/trial conduct implications these raise. We will also review the pilot and feasibility work conducted prior to main trials. Guidelines from the Medical Research Council recommend pilot and feasibility work prior to conducting trials of complex interventions, such as surgery, however the extent to which invasive placebo procedures undergo piloting is unknown.

In addition, we are developing methods to inform the design and conduct of randomised controlled trials with a surgical placebo control. Currently work is on-going to modify a typology used for designing surgical procedures in RCTs (Blencowe, 2016) to make it suitable for use in the design of placebo-controlled trials of surgical procedures.

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Training and capacity building

Our goal was to considerably increase capacity for the efficient delivery of pragmatic RCTs during and beyond the period of Hub funding. We have invested in future clinical and non-clinical academics to lead trials and undertake trials methodology research to improve the health of patients and the public with a particular focus on RCTs in surgery. While a number of research centres provide training in the design and analysis of RCTs, our focus on complex interventions in surgery clearly meets a national skills need. This need will continue to grow as more non-pharmaceutical RCTs are funded through the NIHR PHR, HS and DR and HTA programmes. Further details about the scope of the training opportunities we have offered are detailed below.

PhD, MD and MSc training

The Department of Population Health Science has a thriving post-graduate programme with a track record of successful supervision and completion of PhDs. Since April 2014, (the period covered by ConDuCT-II) 10 PhDs/MDs and one MSc have been awarded. There are 10 current ConDuCT-II PhD/MD students and five ConDuCT-II affiliated PhD students.

For each Hub and Hub-affiliated student, details are given below of: funder; student; project title; supervisors; degree; affiliated Hub theme.

ConDuCT-II PhD, MD and MSc projects (2014 – 2018)

The below list details all Hub-affiliated PhD's and MD's (ongoing and awarded, 2014 – present).

Funder: MRC ConDuCT-II Hub for Trials Methodology Research

1. **Noah Howes**: When is the right time for an innovative procedure to be evaluated in a large multicentre RCT? A case study in sleeve gastrectomy. Supervisors: **Blazeby, Savović, Potter**. October 2013 – September 2015. MD. (Theme 3) **Awarded**
2. **Athanasia Gravani**: The effect and importance of trial site staff training on trial conduct. Supervisors: **Lane, Rogers, Wilson**. October 2013 - September 2016. PhD. (Themes 2 and 3) **Awarded** Spring 2018
3. **Theodoros Mantopoulos**: Incorporating Covariates in Cost-Effectiveness Analysis. Supervisors: **Welton, Dias**. Collaborators: Soares, Saramago (University of York), Sutton (University of Leicester). October 2013 – September 2016. PhD. (Theme 1) **Awarded** Summer 2018

Funder: MRC ConDuCT-II Hub, Royal College of Surgeons of England, and NIHR Academic Clinical Fellowship

4. **Sean Strong** Understanding the role of team work in recruitment to surgical RCTs. Funded by Academic Clinical Fellowship post. Supervisors: **Blazeby, Donovan, Paramasivan, Mills**. October 2011 – September 2016. PhD. (Theme 2) **Awarded** March 2017

Funder: MRC Network of Hubs for Trials Methodology Research

5. **Nicola Farrar:** Exploring patient perspectives of recruitment in randomised controlled trials. Supervisors: **Rooshenas, Elliot, Donovan**. October 2017 – September 2020. PhD. (Themes 2&3). **Ongoing**.
6. **Kirsty Garfield:** Developing a modular resource-use questionnaire for use in RCTs. Supervisors: **Hollingworth, Noble, Thorn**. October 2017-September 2020. PhD. (Theme 1). **Ongoing**.
7. **Lucy Bessant:** Treatment preference in paediatric randomised controlled trials. Supervisors: **Mills, Crawley** (University of Bristol), **Young** (University of Liverpool). October 2014 – November 2018. PhD. (Theme 2). **Ongoing**
8. **Katherine Fairhurst:** Optimising the design and evaluation of pilot work to inform efficient RCTs in surgery. Supervisors: **Avery, Potter, Blazeby**. October 2015 – October 2019. PhD. (Theme 3). **Ongoing**
9. **Rachel Maishman:** Improving measures of recovery after surgery for use in RCTs. Supervisors **Rogers, Reeves, Blazeby** October 2015 – December 2020 PhD (Theme 4). **Ongoing**
10. **Gemma Clayton.** Incorporating external evidence syntheses in the analysis of a clinical trial. Supervisors: **Higgins, Jones, Welton**. October 2015 – December 2018 PhD. (Theme 1). **Ongoing**
11. **Ceri Rowlands:** Optimising recruitment into randomised controlled trials in unplanned general surgery. Supervisors: **Rooshenas, Blazeby**. October 2015 – September 2018. PhD. (Theme 2). **Withdrawn**

Funder: NIHR doctoral fellowship scheme

12. **Natalie Blencowe:** Understanding the complexity of surgical interventions: an exploratory study with implications for randomised trials in surgery. NIHR doctoral fellowship. Supervisors: **Blazeby, Mills**, **Whiting** (University of Bristol). October 2011 - September 2014. PhD. (Theme 2) **Awarded** January 2015.
13. **Karen Coulman:** The patient perspective of living with surgery for morbid obesity: Creating a patient 'core' outcome set and investigating ways to improve follow-up care. NIHR doctoral fellowship. Supervisors: **Owen-Smith** (University of Bristol), **Blazeby**. Feb. 2012 – Feb 2016. PhD. (Theme 2 and Theme 4) **Awarded** June 2016.
14. **Barry Main:** Developing a core information set for informed consent to surgery for oral and oropharyngeal cancer. NIHR doctoral fellowship program. Supervisors: **Blazeby, Donovan, Rooshenas**, **Thomas** (University of Bristol). January 2013 – December 2015. PhD. (Theme 2 and Theme 4) **Awarded** June 2016.
15. **Amber Young:** Optimising evidence-based decision-making for young people with burns by the development of a core outcome set and the identification of outcome measurement tools (COSBy). Supervisors: **Blazeby**. October 2016 – September 2020. PhD. (Theme 4). **Ongoing**

Funder: National School for Primary Care Research.

16. **Leah Bowen:** Investigating the use of emergency healthcare services by children under the age of five. Supervisors: **Heawood**, Purdy (University of Bristol). November 2011 - December 2014. October 2015. PhD. (Theme 2) **Awarded**
17. **Mairead Murphy:** Developing a generic outcome measure for primary care. Supervisors: **Hollinghurst**, Coast (University of Birmingham). January 2013 – December 2015. PhD. (Theme 1 and Theme 4) **Awarded**

Funder: University of Bristol

18. **Rhiannon Macefield:** Improving the assessment of surgical site infection by developing accurate and efficient outcome measures and methods for blinded assessment for use in randomised controlled trials. Supervisors: **Blazeby**, **Avery**. October 2014 – September 2020 (part-time 50% WTE). PhD. (Theme 4) **Ongoing**

Funder: Research for Patient Benefit project grant

19. **Caroline Boulind:** Blinding in randomised controlled trials of surgical interventions. Supervisors: **Blazeby**, **Metcalfe**. August 2009 – 31 July 2015 (part-time). MD (Theme 3) **Awarded**

Funder: MRC Methodology Research Grant

20. **David Phillippo:** Calibration of treatment effects in network meta-analysis using individual patient data. Supervisors: **Dias**, **Welton**, **Ades**. July 2016 – July 2019. PhD. (Theme 1). **Ongoing**
21. **Patricia Guyot:** Expected survival time as a summary statistic in evidence synthesis and economic analysis. Supervisors: **Welton**, **Ades**. Industry-funded by MapiValues November 2008 – December 2010, then MRC funded from December 2010 - May 2013 (75% FTE).. PhD. (Theme 1) **Awarded** July 2014

Hub affiliated PhD students

Funder: MRC Network of Hubs for Trials Methodology Research

22. **Ashma Krishan:** The analysis and reporting of time to event data in randomised controlled trials: impact on evidence synthesis and cost-effectiveness. Supervisors: Tudur-Smith, Dwan, (University of Liverpool), **Welton**. October 2015 – September 2020. PhD. (Theme 1) . **Ongoing**

Funder: NIHR Bristol Biomedical Research Centre

23. **Johnny Mathews:** Understanding surgeon and team expertise to enable safe and transparent early phase evaluation of novel surgical techniques. Supervisors: **Blazeby**, **Blencowe & Elliott**. 6/2/18 – 7/2/22. PhD. (Theme 3) **Ongoing**
24. **Alice Toms:** The legal, regulatory and governance dimensions of surgical innovation. Supervisors: Huxtable, **Hinchliffe** & Birchley. 2/10/17 – 3/10/21. PhD. **Ongoing**

Funder: NIHR Doctoral Fellowship

25. **Bilal Alkhaffaf**: Development of a Core Outcome Set for Gastric Cancer Surgery Effectiveness Trials. Supervisors: **Blazeby**, Cook. PhD. (Theme 4) **Ongoing**
26. **Beth Conroy**: Learning and clustering: combining adjustments for the learning curve and clustering effects in randomised surgical trials. Supervisors: **Blazeby**, Williamson. Jan 2016 – Dec 2020. (Theme 3) **Ongoing**

MSc students

Funder: NIHR CIPHER Study, ConDuCT-II Hub Clinical Primer

27. **Charlotte Murkin**: Developing metrics to screen for parastomal hernia and understand surgical risk factors. Supervisors: **Blazeby**, **Blencowe**, **Rooshenas**. October 2016 – Sept 2018. MSc. (Theme 3) **Awarded**

Personal awards and fellowships (2014 – 2018)

1. PI: Crawley E; Co-app(s): Van de Putte E, Nijhof S, Knoop H, Bleijenberg G, Stallard P, Kessler D, Downing H, Macleod J, Price S. Investigating the treatment of paediatric chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) (MAGNENTA RCT). NIHR Senior Research Fellowship. £864,736. 2014 – 2019. (Themes 2 and 4)
2. PI: Blencowe N. Improving the design of RCT's in surgery: understanding how to describe and standardise co-interventions. Academy of Medical Sciences – Starter grant for clinical lecturers. £26,250. August 2015 – August 2017. (Theme 3)
3. PI: Sach T; Co-app(s): Thomas K, Welton N, Briggs A. Prioritising research for an entire clinical area (Eczema) using value of information (VoI) methods. NIHR Career Development Fellowship. January 2015 – December 2019. (Theme 1)
4. PI: McNair A. The Disclose study: Development and piloting core disclosure for informed consent for surgery. Academy of Medical Sciences. £20,336. 2014 – 2016 (Theme 2)
5. PI: Macefield R. Developing advanced evidence synthesis skills to inform rapid and focused surgical innovation: a training placement between the Bristol BRC (Surgical Innovation theme) and the Manchester BRC (Dermatology theme), Greater Manchester CLAHRC and Cochrane Wounds. NIHR Infrastructure Short Placement Award for Research Collaboration (SPARC). £2,842. April 2018.
6. PI: Sam Brilleman. Co-app(s): Metcalf C. The reporting of treatment non-adherence and its associated impact on economic evaluations conducted alongside randomised trials: a systematic review. NIHR Research Methods Fellowship. £100,000. 2013 – 2015.
7. PI: Shelley Potter. The BRaveR Study - Methods to develop and deliver Better ReseArch to improVe outcomes and inform practice in brEast Reconstruction. NIHR Clinician Scientist Award. NIHR Clinician Scientist Fellowship. £1,118,847. 2017-2022.
8. PI: Jane Blazeby. NIHR Senior Investigator Award. £63,21. 2015-2019.
9. PI: Jonathan Sterne. Co-app(s): Higgins J. NIHR Systematic Reviews Fellowship. £91,000. Awarded 2016.

10. PI: Mairead Murphy. Avon Primary Care Research Collaborative. Personal launching fellowship to disseminate work from PhD and apply for future funding. £47,104. 2017-2018.
11. PI: Natalie Blencowe. Standardising surgical Interventions and Co-interventions: development of a quality assurance intervention for surgical RCTs (STItCh-IT). MRC Clinician Scientist Award. £1,066,082.40. 2019-2024.
12. PI: Angus McNair. Enhancing safe and transparent rectal cancer surgical innovation. NIHR Clinician Scientist Award. £936,495. 2018-2023.
13. PI: Kate Harvey. Co-app(s): Potter S, Holcome C, Mills N. The PreBRA study. Royal College of Surgeons Fellowship. £61,470. 2018-2019.
14. PI: Rhiannon Macefield. Travel award. University of Bristol Alumni. £450. May 2018.
15. PI: Ali Heawood. NIHR Research Capability funding. £32,000. 2017-2018.
16. PI: Russell Thirard. Bayesian methods for the analysis of subgroup of patients in Randomised Clinical Trials (RCTs) and the design of a Study-Within-A-Trial (SWAT) to investigate the effect of audio-recording patients on their recruitment in trials. NIHR Research Methods Fellowship. £93,753. 2017-2019.

Clinical academics in the Hub

Since the initiation of the first Hub 12 academic F2 doctors, four academic clinical fellows (ACFs) and six academic clinical lecturers (ACLs) in surgery have been linked to the Hub as well as a bariatric dietitian and one nurse. All have undertaken methodological research projects supervised by Hub members. All AF2 doctors have been awarded higher degree funding (2 based in Bristol), Three starter grants from the Academy of Medical Sciences have been successfully awarded. These include, i) The development of a core outcome set for breast reconstruction surgery, ii) An exploration into optimal methods for communicating trial outcomes and core information sets to patients, and, iii) Methods to design surgical trials accounting for co-interventions. Three have gained NIHR doctoral fellowships (all completed and PhDs awarded), and one ACL (now a Senior Clinical Lecturer (SCL)) has successfully won a Research for Patient Benefit Grant to examine the feasibility of an RCT in breast reconstruction surgery. In 2015 a new Chair in Vascular Surgery was appointed who had a strong research interest in clinical trials. We also have two affiliated consultant NHS surgeons with honorary academic posts linked to the Hub.

Clinical academic support was also supported in the Hub by an award from the Vice Chancellor. Four clinical primer posts have been awarded. These have consisted of six-month research posts designed to give clinicians with an interest in surgical trials the opportunity to engage in ongoing methodological research, with a view to pursuing a doctoral fellowship (see below).

We are also investing in medical undergraduates and have had six INSPIRE studentships linked to the Hub, with students supervised by Hub members. INSPIRE is a programme where undergraduate students can apply for funding to undertake a month-long research project, designed to encourage undergraduate medical students to get involved in research. Each of these INSPIRE students have had posters accepted in national/international conferences and will co-author study papers. In addition to the INSPIRE studentships, over 20 undergraduates have worked on literature reviews conducted in areas of surgical innovation and blinding of personnel in trials.

Clinical academic case studies

Angus McNair MB ChB, PhD, FRCS, FHEA

Clinical academic surgeon

I am an NIHR Clinician Scientist at the University of Bristol and Honorary Colorectal Surgeon at North Bristol NHS Trust. I am an academic colorectal surgeon with an interest in surgical oncology and organ preserving rectal surgery. My research interests are in outcome methodology, including the development of standardised outcomes for research and clinical practice, and information provision for surgical consent.

I have conducted detailed analyses of outcome selection, measurement, and reporting in surgical trials and developed core outcome sets in colorectal cancer surgery and fistulating perianal Crohn's disease. My current NIHR Fellowship extends this work into early phase surgical studies. I have drawn parallels between outcome measurement in trials and communicating information for patient decision making. This resulted in the development patient centred core information sets to use in surgical consent consultations.

I am passionate about patient involvement in research and have led a large patient consultation exercise for the Association of Coloproctology of Great Britain and Ireland and coordinate patient involvement in the NIHR CIPHER study. I am Deputy Chair of Curative Treatments at Bowel Cancer UK and serve on the scientific committee. Furthermore, I serve on the Board of the National Cancer Research Institute and guide policy and governance.

Karen Coulman, BSc, MSc, PhD, RD

Clinical academic dietitian

I am a Senior Research Associate within the ConDuCT-II Hub at the University of Bristol and an honorary bariatric surgery dietitian at North Bristol NHS Trust. My research interests include the psychosocial aspects of living with obesity, bariatric surgery, and other chronic diseases, trials of behavioural interventions, and how health professionals engage with trials and research. Within the Hub, I have been involved in both the Outcomes theme and the Feasibility and Conduct of Trials (FACT) theme. During my PhD (funded through an NIHR Doctoral Fellowship) I developed a core outcome set for bariatric surgery, and am currently collaborating with a Dutch obesity group to develop core quality of life measures for bariatric surgery. Recently I have been involved in a qualitative study investigating the engagement of trainee surgeons in trials, which is funded through the HTMR (for which I am also a co-applicant on the grant). I am also a clinical primer within the Hub which has supported me to develop a NIHR/HEE ICA clinical lectureship application and have been shortlisted for interview for this award.

Thus far I have published four first-author papers from my PhD (one in PLoS Medicine, two in Obesity Reviews and one in Obesity Surgery), and a fifth is nearing submission. In total I have authored 12 peer-reviewed journal publications (seven first author). I have presented my PhD work at several national and international conferences (four oral presentations – three of which were in the council prize session) and was an invited speaker at the International Federation for the Surgery of Obesity and Metabolic Disorders conference in London in 2017.

Dr Aggie Skorko, MBBS BSc

Clinical Primer

I am an intensive care registrar in Bristol and had recently completed an NIHR academic clinical fellowship (ACF). The Intensive care (ICU) environment is highly complex and relatively few of the processes that occur on a daily basis have been scientifically investigated. Yet they have huge impact on both the healthcare users and providers. The communication that occurs between healthcare professionals and patients and their families has always been of particular interest to me. But it was only during my ACF that I became aware of methodologies that could enable intensive care doctors to understand the needs of our patients and their families to improve their experience. Undertaking the clinical primer to learn more about these research methods has been the perfect opportunity for me to build on the skills gained during my ACF. I am currently half way through my clinical primer and have already been inspired by the unique opportunity to work with a wide range of colleagues afforded by the centre. I have attended an international conference on evidence-based innovation which, together with the centre's regular teaching sessions and meetings, has exposed me to the breadth of research questions that can be scientifically addressed with innovative methodologies. I am in the process of writing a doctoral fellowship application that will bring together expertise from the CONDUCT Hub and the School for Ethics in Medicine to develop a robust method of researching complex communication exchanges on ICU, an opportunity I could never have been afforded without the benefit of the clinical primer at the centre.

School of Population Health Sciences short courses (2014-2018)

In order to further develop future capacity for methodological research, members of the ConDuCT-II Hub regularly contribute to the design and delivery of specialist intensive short courses delivered annually or biannually to academic researchers, trialists, healthcare professionals and postgraduate students within the internationally recognised short course programme hosted by the School of Population Health Sciences. Courses in which Hub members are directly involved include:

1. *Systematic reviews and meta-analysis – courses A and B*. Course organisers: **Higgins, Savović, Jones**. (Theme 1)
2. *Introduction to economic evaluation*. Course organisers: **Noble, Marques** (Theme 1)
3. *Introduction to network meta-analysis*. Course organisers: **Welton, Caldwell** (Theme 1)
4. *Introduction to linear and logistic regression models*. Course organisers: **Welton, MacNeil, Metcalfe** (Themes 1 and 3)
5. *Introduction to Bayesian Data analysis using WinBUGS*. Course organisers: **Dias, Welton, Ades** (Theme 1)
6. *Introduction to Using Conversation Analysis to Study Health Care Encounters*. Course organisers: **Barnes, Jepson** (Theme 2)
7. *Qualitative Research to Optimise Design and Conduct of Randomised Trials*. Course organisers: **Heawood, Mills** (Theme 2)
8. *Introduction to Research Governance*. Course organisers: **Campbell, Shlomo** (Theme 2)
9. *Questionnaire Design, Application and Data Interpretation*. Course organisers: **Lane, Horwood, Avery, Macefield** (Themes 2, 3 and 4)
10. *Introduction to Randomised Controlled Trials*. Course organisers: **Lane, Metcalfe, Brookes, Redmond, Thomas, Tolkien** (Themes 3 and 4)

11. *Design and Analysis of Randomised Controlled Trials*. Course organisers: Redmond, **Brookes** (Theme 4)
12. *Multiple Imputation for Missing Data*. Course organisers: **Tilling**, Cornish (Theme 4)
13. *Advanced Multiple Imputation methods to deal with Missing Data*. Course organisers: **Tilling**, Hughes (Theme 4)
14. *Casual inference in Epidemiology: Concepts and Methods*. Course organisers: Fraser, **Tilling** (Theme 4)
15. *Statistical Methods for Mediation analysis*. Course organisers: Howe, **Tilling** (Theme 4)

Bristol Oxford Surgical Trials Course (BOSTiC): Training in research methods for surgical trainees

BOSTiC is a three day residential course that aims to engage and educate surgeons-in-training in the design and conduct of randomised controlled trials (RCTs) in surgery. It is run annually by members of the Bristol and Oxford Royal College Surgical Trials centres in collaboration with members of the MRC ConDuCT-II Hub.

Below is a report from Samir Pathak, an academic lecturer in the Bristol Surgical Research Centre, about the 2018 course.

Summary of BOSTiC 2018

The 4th annual Bristol Oxford Surgical Trials Course (BOSTiC) was held in Bristol this year at Canynge Hall, University of Bristol. The course is primarily aimed at surgical trainees who are interested in clinical research, with an emphasis on design and conduct of randomised control trials. The course is delivered by a multi-disciplinary team from the Bristol and Oxford Surgical Trials Units who are supported by the Royal College of Surgeons of England. This year the course was attended by surgical trainees from a wide variety of specialities across the UK and even one participant from the USA!

The course ran over three days in June. A variety of teaching methods were utilised to maintain audience engagement and participation such as lectures tutorials and small group forums. The faculty maintain the view that “no question is a bad question.” There is great diversity in terms of the surgical specialities of the participants which also helps in sharing of ideas and experiences.

Day one started with a series of presentations from Professor Jane Blazeby, Professor David Beard and Professor Jonathan Cook around the need for evidence-based medicine, how to formulate a research question and the key elements required for randomised trial design. Following this there were a series of talks on optimising trial recruitment. Ms Shelley Potter also shared her experiences as a new Chief Investigator (CI) in designing the iBRA study. During the day, the groups met with their mentors and initial trial ideas were discussed. The day finished with a course dinner at Aqua restaurant.

The morning sessions on Day 2 built on from the previous day and featured talks on alternative trial designs, experiences of a CI and selecting, measuring and reporting primary and secondary outcomes by Professor Jonathan Cook, Professor Andrew Carr and Dr Kerry Avery. Mr Veeru Kasivisvanathan also gave a fascinating talk on being a CI as a trainee. Professor Chris Rogers summarised key statistical concepts and provided the opportunity for delegates to calculate power and sample sizes for a study. The delegates also continued to work in groups to design their RCTs for presentation on the final day.

BOSTiC aims to enlighten delegates with regards to research methodology but also give them real world insights regarding trial design. Day 3 started with Professor Rob Hinchcliffe providing insights into being a Chief Investigator and Dr Lucy Culliford then spoke around some of the practicalities in running clinical trials. This was followed by an insightful talk by Professor Julian Higgins on how evidence synthesis can help in trial design. Professor Jonathan Cook then spoke to the delegates about structured reporting of clinical trials and the CONSORT statement. The course ended with a dragons' den style presentation with each of the delegate groups presenting their designed RCT which they had worked upon throughout the course. Experienced mentors from both Bristol and Oxford Universities helped guide delegates throughout this process. The winning group designed a trial looking at different surgical techniques for managing the distal ureter during a radical nephrectomy.

Feedback from the course has once again been excellent with 100% of delegates rating the quality of teaching and the course overall as excellent or very good. Below are some of the quotes from the delegates:

"Absolutely brilliant course. Extremely good value for money considering how much I have learnt. Very enjoyable but also really educational. Thank you!"

"This has been my most valuable course, I would happily attend other courses you organise."

From a personal point of view, I found listening to the experience of various Chief Investigator's at different stages of their career to be fascinating. The practicalities of running trials and methods used to optimise recruitment were also very interesting. The take home message for me though was the importance of framing the research question correctly in the first place – and how long that process can take!

Next year's course will be in Oxford- see you there!

Workshops (2014 – 2018)

Hub members have contributed to and/or been awarded funding to deliver a number of successful research and training events both nationally and internationally to disseminate RCT methodology developments more broadly. These include the following (in theme order):

1. *Indirect and mixed treatment comparisons*. Leicester, annually/biannually. Abrams, Ades, Caldwell, Dias, Cooper, Sutton, **Welton**. (Theme 1).
2. *Meta-modelling for value of information calculations*. September 2014. **Welton** (workshop organiser), Mada, Price, Strong, Alam, Baio, Jackson. Funded by: MRC HTMR. (Theme 1).
3. *Methodological challenges in healthcare resource-use measurement: towards good practice*. 10th iHEA/ECHC Congress, Dublin, July 2014. **Thorn, Hollingworth, Evers, Noben, Ramaekers**. (Theme 1).
4. *Health Economics Analysis Plans (HEAPs) workshop*. Bristol, October 2015. **Thorn**, in collaboration with the Northwest Hub. Funded by the MRC HTMR. (Theme 1)
5. *The role of value of information in HTA: are we missing an opportunity?* International society for pharmacoeconomics and outcomes research, 18th Annual European Congress, Italy, November 2015. **Baio, Welton, Strong, Heath**. (Theme 1)
6. *Guidance for evidence synthesis of survival outcomes for cost-effectiveness modelling*. International society for pharmacoeconomics and outcomes research, 18th Annual European Congress, Italy, November 2015. **Jansen, Briggs, Welton**. (Theme 1)

7. *Statistical methods for Value of Information (Short Course)*. University College London, Short Course, June 2016. **Welton**, Strong, Baio, Heath. Funded by MRC HTMR (Theme 1)
8. *Population-adjusted treatment comparisons in health technology assessment: an overview of approaches and perspectives*. ISPOR Improving healthcare decisions, 20th Annual European Congress, Glasgow, November 2017. **Phillippo, Elsada, Belger, Welton**. (Theme 1).
9. *Economic evaluations alongside surgical trials workshop*. Bristol, November 2017. **Hollingworth, Thorn, Blazeby**. (Theme 1)
10. *R for cost-effectiveness analysis workshop*. London, July 2018. **Thom, Williams, Welton, Dixon, Jackson, Soares, Hatswell, Hughes, Mihaylova, Schloackow, Baio G**. Funded by MRC HTMR. (Theme 1).
11. *Mixed methods approaches to understanding trial outcomes; Nursing Midwifery and Health Professionals Workshop*. University of Stirling, February 2014. **Hoddinott**. (Theme 2)
12. *Pilot and feasibility studies workshop*. University of Stirling, September 2014. **Hoddinott**. (Theme 2)
13. *Developing, delivering and evaluating training courses for recruiters to randomised controlled trials*. LUniversity of Bristol, Bristol, March 2014 – August 2015. **Mills, Donovan, Young, Bower, Gamble, Tudur-smith, Holding, Blazeby**. (Theme 2).
14. *Optimising recruitment into RCTs in surgery: a focused workshop for surgeons*. Bristol, March, May 2015, May 2016, January 2018. **MRC ConDuCT-II Hub** in collaboration with the North West HTMR. (Theme 2)
15. *Optimising recruitment into RCTs in surgery: a focused workshop for nurses*. Bristol, April 2015, March 2016 and March 2018. **MRC ConDuCT-II Hub** in collaboration with the North West HTMR. (Theme 2)
16. *Developing, delivering and evaluating training courses for recruiters to randomised trials*. University of Bristol, March 2014 – August 2015. **Mills, Donovan, Young, Bower, Gamble, Tudur-Smith, Holding, Blazeby**. Funded by MRC HTMR. (Theme 2)
17. *Recruitment training workshop for Clinical Research Network nurses*. University of Bristol and NIHR West of England CRN, March 2016. **Mills, Donovan, Elliott, Jepson**. (Theme 2)
18. *Recruitment training workshop for Clinical Research Network medics*. University of Bristol and NIHR West of England CRN, June 2016. **Mills, Donovan, Elliott, Jepson, Rooshenas** (Theme 2)
19. *Recruitment and informed consent training*. CONservative Treatment of Appendicitis in Children – a randomised controlled trial (Feasibility) recruitment training, Southampton General Hospital, St Georges Hospital London, Royal United Hospital Bath, December 2016, and Jan, July and November 2017. **Beasant, Parslow** (Theme 2).
20. *Generating student recruiters for randomised trials (GRANULE)*. Birmingham, Bristol, June 2016. **Rooshenas, Mills, Blazeby, Glaseby, Nepogodiev, Bach, Bhangu**. (Theme 2)
21. *Optimising qualitative research in trials: Tips for success from funding to delivery*. QUESTS Qualitative research in Trials, Galway, October 2017. **Wilson, Conefrey**. (Theme 2)
22. *Excellence in qualitative research in trials*. University of Bristol, Bristol, November 2017. **Horwood**. (Theme 2).
23. *Optimising setup and recruitment of multicentre complex randomised controlled trials*. 4th International Clinical trials methodology conference, Liverpool, May 2017. **Realpe**. (Theme 2).
24. *Optimising recruitment*. Tomorrow's leaders – Clinical trials in surgical oncology, London, December 2017. **Rooshenas**. (Theme 2).

25. *Adaptive approaches to randomised trials of non-pharmaceutical interventions*. Adaptive Designs Research Workshop, Cambridge, January 2014. **Metcalfe**. (Theme 3).
26. *Pilot and feasibility studies workshop*. University of Stirling, Stirling, September 2014. **Hoddinott**. (Theme 3).
27. *Clinical trials methodology: key issues for successful design and conduct - a focused workshop for Academic Clinical Trainees*. London, July 2014. **Blazeby, Clarke, Armitage, Colby, Benari, Montgomery**. Funded by MRC HTMR. (Theme 3).
28. *Optimising the design and evaluation of pilot work to inform efficient RCTs: a workshop to consider the key issues and areas for future research*. Royal College of Surgeons of England, London, March 2014. **Avery, Blazeby**. (Theme 3).
29. *Clinical trials methodology: key issues for successful design and conduct – a focused workshop for Academic Clinical Trainees*. London, July 2014. **Blazeby**. Funded by MRC HTMR. (Theme 3).
30. *Introducing a revised risk of bias tool for randomised trials*. Cochrane Colloquium, Vienna, Austria, October 2015. **Savovic, Higgins, Sterne, Boutron, Hrobjartsson**. (Theme 3).
31. *How to be a good chief investigator*. London, September 2015. **Armitage, Blazeby, Williamson, Marson**. Funded by the MRC HTMR. (Theme 3).
32. *Using feasibility outcomes to inform the main trial*. Royal College of Surgeons Future of Surgery workshop, London, May 2016. **Blazeby** (Theme 3).
33. *Less and better surgical research needed: using pilot and feasibility work to optimise trial design*. 'Better trials make better surgeons' workshop, North West Surgical Trials Centre, Warrington, June 2016. **Blazeby** (Theme 3).
34. *Principles guiding early phase trial design for surgical innovation*. Practicalities and Ethics of trial design workshop, London, October 2016. **Blazeby** (Theme 3).
35. *International committee of medical journal editors proposal on sharing clinical trial data – invited workshop*. Academy of Medical Sciences, London, September 2015. **Lane**. (Theme 3).
36. *Randomised controlled trials critical appraisal*. 8th Annual surgical Trainees' Research, Audit and Quality Improvement Training. Bristol, November 2016. **Avery, Blencowe, Cousins, Macefield, Main**. (Theme 3).
37. *Identifying and assessing different approaches to developing complex interventions: An introduction to the INDEX Study*. Society for social medicine, Manchester, September 2017. **O'Cathain, Hoddinott, Duncan, Yardley, Turner, Croot, Sworn, Rousseau**. (Theme 3).
38. *Sources of bias in randomised studies of interventions: a casual inference perspective*. Victorian centre for biostatistics, Melbourne, Australia, March 2018. **Sterne**. (Theme 3).
39. *Assessing risk of bias in randomised trials: ROB 2.0*. Cochrane Colloquium, September 2018, Edinburgh. **Sterne, Higgins, Savovic, McAleenan**. (Theme 3).
40. *Methods for COS development*. COMET 4th meeting, Rome, November 2014 and COMET 6th meeting, Amsterdam, November 2016. **Blazeby, Brookes, McNair**. (Theme 4).
41. *What should we measure? Core Outcome Sets and Patient Reported Outcome Measures*. CFS/ME Research Collaborative (CMRC) annual meeting. Bristol, September 2014. **Brookes**. (Theme 4).
42. *Mixed methods approaches to understanding trial outcomes; Nursing, midwifery and health professionals workshop*. University of Stirling, Stirling, February 2014. **Hoddinott**. (Theme 4).
43. *Involving the public in core outcome set development*. COMET (Core Outcome Measures in Effectiveness Trials) PPI event. London, March 2014. **Brookes**. (Theme 4).

44. *Developing core outcome/information sets: methodological issues*. COMET Methodological Workshop. Bristol, June 2014. **Blazeby, Brookes** (Theme 4).
45. *NCRI Future of Surgery workshop - "Trials are only as credible as their endpoints": Defining the future outcomes of surgical research*. Royal College of Surgeons of England, London, May 2016. **McNair, Avery** (Theme 4)
46. *Workshop on multimorbidity*. Long term Conditions group, NHS England, Leeds, August 2016. **Salisbury** (Theme 4).
47. *Improving the design of clinical trials with PROs: guidance for protocol writers*. International society for quality of life research, 24th Annual Conference, Philadelphia USA, October 2017. **Calvert**. (Theme 4).
48. *Improving the evaluation of medical devices with development of a generic core outcome set: a key stakeholder workshop for industry, innovators, clinicians, trialists, journal editors and health policy makers*. Bristol, October 2018. **Hinchliffe, Blazeby, Williamson, Cousins, Avery, Potter, Sundstrom**. Funded by the MRC HTMR. (Theme 4).
49. *MRC-NIHR methodology state-of-the-art workshop on methods for placebo comparator group selection and use in surgical trials*. Oxford, December 2018. Beard, Cook, **Blazeby**, Campbell, Pinkney, Cuthbertson, Tracey, Buchbinder, Prof Savulescu, Farrah-Hockley (patient representative), **Blencowe**, Carr. Funded by the MRC HTMR (Theme 4).

Other training and capacity building events (2014 – 2018)

The Hub has contributed to a number of other training and capacity-building events. Hub members from across all themes have been invited to talk at over 150 conferences over the course of ConDuCT-II, including 27 international conferences and 9 where Hub members have delivered the keynote speech. Members have also delivered invited sessions/webinars and acted as invited panel members at a number of international conferences.

In addition, Hub members have disseminated work through online blogs and magazines, online educational video series, engagement stands at national conferences, podcasts and television interviews.

Case studies: Training and capacity building

Theme 1: Nicky Welton, PhD, MSc, BSc
MRC ConDuCT Joint Theme 1 lead

I graduated with a BSc in mathematics from Sheffield University, an MSc in Statistics from University College London, and a PhD in mathematical biology from the University of Bristol. Following my PhD, I worked for a short time as a statistician at the UK Transplant Support Service Authority, before moving back to academia, as a Lecturer in Statistics at the University of the West of England (UWE) in Bristol. In 2002, I joined the Multi-parameter Evidence Synthesis (MPES) research group, funded by the MRC Health Services Research Collaboration at the University of Bristol, where I developed interests in methods for evidence synthesis in health technology assessment, network meta-analysis, extrapolating survival curves, bias adjustment in evidence synthesis, use of evidence in economic models, value of information analysis. I co-led the theme on Value of Information methods in the original ConDuCT Hub, which together with an MRC Methodology Research Fellowship helped me to develop a programme of research work in evidence synthesis and value of information methods to improve efficient trial design, and build my own research team of statisticians and health

economists. I developed a further program of work to consolidate my evidence synthesis and value of information work with a focus on surgical trials co-leading theme 1 in ConDuCT-II. The development opportunities provided by the ConDuCT and ConDuCT-II Hubs have been a key factor in me recently obtaining core funding and being promoted to Professor of Statistical and Health Economic Modelling. I now lead the Multi-Parameter Evidence Synthesis research group and act as Director of the Clinical Guidelines Technical Support Unit, and Director of the departments Short Course Program.

Theme 2: Nicola Farrar

MRC ConDuCT Hub funded PhD student (Oct 2017-Sept 2020)

Thesis title: Exploring patient perspectives for recruitment in randomised controlled trials

I completed my undergraduate degree in Politics at the University of Bristol in 2013. I then moved to the University of Oxford to work in the Surgical Intervention Trials Unit (SITU) as a Clinical Research Coordinator. I worked on a number of randomised controlled trials (RCTs) whilst there, including three pilot/feasibility studies. The unit collaborated with the QuinteT (Qualitative Research Integrated within Trials) group on several RCTs and it was whilst I was working at SITU that I was first introduced to the QuinteT Recruitment Intervention (QRI) – an intervention designed to optimise RCT recruitment. In 2016 I returned to Bristol to work as a Research Governance Manager at NHS Blood and Transplant. My work prior to commencing my PhD gave me a strong grounding in RCT design, trial management and research ethics. I was particularly interested in trial recruitment, having worked on studies which struggled to recruit to time or to target.

I joined the MRC ConDuCT-II Hub in October 2017 as a Hub funded PhD student supervised by Dr Leila Rooshenas, Dr Daisy Elliott, Dr Marcus Jepson, and Professor Jenny Donovan from the University of Bristol and Professor Bridget Young from the University of Liverpool. The aim of my PhD is to understand how patients make their decisions about RCT participation. I will achieve this through the analysis of audio-recordings of RCT recruitment consultations, which are routinely collected in a study undertaking a QRI, linked to interviews with patients who have been approached to take part in the respective RCT. Through these methods, I intend to explore potential trial participants' perspectives of RCT recruitment processes, their interpretation and understanding of the information that is communicated to them about the RCT, and what other sources patients consult (e.g. family, the media) to help make their decision.

I will be implementing the above methods in a sample of different RCTs which will form 'case studies' within the context of my PhD. Being integrated within the QuinteT team I was able to complete an in-depth review of all studies undertaking a QRI and purposefully selected three RCTs for inclusion as case studies. The review included mapping the consent process and patient pathway and the RCTs were selected based on their challenging pathways, diverse patient populations and types of intervention. I work closely with the lead researchers for the RCTs in which I am conducting interviews and meet regularly with the wider RCT teams.

I have recently started undertaking qualitative interviews with patients who have declined participation in one of the RCT case studies. Interviews are either being conducted face to face or over the phone. One benefit of conducting interviews face to face is that it allows family members or carers to be present and share their experience of the recruitment process as well. Currently, I am liaising with local site staff to coordinate the invitation of patients to take part in interviews who have also consented to having their recruitment consultations recorded. This will allow linked analysis between recruitment consultation audio-recordings and patient interviews.

Undertaking this PhD has given me the opportunity to develop my methodological skills. Through membership of the Population Health Science department, I have had access to many School short courses, including: An introduction to Conversation Analysis; An introduction to Qualitative Research and An introduction to RCTs. My involvement with the Hub has provided me with networking opportunities with colleagues from other research areas and universities through the HTMR Annual Meeting and student meetings.

I have also been able to enhance my oral and poster presentation skills by attending the Population Health Science Institute Symposium, where I presented a poster, and by presenting my work at the 2018 HTMR Annual Meeting. I have also presented at the University of Liverpool when I went to meet my supervisor and her team. This was a great opportunity to get feedback on my early work and discuss other areas of the research that I could explore.

Theme 3: Natalie Blencowe BMedSci BMBS (Hons) Dip Med Ed PhD FRCS

Affiliated Hub member, Specialty Registrar in General Surgery and NIHR Clinical Lecturer. PhD awarded January 2015 (PhD NIHR Doctoral Fellowship) and NIHR Clinician Scientist (April 2019).

I graduated in Medicine from Nottingham University with a research interest fuelled by a BMedSci and commitment to evidence-based surgery. Following basic surgical training (Bristol) I was awarded a NIHR Academic Clinical Fellowship and National Training Number in the Severn Deanery (supervised by Blazeby) and joined the Hub. During this time I attended specific Hub courses (qualitative research in RCTs, trial recruitment workshops, COMET meetings, and the HTMR MRC student symposiums). I worked with Hub members on a randomised feasibility study proposal, ROMIO (Randomised Oesophagectomy: Minimally Invasive or Open, now funded by the HTA). This involved conducting systematic reviews, helping to write sections of the protocol and patient information leaflets, categorisation of adverse events, and attending and presenting at trial management group meetings.

Under the supervision of two Hub members (Blazeby and Mills) I successfully gained an NIHR doctoral fellowship award (Understanding complexity in surgical interventions: an exploratory study with implications for trials, training & practice. 2011-2014, £306,308 NIHR-DRF-2011-04-016). This explored how qualitative research methods can be applied in the operating theatre to standardise surgical interventions in RCTs. My PhD was successfully awarded in January 2015. I began a NIHR Clinical Lectureship in March 2015, which is also affiliated with the Hub. This appointment provides me with protected research time, enabling me to continue to develop academic skills alongside clinical training. I was recently awarded an MRC Clinician Scientist Fellowship (Standardising surgical Interventions and Co-interventions: development of a quality assurance intervention for surgical RCTs. 2019-2024, £1066082.40 MR/S001751/1) which will start in April 2019.

My involvement with the Hub has immersed me into a research methodology environment and provided first-hand insight into research infrastructure and leadership. This has been complemented by a distance learning Certificate in Clinical Trials (London School of Hygiene and Tropical Medicine) and a Diploma in Medical Education, both of which I obtained with distinction. I am principal investigator on an Academy of Medical Sciences grant (Methods to describe and standardize co-interventions in surgical RCTs, £26,250). I am a co-applicant on three HTA funded studies (Bluebelle: feasibility study of complex, simple and absorbent wound dressings in elective surgery, £400,000; UK Cohort study to Investigate the prevention of Parastomal Hernia and inform a Randomised trial (CIPHER), £1,041,678); Sunflower: an RCT to establish the effectiveness of expectant management versus MRCP before cholecystectomy, £2,853,627.80),

two MRC Hubs for Trial Methodology grants and an MRC grant for a state of the art workshop on methods for placebo comparator group selection and use in surgical RCTs. I am also a named contributor to the NIHR Bristol Biomedical Research Centre, am co-lead of one of the Surgical Innovation theme workstreams and am co-lead for training. I established the SPARCS (Severn and Peninsula Audit and Research Collaborative for Surgeons, <http://www.sparcs.org.uk/>) initiative for surgical trainees to contribute to multicentre studies and learn trials methodology. I am currently the academic representative for the Association of Surgeons in Training and through this role have designed and delivered a UK-wide survey of academic surgical trainees and a Delphi survey to inform the modernisation of research requirements for the Certificate for Completion of Training. I have led or contributed to 63 peer reviewed publications, 12 invited presentations, 30 international and 54 national presentations (including ten prizes).

*Theme 4: Shelley Potter PhD, MRCS, MFDS, MBChB (Hons), BDS (Hons), BMSc (Hons)
Consultant Senior Lecturer in Oncoplastic Breast Surgery and NIHR Clinician Scientist*

I graduated from Medical School at Bristol University in 2001 with Honours and an intercalated BSc in Molecular and Cellular Pathology (1st Class Honours). After completing my house jobs and basic surgical training in Bristol, I spent a year in the Breast Unit at North Bristol NHS Trust which inspired me to pursue a career in breast surgery.

My main research interest is improving outcomes for women undergoing breast reconstruction following mastectomy for breast cancer. I took time out of clinical work to undertake a PhD investigating the feasibility of clinical trials in breast reconstruction in the now-former School of Social and Community Medicine. This work was affiliated with the first methodology Hub, ConDuCT, during 2008-2011. My PhD work highlighted the need for well-designed pragmatic multicentre RCTs and prospective cohort studies with standardised outcomes to provide evidence to inform decision-making for reconstructive surgery. Following the successful award of my PhD, I was appointed as a Clinical Lecturer in the Bristol Centre for Surgical Research in October 2012.

I have been a member of the ConDuCT-II outcomes theme throughout my clinical lectureship and have contributed to and applied Hub-developed methods for identifying outcomes of importance to patients and healthcare professionals. I led the BRAVO (Breast Reconstruction and Valid Outcomes) Study, funded by an Academy of Medical Sciences Clinical Lecturer Starter Grant which developed a core outcome set for reconstructive breast surgery and as part of this project have undertaken methodological work to explore the impact of different stakeholder groups and subgroups on the outcomes that are agreed for the final core set.

In 2016, I was awarded an NIHR Clinician Scientist (CS) Fellowship and then appointed as a Consultant Senior Lecturer in Oncoplastic Breast Surgery in 2017, having completed a highly prestigious National Training Interface Group Oncoplastic Fellowship in Liverpool and been awarded a Certificate of Completion of Training.

My CS work builds on my previous projects and will develop a core measurement set for reconstructive breast surgery and determine the feasibility of recruiting patients to a randomised trial in implant-based breast reconstruction the design of which will be based on the outcomes of the iBRA study. I also aim to develop an interest in health economics and am undertaking work to explore the potential of microcosting as a preferred method for resource use assessment in clinical trials. I have recently secured an NIHR Research for Patient Benefit grant for the BRIGHTER study which aims to explore the long-term outcomes of breast reconstruction in the National Mastectomy and Breast Reconstruction Audit cohort.

I am Chief Investigator for the NIHR Research for Patient Benefit funded iBRA (Implant Breast Reconstruction evAluation) study, a prospective multicentre cohort study to inform the feasibility, design and conduct of a pragmatic RCT comparing different approaches to implant-based breast reconstruction and have also led a number of large trainee collaborative projects in oncoplastic and reconstructive breast surgery. These include the iBRA-2 study which explored the impact of immediate breast reconstruction on time to adjuvant therapy and the TeaM Study (funded by the Association of Breast Surgery) which aimed to determine the practice and short-term outcomes of therapeutic mammoplasty.

I also co-lead workstream 3 within the surgical innovation theme of the NIHR Bristol BRC, specifically focusing on the measurement, selection and reporting of benefit and harms outcomes of early-phase studies. My involvement with the ConDuCT-II Hub and developed methodology will transfer to the work we are undertaking in the BRC in this important area to improve standardisation in the way surgical innovation is monitored and reported.

Advisory functions (2014 – 2018)

Support for the wider trials community is central to the Hub's activities.

Grant committees

Members serve on numerous grant committees including – MRC-NIHR Methodology Research Programme Panel (Peters); MRC Public Health Intervention Development (PHIND) scheme (Campbell); South-west region advisory committee for the NIHR Research for Patient Benefit funding scheme (Metcalf, Turner (qualitative expert), Barnes, Blencowe); MRC Clinical Training and Career Development Panel (Blazeby); NIHR CTU Standing Advisory Committee (Blazeby; Peters, 2007- 2014); NIHR CLAHRC West Research Advisory Panel (Peters – Chair); NIHR Fellowship Programme Reviews Panel for Career Development, Senior and Transitional Research Fellowships (Blazeby); NIHR research methods fellowships and internships expert review panel (Higgins, Welton); NIHR systematic review fellowships (Higgins); NIHR HTA commissioning board (Turner, Rogers); NIHR HTA funding board (Hollingworth); NICE technology appraisals cancer drugs fund (Welton); Cancer Research UK Clinical Trials Awards and Advisory Committee (Blazeby); Bowel Cancer UK (McNair); Garnet Passe and Rodney Williams Foundation fund (Main).

Methodology Advisory Service for Trials (MAST)

MAST provides additional support to colleagues based in a Clinical Trials Unit or Research Design Service with non-standard methods queries. Through MAST, the Hubs and the Network support researchers, statisticians and other methodologists in Clinical Trials Units and Research Design Services who encounter challenges with non-standard methods in trials, which are not easily answered by the current literature or guidance. This support includes the opportunity to discuss the advantages and disadvantages of different methods, connection to a relevant expert in the Network who might collaborate on the trial, or the development of a SWAT to help resolve uncertainties.

Over the course of the Hub there have been a number of national and local enquiries for advice made to all themes. Enquiries have included help with economic analysis plans for proposed and ongoing RCTs, the integration of qualitative research in RCTs and methods of blinding patients to treatment allocation. The majority of enquires related to requests for training and advice related to optimising recruitment in difficult trials and advice on outcomes in RCTs, including identification of outcomes, generating Delphi surveys, conducting consensus meetings and the use of outcome measures developed by the Hub.

Trial governance committees and other advisory functions

Members sit on various Trial Management, Steering and Data Monitoring Committees.

Members are present on steering committees for 12 studies and data monitoring committees for five trials. Of these, members act as committee chair in six studies. For example, Blazeby chairs TSCs for surgical trials involving challenging methods (e.g. surgery vs non-surgery, complex recruitment pathways and trials in the emergency setting).

Members also serve in an advisory capacity on a number of groups and organisations, including - the CONSORT Pilot and Feasibility Study Reporting Guideline Group (Hoddinott, O'Cathain); Mammary Fold Academic and Research Collaborative (Potter – Chair); Bowel Cancer UK Critical

Research Gaps (McNair); Research Methods to the South and West Research Design Service (Campbell); MRC/NIHR Methodology Research Programme Exploratory Trials Guidance: Consensus Group (Hoddinott and O’Cathain); Working Group to update MRC Complex Intervention Guidance (Hoddinott and O’Cathain); MRC HTMR Network Summit and Expert Panel on the integration of quantitative and qualitative data findings in clinical trials (Wade); Definitive Intervention and Feasibility Awards (DIFA) Expert Panel, Health Research Board (Ireland) (Peters – expert panel chair); NCRI future of surgery (McNair – outcomes lead), British Journal of Surgery council (Blazeby); Wounds Research Network (Macefield); NCRI Breast Clinical Studies Group (Potter); Association of Breast surgery Academy (Potter); Cochrane Scientific Committee (Higgins); Cochrane Comparing Multiple Interventions Methods Group (Higgins); NICE Service Guidance Methods Expert Working Group (Welton); NIHR Complex Reviews Support Unit Advisory/Governance Committee (Welton); NICE Technology Appraisal Committee B (Welton); NIHR Complex Reviews Support Unit (Welton); Singapore Ministry of Health (Salisbury - visiting expert); Commission on Patient Centred Care (RCGP) (Salisbury); Diabetes UK Clinical Studies Group (Hinchliffe); Vascular Society of Great Britain and Ireland (Hinchliffe); NIHR HTA Commissioning Board (Hoddinott, Rogers).

Hub members also serve on the editorial boards of *Pilot and Feasibility Studies* (Hoddinott), *Trials* (Mills, Potter), *British Journal of Surgery* (Hinchliffe), *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins), *Health Expectations* (Barnes), *Statistical Methods in Medical Research* (Metcalf), *Medical Decision Making* (Welton), *Research Synthesis Methods* (Welton), *British Journal of Health Psychology* (Horwood) and *Clinical Trials* (Blazeby).

Research prizes and recognitions (2014 – 2018)

1. **Barry Main** won best poster prize for 'Reporting outcomes in randomised trials of definitive treatments for head and neck cancer: a systematic review', Main B, Beasley M, Thomas S, McNair A, Donovan J, Blazeby J, at the British Association for Head & Neck Oncologists meeting, London, April 2015.
2. **Natalie Blencowe** received the Sylvan Green Award at the Society for Clinical Trials 37th Annual Meeting, Montreal, May 2016.
3. **Natalie Blencowe, Leila Rooshenas and Jane Blazeby** won a poster prize for “‘It’s always too early until suddenly it’s too late’”: designing surgical RCTs relevant to patients, staff and changing technologies’, at the Society for Clinical Trials meeting, Montreal, May 2016.
4. **Charlotte Murkin** won the Billroth Young Surgeon award at the European Hernia Society in Vienna, May 2017.
5. **Sia Gravani** received a poster presentation award for the poster, ‘Training of staff within the conduct of Randomised Controlled Trials (RCTs): a systematic review of the literature’, at the 2nd Annual Faculty of Medicine and Dentistry Postgraduate away day, University of Bristol, August 2016.
6. **Jane Blazeby, Esther Crawley, Rona Campbell, and Chris Salisbury** received NIHR Senior Investigator (2015 –2019, 2014 – 2019, 2015 – 2020, 2016, respectively).
7. **Jane Blazeby** won the Ernest Miles Award from the Association for Cancer Surgery and the Royal College of Surgeons of England meeting, November 2017.
8. **Julian Higgins** won the Olkin award for distinguished lifetime achievement in research synthesis methodology (2016), the Thomson Reuters (2015) and Clarivate Analytics (2016) Highly Cited Researcher awards.
9. **Kasia Bera** was the E Poster Winner in category ‘Randomised Clinical Trials’ for the poster ‘A methodological study of wound closure: dissecting complex interventions into measurable bites’, Bera K, Gould Brown H, on behalf of the Bluebelle study, at the the Association of Surgeons of Great Britain and Ireland (ASGBI) meeting, Belfast, May 2016.
10. **Mairead Murphy** won the prize for best PhD in the faculty of health at the University of Bristol, 2017.
11. **Shelley Potter** won the highly commended Academy of Medical Sciences South West Early Career Researchers Prize, 2016.
12. **Shelley Potter** won the prize for best research project in development at the Society of Academic and Research Surgery, Durham, 2015.
13. A paper by **Wiles, Thomas, Turner, Garfield, Kounali, Campbell, Kessler, Kuyken, Lewis, Morrison, Williams, Peters, Hollinghurst S**, ‘Long-term effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaIT randomised controlled trial’ won the 2017 Royal College of General Practitioners Research Paper of the Year Award in the Neurology, Mental Health and Dementia category and overall.

Outputs (2014 – 2018)

There have been numerous outputs from the ConDuCT-II Hub. Full lists of all grants and publications can be found in Appendices 2 and 3. Key grants and publications per theme are listed below.

Key grants

Given below are selected examples of grants representative of each theme.

Theme 1: Prioritisation and trial design for cost-effectiveness analysis

PI: Welton NJ; Co-app(s): Ades AE, Dias S. Model Based Network Meta-Analysis for Pharmacometrics and Drug-Development. Jointly funded by MRC Methodology Research Programme and Pfizer Ltd, as an MRC Industry Collaboration. £327,555 in total (MRC + Pfizer contributions). January 2015 – December 2017.

This grant related to the work described on page 14 'Impact case study 2 (year 2): Model-Based Network Meta-Analysis; a framework for evidence synthesis of clinical trial data'. The link with industry is a unique feature, and allows us access to datasets for the development of methods, and also allows for direct dissemination of methods, to facilitate impact of new methods directly to industry.

PI: Thorn JC; Co-app(s): Noble SM, Hollingworth W. Programme in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluations (PECUNIA) European Union H2020-SC1-2017-Single-Stage-RTD. €2,999,943.75. January 2018 - December 2020.

This Horizon 2020 grant is an ambitious project to develop standardised, harmonised and validated methods for the assessment of costs and outcomes of healthcare interventions within and across European countries, involving ten partners across six countries.

PI: Welton NJ. Co-app(s): Ades AE, Dias S, Phillippo DM. Calibration of multiple treatment comparisons using individual patient data. MRC Methodology Research Programme. £308,461. January 2017 – December 2019.

This project aims to develop methods for population adjustment in indirect comparisons and network meta-analysis when individual patient data is available from at least one study.

PI: Dias S; Co-app(s): Welton NJ (Bristol Lead), Ades AE, Phillippo D, Abrams KA, Sutton A, Bujkiewicz S, Gray L, Sheehan N. Inferring relative treatment effects from combined randomised and observational data. MRC MRP. £726,176. January 2019 – December 2021.

This is a collaboration between the Universities of Bristol, Leicester, and York to explore the combination of observational and randomised evidence to infer relative treatment effects.

Theme 2: Integrative and dynamic research methods to optimise recruitment to RCTs

PI: Blazeby J; Co-app(s): Donovan JL, Welbourn R, Andrews R, Wordsworth S, Thompson J, Perkins M. Gastric Bypass, adjustable gastric Banding or Sleeve gastrectomy surgery to treat severe and complex obesity: a multi-centre randomised controlled trial. NIHR HTA. £3,939,934. 2015 – 2018

The By-Band-Sleeve RCT integrated the Quintet Recruitment Intervention (QRI) in its internal pilot phase through to the main RCT stage. This key grant highlights the impact of the QRI, and

the ways in which its adaptive and flexible nature can address an array of recruitment issues at different stages of the RCT timeline (please see 'Impact Case Study 1' for theme 2). Note that this trial also incorporates the development of a Core Outcome Set (theme 4) and a trial adaptation to include three groups (theme 3).

PI: Mills N; Co-apps: Donovan JL, Young B, Bower P, Gamble C, Tudor Smith C, Holding P, Blazeby JM. Developing, delivering and evaluating training courses for recruiters to randomised trials. MRC HTMR £36,962. March 2014 – August 2016.

This grant demonstrates the first of three consecutive grants to synthesise cross-trial QRI data and develop evidence-based training material for recruiters to enhance recruitment practice. A before-after evaluation of the effectiveness of training revealed increases in self-confidence, raised awareness of the hidden challenges of recruitment and self-reported improvements in how they conveyed key elements of the RCT discussion (Mills 2018). Since then, further funding was acquired from the local NIHR CRN network to deliver more training, and further funding has been secured from the MRC HTMR Network to optimise dissemination and impact of the training. Since the development of the training intervention, we have also had a number of one-off requests for training, and set up collaborations with the NIHR and other universities to incorporate discrete elements within other training initiatives.

PI: McIntosh S; QRI lead: Paramasivan S; Co-apps: Coles C, Dodwell D, Gaunt C, Lyburn I, Pinder S, Pirrie S, Potter S, Rea D, Roberts T, Sharma N, Stobart H, Taylor-Phillips S, Wallis M, Wilcox M. SMALL: A Phase III, randomised, multi-centre trial addressing overtreatment of small, screen-detected breast cancer by comparing standard surgery with minimally invasive vacuum-assisted excision. NIHR HTA. £2,395,249.50. October 2018 – December 2022.

This recently awarded grant (October 2018) for the SMALL RCT integrates a QRI throughout the recruitment period of 4 years. The RCT has an 18-month internal pilot, with a recruitment target of 141 patients and at the end of the main phase, a target of 800 patients. The trial is anticipated to be challenging to recruit to as it compares in-patient standard open surgery with general anaesthesia against minimally invasive vacuum-assisted excision (VAE) with local anaesthesia to treat small, screen-detected breast cancers. VAE is widely used for other purposes, but has previously not been used for these type of cancers and is therefore being repurposed in this RCT. It is anticipated that recruiters and patients will have issues in relation to equipoise that need to be addressed with an intense QRI. Generic lessons learnt from QRIs in previous RCTs (from the cross-trial synthesis papers and training described above) will inform training, as will more tailored solutions based on this specific RCT.

Theme 3: Improving feasibility study designs and conduct to enhance trial quality and results

PI: Lane; Co-app(s): Coulman K, Blencowe N, Blazeby J, Daykin A, Cook J, Pinkney T, Bulbulia R, Marson T, Arenas-Pinto A. Developing a medical work force that designs, participates in, and implements findings of trials to improve evidence based practice: a case study in surgery'. MRC HTMR. £49,969. December 2016 – October 2018

This study is investigating surgical trainees' and surgeons' experiences of participating in clinical trials, including barriers and facilitators to successful trial conduct, using observations of key surgical trial meetings, and qualitative semi-structured interviews. Findings will be used to develop training methods to enhance clinician engagement in trials and inform the medical curriculum in training clinicians of the future in research methods. This work will also form the basis of a continued research programme addressing clinician engagement in trials. The

qualitative data collection and analysis have been completed and results will be presented at an expert meeting in October 2018 prior to publication.

Theme 4: Outcomes in RCTs – assessment, reporting and integration in decision-making

PI: Blazeby J. Co-app(s): Andronis L, Coast J, Donovan JL, Draycott T, Gooberman-Hill R, Magill L, Mathers J, Reeves B, Rogers C, Calvert M, Pinkney T, Longman R, Woodward M, Blencowe N, Hurley K, Torrance A, Young T. The Bluebelle Study: a feasibility study of complex, simple and absent wound dressings in elective and unplanned surgery. NIHR HTA. £444,264. June 2014 – June 2016

The overall aim of the Bluebelle study was to establish whether it is possible to carry out a major randomised trial to compare the effectiveness and cost-effectiveness of complex, or simple, and/or no dressing to reduce SSI following elective surgery. Within Bluebelle, we have developed and tested three outcome measures, including a patient- and observer-completed questionnaire to measure SSI in the main trial, a practical measure for wound management and a measure of patients' experiences of surgical wounds.

CI: Toogood G. Co-app(s): Beckingham I, Vohra R, Reeves B, Rogers C, Albazaz R, Jepson M, Avery K, Blazeby J, Guthrie J, Booth E, Hollingworth W, Hanna T, Blencowe N, Jennings N, Culliford L, Gaunt C, Hiles T, Johnstone D, Griffiths E, Revesai S, Mikulski A. A randomised controlled trial to establish the clinical and cost effectiveness of expectant management versus pre-operative imaging with MRCP in patients with symptomatic gallstones undergoing laparoscopic cholecystectomy at low or moderate risk of common bile duct stones: The Sunflower Study. NIHR HTA. £2,900,000. June 2018 – May 2024

Sunflower is a large multicentre RCT aiming to recruit 13,680 participants across the UK. One third of participants will be randomised to MRCP and two thirds straight to laparoscopic cholecystectomy. The trial has embedded methodological work including a QuinteT Recruitment Intervention (QRI) integrated into the study for the duration of the recruitment period (led by Jepson), and a detailed PPI plan (led by Avery) convening a PPI group to inform study design and conduct.

Key publications

Given below are selected examples of publications representative of each theme.

Theme 1: Prioritisation and trial design for cost-effectiveness analysis

Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, Davies P, Kleijnen J, Churchill R and the ROBIS group. ROBIS: a new tool to assess the risk of bias in systematic reviews was developed. J Clin Epidemiol. 2015; 69:225-345 (doi:10.1016/j.jclinepi.2015.06.005)

ROBIS is a new tool for assessing bias in systematic reviews. Because systematic reviews serve a vital role in clinical decision making and resource allocation, decision makers should expect consistent and unbiased standards across topics. Systematic flaws or limitations in the conduct of a review have the potential to bias results. Bias can arise at all stages of the review process; users need to consider these potential biases when interpreting the results and conclusions of a review. Several tools exist for critical appraisal and quality assessment of systematic reviews, but none were specifically aimed to assess the risk of bias in reviews. All previously available

tools have a broader objective of critical appraisal or focus specifically on meta-analyses. We developed the ROBIS tool to fill this gap.

ROBIS has been developed using rigorous methodology and is aimed at four broad categories of reviews: interventions, diagnosis, prognosis and aetiology. The tool is completed in 3 phases: (1) assess relevance (optional), (2) identify concerns and (3) judge risk of bias. Phase 2 covers four domains through which bias may be introduced into a systematic review: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Phase 3 assesses the overall risk of bias in the interpretation of review findings. We hope that ROBIS will help improve the process of risk of bias assessment in overviews and guidelines, leading to robust recommendations for improvements in patient care.

Thorn JC, Brookes ST, Ridyard C, Riley R, Hughes DA, Wordsworth S, Hollingworth W. Core Items for a Standardized Resource Use Measure (ISRUM): Expert Delphi Consensus Survey. Value Health. 2017; 21(6):640-9 (doi:10.1016/j.jval.2017.06.011)

The ISRUM project aimed to identify the core items that should be included in a standardised resource-use measure that could be used in a wide range of trials. The project entailed a Delphi consensus survey of professional health economists with experience of working on economic evaluations alongside RCTs in the UK. To derive an initial 'long list' of potentially suitable items, instruments that were held in DIRUM (the database of instruments for resource-use measurement, www.dirum.org) were reviewed, and relevant items were extracted. Example items included 'number of operations/procedures undergone' and 'type of professional seen at home'. Following deduplication and thematic merging of similar items, a list of 60 items was presented to a Delphi panel, who were asked to rate each item on a scale of 1-9 according to how strongly they felt the item should appear in a short, generic resource-use instrument for completion by patients. Predefined consensus criteria were applied after the first round: a shorter list of 34 items was then sent back to respondents along with group summary information (such as the median score). Respondents were asked to re-rate the items taking into account the group feedback. Predefined consensus criteria were again applied, and the results were discussed in some detail at a final item selection meeting.

A fully validated standardised resource-use questionnaire would improve the conduct of economic evaluations by increasing data quality, improving comparability between studies and reducing research burden. The main output from the project was a list of ten items that are currently being developed into a standardised resource-use instrument (relevant to an economic evaluation conducted from the perspective of the NHS) by a Hub-funded PhD student (Garfield).

Jones HJ, Welton NJ, Sutton AS, Ades AE. Use of a random effects meta-analysis in the design and analysis of a new clinical trial. Stat Med. 2018; (doi: <https://doi.org/10.1002/sim.7948>) [Epub ahead of print]

In designing a randomised controlled trial, it has been argued that trialists should consider existing evidence about the likely intervention effect. One approach is to form a prior distribution for the intervention effect based on a meta-analysis of previous studies and then power the trial on its ability to affect the posterior distribution in a Bayesian analysis. Alternatively, methods have been proposed to calculate the power of the trial to influence the "pooled" estimate in an updated meta-analysis. These two approaches can give very different results if the existing evidence is heterogeneous, summarised using a random effects meta-analysis. We argue that

the random effects mean will rarely represent the trialist's target parameter, and so, it will rarely be appropriate to power a trial based on its impact upon the random effects mean. Furthermore, the random effects mean will not generally provide an appropriate prior distribution. More appropriate alternatives include the predictive distribution and shrinkage estimate for the most similar study. Consideration of the impact of the trial on the entire random effects distribution might sometimes be appropriate. We describe how beliefs about likely sources of heterogeneity have implications for how the previous evidence should be used and can have a profound impact on the expected power of the new trial. We conclude that the likely causes of heterogeneity among existing studies need careful consideration. In the absence of explanations for heterogeneity, we suggest using the predictive distribution from the meta-analysis as the basis for a prior distribution for the intervention effect.

Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ. Sensitivity of treatment recommendations to bias in network meta-analysis. JRSSA. 2018; 181:843-67 (doi:10.1111/rssa.12341)

Network meta-analysis (NMA) pools evidence on multiple treatments to estimate relative treatment effects. Included studies are typically assessed for risk of bias; however, this provides no indication of the impact of potential bias on a decision based on the NMA. We propose methods to derive bias adjustment thresholds which measure the smallest changes to the data that result in a change of treatment decision. The methods use efficient matrix operations and can be applied to explore the consequences of bias in individual studies or aggregate treatment contrasts, in both fixed and random-effects NMA models. Complex models with multiple types of data input are handled by using an approximation to the hypothetical aggregate likelihood. The methods are illustrated with a simple NMA of thrombolytic treatments and a more complex example comparing social anxiety interventions. An accompanying R package is provided

Theme 2: Integrative and dynamic research methods to optimise recruitment to RCTs

Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, Mills N, Wilson C, Paramasivan S, Blazeby JM. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention. Trials. 2016; 17:283 (doi.10.1186/s13063-016-1391-4)

This paper outlines the QuinteT Recruitment Intervention (QRI), a complex intervention that emerged from the NIHR ProtecT trial to facilitate informed decision-making by patients about RCT participation and increased recruitment. The paper is of particular significance because it is the first time that the final version of the QRI has been laid out in detail in relation to its development, implementation and its applicability to the feasibility/pilot or main phase of an RCT. The QRI uses a combination of standard and innovative qualitative research methods with some simple quantification to understand recruitment and identify challenges, and offers flexible tailored approaches to feedback and support recruiters in optimising recruitment. The QRI can facilitate recruitment to the most controversial and important RCTs and is therefore likely to be of interest to various stakeholders – CIs developing proposals for RCTs with anticipated recruitment challenges, clinical trials units with RCTs with lower than expected recruitment, and funding bodies aiming to promote efficient recruitment in pragmatic RCTs.

Donovan JL, Paramasivan S, de Salis I, Toerien MG. *Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials*. *Trials*. 2014; 15:5 (doi:10.1186/1745-6215-15-5)

This seminal paper has formed a crucial part of the training and capacity building measures carried out by theme 2 members, since its publication in 2014. The paper outlines the synthesis of interview data collected from six RCTs and produces a nuanced and detailed account of the recruitment process from recruiters' perspectives. This highly-cited paper demonstrated that while recruiters (doctors and nurses) readily outlined the clear obstacles to recruitment (organisational difficulties, fewer than eligible patients, patients' treatment preferences), previously hidden challenges related to their roles as clinicians and researchers also emerged. These challenges were not known to RCT Chief Investigators. The paper identified the training and support needs that would help both doctors and nurses to recruit.

O'Cathain A. *A practical guide to using qualitative research within randomised controlled trials*. Oxford University Press: Oxford. 2018

In keeping with the broader remit of theme 2 on the integration of qualitative research into RCTs, theme member Professor Alicia O'Cathain has recently published a practical guide to using qualitative research at all stages of an RCT. The book offers an overview of qualitative research in the context of RCTs, practical guidance for using it within RCTs and advice on engaging relevant stakeholders. The book is targeted at researchers who are leading, undertaking or planning to use qualitative research with RCTs.

Theme 3: Improving feasibility study designs and conduct to enhance trial quality and results

Blencowe N, Mills N, Cook J, Donovan J, Rogers CA, Whiting P, Blazeby JM. *Methods for standardising and monitoring the delivery of surgical interventions in randomised clinical trials*. *Br J Surg*. 2016; 103(10):1377-84 (doi:10.1002/bjs.10254)

One of the major challenges in RCTs in surgery is achieving standardisation of surgical interventions across surgeons and centres. Unlike medical RCTs, where tablets can be manufactured to exacting standards, surgical operations given the same 'label' can be performed in lots of different ways. There may be variations in where incisions are placed, the types of instruments used and in the sequence of steps performed. Consequently, surgeons often dismiss trial results because the interventions were not delivered exactly 'their way'. This paper describes a novel typology to inform the design of all types of surgical intervention in trials, which was developed using iterative analyses of the literature. The typology allows interventions to be deconstructed into component parts, and standardisation of each component achieved using a 'traffic light system' - prohibited (red), optional (amber) and mandatory (green). The paper illustrates the typology with worked examples of interventions in surgical trials.

Daykin A, Selman LE, Cramer H, McCann S, Shorter GW, Sydes MR, Gamble C, Macefield R, Lane JA, Shaw A. *We all want to succeed, but we've also got to be realistic about what is happening: An ethnographic study of relationships in trial oversight and their impact*. *Trials*. 2017; 18:612 (doi:10.1186/s13063-017-2305-9)

The oversight and conduct of a randomised controlled trial involves several stakeholders, including a Trial Steering Committee (TSC), Trial Management Group (TMG), Data Monitoring Committee (DMC), funder and sponsor. This study aimed to examine how the relationships

between these stakeholders affect the trial oversight process and its rigour, to inform future revision of MRC Good Clinical Practice guidelines. Using an ethnographic study design, we observed the oversight processes of eight trials and conducted semi-structured interviews with members of the trials' TSCs and TMGs, plus other relevant informants, including sponsors and funders of trials. Thematic analysis indicated that recent developments in trial design and conduct have been accompanied by changes in roles and relationships between trial oversight groups. Recognising and respecting the value of differing priorities among those involved in running trials is key to successful relationships between committees, funders and sponsors. Clarity regarding appropriate lines of communication, roles and accountability is needed. We present 10 evidence-based recommendations to inform updates to international trial guidance, particularly the MRC guidelines.

Daykin A, Clement C, Gamble C, Kearney A, Blazeby J, Clarke M, Lane AJ, Shaw A. "Recruitment, recruitment, recruitment" - the need for more focus on retention: A qualitative study of five trials. Trials. 2018; 19:76 doi.org/10.1186/s13063-018-2467-0

Loss to follow-up (attrition) is a frequent problem in clinical trials and can introduce bias or reduce power. Thus, understanding retention issues and strategies to address these are important. As part of a multi-method project, this qualitative study aimed to explore retention strategies used by trial teams and factors which may influence strategy adoption. A purposive sample of active trials was selected from the UK NIHR HTA portfolio of ongoing trials in 2014/2015. Semi-structured interviews with several trial team members from each trial and supplementary interviews with experienced trial managers explored strategies in collecting clinical outcome data and retaining participants. Interview data were analysed thematically using techniques of constant comparison. The role of trial staff and their underlying behaviours influence retention practices and, combined with emphasis on recruitment targets, can be detrimental to motivation and retention activities. There is a need to consider how to train and support trial staff involved in retention practices and recognition of retention from funding bodies and oversight organisations.

Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson C, Williams H, Blazeby JM, members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open. 2017; 7:e13537 (doi:10.1136/bmjopen-2016-013537)

Designing studies with an internal pilot phase may optimise the use of pilot work to inform more efficient randomised controlled trials (RCTs). Careful selection of preagreed decision or 'progression' criteria at the juncture between the internal pilot and main trial phases provides a valuable opportunity to evaluate the likely success of the main trial and optimise its design or, if necessary, to make the decision not to proceed with the main trial. Guidance on the appropriate selection and application of progression criteria is, however, lacking. A structured literature review and exploration of stakeholders' (trialists, methodologists, statisticians, funders) opinions at a Medical Research Council (MRC) Hubs for Trials Methodology Research workshop were undertaken. Key issues to consider in the optimal development and review of operational progression criteria for RCTs with an internal pilot phase are outlined including 10 top tips for the development, use and reporting of progression criteria for internal pilot studies. Systematic and transparent reporting of the design, results and evaluation of internal pilot

trials in the literature should be encouraged in order to facilitate understanding in the research community and to inform future trials.

Theme 4: Outcomes in RCTs – assessment, reporting and integration in decision-making

Brookes ST, Macefield RC, Williamson PR, McNair A, Potter S, Blencowe N, Strong S, Blazeby J. Three nested randomised controlled trials of dual or single stakeholder feedback within Delphi surveys during core outcome and information set development. Trials. 2016; 17:409 (doi:10.1186/s13063-016-1479-x)

The widespread implementation of core outcome sets (agreed minimum sets of outcomes to be measured and reported in all clinical effectiveness trials of a particular condition or intervention) will facilitate evidence synthesis and better inform clinical practice. Whilst a variety of methods are used to develop such core sets, developers are increasingly using Delphi surveys, which require participants to anonymously rate the importance of outcomes in sequential questionnaires, with feedback provided in subsequent rounds such that participants can consider the views of others. This feedback is a key characteristic of the Delphi, however evidence-based guidelines for optimal provision of feedback are lacking. This methodological paper presents three RCTs nested within the development of three surgical core sets. It examines the impact of feedback from peer group only or multiple stakeholder groups on subsequent prioritisation of outcomes and levels of agreement between stakeholder groups. The work found that type of feedback impacted on the items retained for consideration in the final core set in all three trials. In addition, consensus between stakeholder groups was consistently greater amongst those receiving multiple feedback than those receiving peer group feedback only. The paper recommends that all Delphi survey participants should receive feedback from each key stakeholder group separately. This paper contributes significantly to the current literature regarding the optimal development of COSs and has informed international guidance provided by the COMET (Core Outcome Measurement for Effectiveness Trials) Initiative.

MRC HTMR Network grants

MRC HTMR network grants awarded to Hub members are listed below by theme (2014 – 2018).

Theme 1: Prioritisation and trial design for cost-effectiveness analysis

1. PI: Welton N; Co-app(s): Barton P, Jackson C, Price MJ. Meta-Modelling for Value of Information Calculations Workshop. £9,160. April 2014 – June 2016.
2. PI: Thom H; Co-app(s): Welton N, Jackson C. Efficient sample schemes for estimation of value of information of future research. £34,756. April 2015 – March 2017.
3. PI: Thorn J; Co-app(s): Members of the Northwest Hub, CTSU Hub. Health Economics Analysis Plans (HEAPs) workshop. £9,630. 2015
4. PI: Savović J; Co-app(s): Higgins J, Sterne J, Clarke M, Kirkham J, Hróbjartsson A, Boutron I, Whiting P, Altman D, Moher F, Reeves B, Turner L, Eldridge S, Li T, Tierney J, Vale C, Emberson J, White I. Refinement of and extension to the Cochrane Risk of Bias tool for Randomised trials. £50,000. May 2015 – April 2016

5. PI: Thorn; Co-app(s): Hughes D, Ridyard C, Hollingworth W, Noble S, Wordsworth S, Mihaylova B, Wilson E, Petrou S, Dritsaki M. IMPACT: Health Economics Analysis Plans: developing content guidance through consensus. £6,840. September 2018 – May 2019.
6. PI: Thorn; Co-app(s): Hollingworth W, Noble S, Hughes D, Wordsworth S, Ridyard C, Garfield K. IMPACT: Identification of items for inclusion in a standardised resource-use measure. £TBC. December 2018 – November 2019.
7. PI: Welton; Co-app(s): Barton P, Jackson C, Price MJ. Meta-Modelling for Value of Information Calculations Workshop. £9,160. April 2014 – September 2014.

Theme 2: Integrative and dynamic research methods to optimise recruitment to RCTs

1. PI: Mills N; Co-app(s): Donovan JL, Young B, Bower P, Gamble C, Tudor Smith C, Holding P, Blazeby J. Developing, delivering and evaluating training courses for recruiters to randomised trials. £36,962. March 2014 – August 2016.
2. PI: Gamble C; Co-app(s): Williamson P, Clarke M, Mills N, Blazeby J, Bower P, Young B, Tudor-Smith C, Donovan J, Harman N, Treweek S. Development of a central resource for research in recruitment in clinical trials (ORCCA database). £90,261. March 2014 – August 2016.
3. PI: O’Cathain; Co-app(s): Young B, Horwood J, Richards D, Hill J. Advancing the integration of mixed methods in clinical trials: a two day summit. £9,950. December 2016 - July 2017.
4. PI: Mills; Co-app(s): Rooshenas L, Young B, Blazeby JM, Bower P, Tudor Smith C, Gamble C, Donovan JL. Advancing training for health professionals and trialists to optimise RCT recruitment and informed consent. £10,000. September 2018 – June 2019.

Theme 3: Improving feasibility study designs and conduct to enhance trial quality and results

1. PI: Blazeby J; Co-app(s): Williamson P, Eldridge S, Gamble C, Blatch-Jones A, Avery K, O’Cathain A, Hoddinott P, Hopewell S, Thabane L, Lancaster G, Coleman C, Bond C, Duley L. Guidance to optimise pilot study design and conduct: A joint HTMR and NIHR HTA 'Research on Research' proposal. £30,596. September 2016 – August 2017.
2. PI: Armitage J; Co-app(s): Blazeby J, Williamson P, Marson T. How to be a good chief investigator – three workshops to build capacity for UK trialists £20
3. PI: Blazeby J; Co-apps Members of all the HTMR Hubs. Clinical trials methodology: key issues for successful design & conduct – a focused workshop for Academic Clinical Trainees. £8,641. May 2014 – November 2014.
4. PI: Lane A; Co-app(s): Coulman K, Blencowe N, Blazeby J, Daykin A, Cook J, Pinkney T, Bulbulia R, Marson T, Arenas-Pinto A. Developing a medical work force that designs, participates in, and implements findings of trials to improve evidence-based practice: a case study in surgery. £49,969. December 2016 – December 2017.
5. PI: Williamson P; Co-app(s): Lang R, Bowman L, Sydes M, Blazeby J, Clarke M, Wang D, Bhangu A. What might a global Health Trials Methodology Research Agenda look like? MRC HTMR. £14,436. September 2016 - August 2016.

Theme 4: Outcomes in RCTs – assessment, reporting and integration in decision-making

1. PI: Thorn J; Co-app(s): Hollingworth W, Noble S, Brookes S. Identification of items for inclusion in a standardised resource-use measure. £19,612. February 2015 – January 2016
2. PI: Kirkham JJ; Co-app(s): Williamson PR, Gamble C, Higgins J, Dwan K, Copas J. Development of an interactive website for outcome reporting bias research. £7,461. July 2015 – December 2015.
3. PI: Hinchliffe R; Co-app(s): Blazeby J, Williamson P, Cousins S, Avery K, Potter S, Sundstrom L. Improving the evaluation of medical devices with development of a generic core outcome set: a key stakeholder workshop for industry, innovators, clinicians, trialists, journal editors and health policy makers. £9,938.50. January 2018 – June 2018.

Appendix 1: Hub theme leads, members, researchers and affiliates (2018)

Theme 1: Prioritisation and trial design for cost effectiveness analysis				
ROLE	NAME	EMAIL	INSTITUTION / JOB TITLE	RESEARCH INTERESTS
Theme co-lead & deputy director of the C-II Hub	Prof. Will Hollingworth	William.Hollingworth@bristol.ac.uk	Uni of Bristol / Prof of health economics	Interests centre on the optimal design of RCTs to provide accurate & precise evidence on cost-effectiveness & inform policy. Specific interests include the design of RCTs when cost is the most important 'outcome' & the measurement of patient-reported resource use in trials.
Theme co-lead	Prof. Nicky Welton	Nicky.Welton@bristol.ac.uk	Uni of Bristol / Professor in statistical and health economic modelling	Use of existing evidence in the prioritisation & design of RCTs, in particular the role of evidence synthesis & Vol analyses. Design questions include: which treatments to include; sample size; length of follow-up; & choice of outcomes to measure.
Member	Prof. Julian Higgins	Julian.Higgins@bristol.ac.uk	Uni of Bristol / Prof of evidence synthesis	Appraisal & synthesis of research evidence, with a primary focus on clinical trials; methodology & applications in systematic reviews, meta-analysis, and critical evaluation of primary research & planning of future clinical trials.
Member	Prof. Chris Metcalfe	Chris.Metcalfe@bristol.ac.uk	Uni of Bristol / Professor in medical statistics	Medical statistics & study design.
Member	Dr. Sian Noble	S.M.Noble@bristol.ac.uk	Uni of Bristol / Senior lecturer in health economics	Methodological interests in improving the validity of resource use measures through better design of resource use data collection instruments & the use of resource use logs to reduce recall bias. Also the use & validity of routine data in economic evaluations of RCTs.
Member	Dr. Jelena Savovic	J.Savovic@bristol.ac.uk	Uni of Bristol / Research Fellow in Evidence Synthesis	Evidence synthesis & methodology.
Member	Prof. Jonathan Sterne	Jonathan.Sterne@bristol.ac.uk	Uni of Bristol / Prof of medical statistics & epidemiology & head of the school of social & community medicine	Empirical evidence on sources of bias in results of RCTs, assessing risk of bias in RCT results, causal inference approaches to analysis of RCTs, superiority, non-inferiority & equivalence designs.
Senior Research Associate	Miss Edna Keeney	edna.keeney@bristol.ac.uk	Uni of Bristol/Senior Research Associate in Health Economics/Evidence Synthesis	Cost-effectiveness modelling and evidence synthesis. Working alongside members of the Health Economics at Bristol (HEB) team and the Multi-parameter Evidence Synthesis (MPES) research group. Scientific Coordinator of the NICE Guidelines Technical Support Unit
Senior Research Associate	Miss Claire Williams	Claire.williams@bristol.ac.uk	Uni of Bristol / Senior research assoc in statistical and health economic modelling	
Research Associate	Dr. Jo Thorn	Joanna.Thorn@bristol.ac.uk	Uni of Bristol / Senior research assoc in health economics	All aspects of costing methodology in RCTs, but particularly understanding & improving the methods by which we ask patients about the resources that they themselves have used.
Affiliate	Prof. Jo Coast	J.Coast@bristol.ac.uk	Uni of Bristol / Prof in the economics of health & care	Methodological interests in economic evaluation alongside RCTs, including issues around appropriate outcome measurement for economic evaluation, collection of resource use data for economic evaluation & conducting economic evaluation alongside RCTs of complex interventions.
Affiliate	Dr. Pdraig Dixon	padraig.dixon@bristol.ac.uk	Uni of Bristol / Senior research assoc in health economics	I am interested in economic evaluations undertaken alongside RCTs.
Affiliate	Dr. Hayley Jones	Hayley.Jones@bristol.ac.uk	Uni of Bristol / Statistical research fellow	Multi-parameter evidence synthesis; how evidence synthesis can inform the design & analysis of RCTs.
Affiliate	Dr. Elsa Marques	E.Marques@bristol.ac.uk	Uni of Bristol / Research assoc in health economics	Economic evaluation alongside RCTs for health care interventions; economic modelling & evidence synthesis methods; designing economic evaluations alongside trials.

Affiliate	Mr Hugo Pedder	Hugo.pedder@bristol.ac.uk	Uni of Bristol / Senior research assoc in statistical modelling	
Affiliate	Dr. Matthew Page	Matthew.Page@bristol.ac.uk	Uni of Bristol / Research associate	Evidence synthesis, bias and methodologies.
Affiliate	Prof. Tracey Sach	T.Sach@uea.ac.uk	Uni of East Anglia / Professor in health economics	NIHR Career Development Fellowship: research into whether value of information analyses can be used to prioritise & design research to address the treatment uncertainties identified by the James Lind Alliance Priority setting partnerships (JLAPSP). The JLAPSP for eczema will be used as a case study.
Affiliate	Dr Debbi Caldwell	D.M.Caldwell@bristol.ac.uk	Uni of Bristol / Senior Lecturer in Public Health Research	Network meta-analysis of complex interventions; quantitative synthesis of public health RCTs and systematic review methodology
Affiliate	Dr. Howard Thom	howard.thom@bristol.ac.uk	Uni of Bristol / Research assoc in health economics modelling	Development of methodologies for mixed treatment comparisons, health economic modelling & Vol, with particular interest in the effect of structural assumptions on the conclusions of economic models & the development of rigorous approaches to quantifying these effects & choosing between structures.
Affiliate	Dr Caoimhe Rice	Caoimhe.rice@bristol.ac.uk	Uni of Bristol / Research assoc in health economics	
PhD student	Ms. Gemma Clayton	Gemma.Clayton@bristol.ac.uk	Uni of Bristol (commenced Oct 2015)	PhD title: Incorporating external evidence syntheses in the analysis of a clinical trial
PhD student	Ms. Ashma Krishan	Ashma.krishan@liverpool.ac.uk	Uni of Liverpool (commenced Oct 2015)	PhD title: The analysis & reporting of time to event data in RCTs: impact on evidence synthesis & cost-effectiveness
PhD student	Mr David Phillippo	david.phillippo@bristol.ac.uk	Uni of Bristol/ Research associate in evidence synthesis.	Interests include bias adjustment thresholds for treatment decisions in network meta-analysis, and methods for adjusted indirect comparisons.
PhD student	Miss Kirsty Garfield	Kirsty.Garfield@bristol.ac.uk	Uni of Bristol / Research associate in health economics	PhD title: Developing a modular resource-use questionnaire for use in RCTs

Theme 2: Integrative and dynamic research methods to optimise recruitment to RCTs				
ROLE	NAME	EMAIL	INSTITUTION / JOB TITLE	RESEARCH INTERESTS
Theme lead	Prof. Jenny Donovan	Jenny.Donovan@bristol.ac.uk	Uni of Bristol / Prof of social medicine	Integrating qualitative research in RCTs to improve design, recruitment & conduct. Developing & implementing feedback, training & support for those undertaking recruitment to RCTs to optimise recruitment & informed consent.
Member & director of the C-II Hub	Prof. Jane Blazeby	j.m.blazeby@bristol.ac.uk	Uni of Bristol / Prof of surgery	Expertise in methods to optimise i) outcome assessment, including PROs & blinding ii) design & conduct of pragmatic trials especially with invasive interventions including optimising methods to protocolise & monitor complex health care interventions & iii) team working & trial recruitment.
Member	Prof. Rona Campbell	Rona.Campbell@bristol.ac.uk	Uni of Bristol / Prof of public health research	Public health research.
Member	Prof. Patricia Hoddinott	p.m.hoddinott@stir.ac.uk	Uni of Stirling / Chair in primary care	Applying qualitative research methods to the design & delivery of RCTs, informed by ecological & systems approaches.
Member	Prof. Alicia O'Cathain	a.ocathain@sheffield.ac.uk	Uni of Sheffield / Prof of health services research	Using qualitative research with RCTs.
Member	Prof. Kate Tilling	Kate.Tilling@bristol.ac.uk	Uni of Bristol / Prof of medical statistics	Implications of missing data on bias in RCTs, & in particular, on using randomisation within RCTs to examine ways to minimise missing data, & on alternative ways to collect data (e.g. linkage, self-report). Other interests include analyses of longitudinal outcomes in RCTs.
Member/Research Fellow	Dr. Nicky Mills	Nicola.Mills@bristol.ac.uk	Uni of Bristol / Research fellow	Encouraging & supporting the integration of standard & innovative qualitative research methods to improve the design & conduct of RCTs with a particular focus on understanding & improving trial recruitment & informed consent, including the role & management of patient treatment preferences & training recruiters to recruit more effectively.

Member/ Research Fellow	Dr. Daisy Elliott	Daisy.Elliott@bristol.ac.uk	Uni of Bristol / Research fellow in qualitative health services research	My research interests are recruitment to clinical trials and methods for training recruiters.
Member/Research Fellow	Dr. Sangeetha Paramasivan	Sangeetha.Paramasivan@bristol.ac.uk	Uni of Bristol / Research Fellow	Applying a range of qualitative & quanti-qualitative research methods to identify & address recruitment issues in trials across different clinical contexts.
Affiliate	Dr. Leila Rooshenas	Leila.Rooshenas@bristol.ac.uk	Uni of Bristol / Lecturer in qualitative health science	Use of qualitative methods to optimise recruitment & information provision in RCTs, inform study design & investigate adherence practices.
Affiliate	Miss Samantha Husbands	Samantha.Husbands@bristol.ac.uk	Uni of Bristol/ Research assoc in qualitative research	Samantha (Sam) is member of the QuinteT group, working in the School of Population Health Sciences. Sam's research interests focus on the use of qualitative methods to optimise recruitment and informed consent to clinical trials. Sam is currently working on two trials, HAND-1 (Needle fasciotomy versus limited fasciotomy for the treatment of Dupuytren's contractures of the fingers) and VOCALIST (Laryngeal Reinnervation vs Type I Thyroplasty for Unilateral Vocal Fold Paralysis).
Affiliate	Dr Carmel Conefrey	carmel.conefrey@bristol.ac.uk	Uni of Bristol/ Research assoc for Quintet programme	Employing qualitative methods to optimise recruitment to RCTs
Affiliate	Dr. Suzanne Audrey	Suzanne.Audrey@bristol.ac.uk	Uni of Bristol / Senior research fellow	Development & implementation of process evaluation within RCTs; member of the MRC PHRN (Public Health Research Network) working group, currently developing guidance on process evaluation of complex public health interventions.
Affiliate	Dr. Kerry Avery	Kerry.Avery@bristol.ac.uk	Uni of Bristol / Senior Lecturer	Improving the design of pilot work & developing guidance to evaluate the use & success of pilot work to optimally inform main trials.
Affiliate	Dr. Rebecca Barnes	Rebecca.Barnes@bristol.ac.uk	Uni of Bristol / Senior research fellow in applied conversation analysis	Communication in health care; qual. research methods, specialising in conversation analysis.
Affiliate	Dr. Helen Cramer	Helen.Cramer@bristol.ac.uk	Uni of Bristol / Research fellow, researcher in residence	Anthropological methods (e.g. ethnography) & health related qualitative research.
Affiliate	Dr. Esther Crawley	Esther.Crawley@bristol.ac.uk	Uni of Bristol / Reader in child health	Interests in methods that improve recruitment to paediatric RCTs. My research uses qualitative methods to improve recruitment, investigate preference & reduce post randomisation drop out.
Affiliate	Dr. Ali Heawood	Ali.Heawood@bristol.ac.uk	Uni of Bristol / Senior res. fellow in primary care	Qualitative health services research methods.
Affiliate	Dr. Jeremy Horwood	J.Horwood@bristol.ac.uk	Uni of Bristol / Research fellow, senior research fellow in ethnography/qualitative social science	I have an interest in interlocking qualitative methods & clinical interventions. My research interests include patient & clinical staff experience of recruitment & trial involvement.
Affiliate	Dr. Talia Isaacs	t.isaacs@ucl.ac.uk	UCL / Senior lecturer in applied linguistics & TESOL	Second language assessment; the conversational discourse between doctors & patients & links to stakeholder perceptions and health outcomes.
Affiliate	Dr. Marcus Jepson	Marcus.Jepson@bristol.ac.uk	Uni of Bristol / Research Fellow / Lecturer in qualitative health science	I have a particular methodological interest in the application of conversation analysis to understand how trial information is presented to and discussed with patients.
Affiliate	Dr. Judi Kidger	Judi.Kidger@bristol.ac.uk	Uni of Bristol / Research fellow in public health	Qualitative research with expertise in mental health; interested in the application of qualitative methods to understand participants' experiences of 'real world' public health interventions & to examine questions of acceptability & feasibility.
Affiliate	Dr. Alba Realpe	A.X.Realpe@warwick.ac.uk	Uni of Warwick / Research fellow	Healthcare communication, interactional analysis, qualitative research, co-production, long-term health conditions & research methods in psychology.
Affiliate	Dr. Katrina Turner	Katrina.Turner@bristol.ac.uk	Uni of Bristol / Senior lecturer	I design & oversee qualitative studies nested within RCTs. Findings from these studies have been used to improve trial design & recruitment, assess fidelity to the intervention being assessed, & to illuminate possible reasons for the main trial results.

Affiliate	Dr. Julia Wade	Julia.Wade@bristol.ac.uk	Uni of Bristol / Research fellow/ Lecturer in qualitative health science	I investigate how to a) evaluate and b) improve the quality of patient understanding during informed consent discussions as they take place during trial recruitment consultations.
Affiliate	Dr. Caroline Wilson	Caroline.Wilson@bristol.ac.uk	Uni of Bristol / Senior research assoc	Qualitative methods; cancer trials; recruitment.
Affiliate	Dr Jemima Dooley	Jemima.dooley@bristol.ac.uk	Uni of Bristol / Research assoc	Qualitative methods
PhD student	Miss. Lucy Beasant	Lucy.Beasant@bristol.ac.uk	Uni of Bristol (commenced Oct 2014) Senior research associate CFS/ME	PhD title: Treatment preference in paediatric randomised controlled trials
PhD student	Miss Nicola Farrar	Nicola.farrar@bristol.ac.uk	Uni of Bristol /	

Theme 3: Improving feasibility study designs and trial conduct to enhance trial quality and results				
ROLE	NAME	EMAIL	INSTITUTION / JOB TITLE	RESEARCH INTERESTS
Theme co-lead & director of the C-II Hub	Prof. Jane Blazeby	j.m.blazeby@bristol.ac.uk	Uni of Bristol / Prof of surgery	Expertise in methods to optimise i) outcome assessment, including PROs & blinding ii) design & conduct of pragmatic trials especially with invasive interventions including optimising methods to protocolise & monitor complex health care interventions & iii) team working & trial recruitment.
Theme co-lead	Dr. Athene Lane	Athene.Lane@bristol.ac.uk	Uni of Bristol / Reader in trials research	Trial conduct; trial design; questionnaire design & utilisation.
Member	Dr. Jonathan Cook	jonathan.cook@ndorms.ox.ac.uk	Uni of Oxford / Assoc professor (Centre for statistics in medicine)	Main research interest is in the design, conduct, analysis & reporting of surgical trials. Other interests: specification of the target difference in sample size calculation & methods for improving recruitment.
Member	Prof. Jenny Donovan	Jenny.Donovan@bristol.ac.uk	Uni of Bristol / Prof of social medicine	Integrating qualitative research in RCTs to improve design, recruitment & conduct. Developing & implementing feedback, training & support for those undertaking recruitment to RCTs to optimise recruitment & informed consent.
Member	Prof. Chris Metcalfe	Chris.Metcalfe@bristol.ac.uk	Uni of Bristol / Prof in medical statistics	Medical statistics & study design.
Member	Prof. Alan Montgomery	Alan.Montgomery@nottingham.ac.uk	Uni of Nottingham / Prof of medical statistics & clinical trials	Outcome assessment; recruitment & retention of sites & participants; application of statistical methods for design & analysis of complex trials.
Member	Prof. Tim Peters	Tim.Peters@bristol.ac.uk	Uni of Bristol / Prof of primary care health services research and head of school (SOCS)	A statistician & trialist with methodological interests including cluster trials, subgroup analysis & interdisciplinary issues in pragmatic trials including those involving economic evaluations. Also engaged in methodological research on discrete choice experiments & the measurement of capability.
Member	Prof. Chris Rogers	Chris.Rogers@bristol.ac.uk	Uni of Bristol / Prof in medical statistics	Surgical trials design & statistics.
Member	Dr. Nicola Wiles	Nicola.Wiles@bristol.ac.uk	Uni of Bristol / Reader in epidemiology	Novel methods of data capture for outcome measurement e.g. web-based approaches; understanding the barriers to recruitment & follow-up in trials of complex interventions
Senior Research Fellow	Dr. Kerry Avery	Kerry.Avery@bristol.ac.uk	Uni of Bristol / Senior Lecturer	Improving the design of pilot work & developing guidance to evaluate the use & success of pilot work to optimally inform main trials.
Senior Research Associate	Dr. Karen Coulman	Karen.Coulman@bristol.ac.uk	Uni of Bristol / Senior research assoc in randomised trials methodology, Senior research assoc in outcome methods for randomised controlled trials	
Senior Research Associate	Ms Clare Clement	c.c.clement@bristol.ac.uk	Uni of Bristol/Senior research assoc (qualitative research in randomised trials	My research interests include the advancement of integrating qualitative and quantitative methods particularly within trials, health and illness experiences and perceptions of health services from the perspectives of patients and health care intervention development, evaluation and improvement.
Affiliate	Miss Natalie Blencowe	Natalie.Blencowe@bristol.ac.uk	Uni of Bristol / Academic clinical lecturer in general surgery	Description, standardisation & monitoring of surgical interventions within RCTs, process evaluations as part of feasibility studies, & surgical innovation.

Affiliate	Mr Ben Byrne	bb15832@bristol.ac.uk	Uni of Bristol / Research fellow	Interest lies in understanding the role of contextual factors, such as teamwork and communication, in determining the delivery and outcomes of surgical care / trials.
Affiliate	Dr. Jo Crocker	Joanna.Crocker@phc.ox.ac.uk	Uni of Oxford / Research fellow	Evaluating & assessing the impact of patient & public involvement (PPI) in research.
Affiliate	Dr. Lucy Culliford	Lucy.Culliford@bristol.ac.uk	Uni of Bristol / Research fellow	I am involved in the design and delivery of a wide range of randomised controlled trials in a number of disciplines and settings. This includes surgical trials as well as clinical trials of Investigation Medical Products, and covers cardiac surgery, ophthalmology and cancer.
Affiliate	Dr. Anne Daykin	Anne.Daykin@bristol.ac.uk	Uni of Bristol / Research assoc	Involved in exploring the role of Trial Oversight Committees and their impact on trial conduct, understanding the reasons for attrition in RCTs & developing evidence to prevent it. Methodological interests in RCTs include exploring the optimum usage of mixed methods to enhance the rigor of trials.
Affiliate	Miss. Daisy Gaunt	daisy.gaunt@bristol.ac.uk	Uni of Bristol / Research associate in medical statistics	An early career statistician within Bristol Randomised Trials Centre, working on two trials; tele-health interventions for long-term conditions (Healthlines) & paediatric chronic fatigue (SMILE). I am also working on estimating the optimal treatment effect in surgical RCTs, incorporating a learning curve.
Affiliate	Prof. Kerry Hood	HoodK1@cf.ac.uk	Uni of Cardiff / Prof of statistics	Methodological interests in the design of evaluation studies that allow for complex interventions, people or environments, outcome measurement and research inclusivity.
Affiliate	Miss. Shelley Potter	Shelley.Potter@bristol.ac.uk	Uni of Bristol / Consultant senior lecturer in oncological breast surgery / NIHR Clinician Scientist	Selection of outcomes for use in trials. Use of qualitative research to explore issues surrounding participation & recruitment into trials.
PhD student	Miss. Katherine Fairhurst	katherine.fairhurst@bristol.ac.uk	Uni of Bristol (commenced Oct 2015) MRC clinical research training fellow	PhD title: Optimising the design and evaluation of pilot work to inform efficient RCTs in surgery
PhD student	Miss. Sia Gravani	A.Gravani@bristol.ac.uk	Uni of Bristol (commenced Oct 2013)	PhD title: Investigating methods to improve the conduct of RCTs
PhD student	Mr Bilal Alkhaffaf	Bilal.alkhaffaf@cmt.nhs.uk	Central Manchester University Hospitals NHS Foundation Trust	PhD title: Development of a core outcome set for gastric cancer surgery effectiveness trials
NIHR Doctoral Fellowship	Miss Beth Conroy	E.J.Conroy@liverpool.ac.uk	University of Liverpool	PhD title: Learning and clustering: combining adjustments for the learning curve and clustering effects in randomised surgical trials

Theme 4: Outcomes in RCTs: assessment, reporting and integration in decision-making				
ROLE	NAME	EMAIL	INSTITUTION / JOB TITLE	RESEARCH INTERESTS
Theme co-lead & director of the C-II Hub	Prof. Jane Blazeby	j.m.blazeby@bristol.ac.uk	Uni of Bristol / Prof of surgery	Expertise in methods to optimise i) outcome assessment, including PROs & blinding ii) design & conduct of pragmatic trials especially with invasive interventions including optimising methods to protocolise & monitor complex health care interventions & iii) team working & trial recruitment.
Theme co-lead	Ms. Rhiannon Macefield	R.Macefield@bristol.ac.uk	Uni of Bristol / Senior research assoc	Incorporating clinically meaningful PROs into clinical trials, & methods to improve trial conduct.
Member	Prof. Richard Huxtable	R.Huxtable@bristol.ac.uk	Uni of Bristol / Professor in medical ethics and law	I work in medical law & ethics. My research interests are in end-of-life care, surgery, paediatrics & clinical ethics. I trained in socio-legal studies, & my methodological interests span law, bioethics & empirical bioethics.
Member	Prof. Chris Rogers	Chris.Rogers@bristol.ac.uk	Uni of Bristol / Prof in medical statistics	Surgical trials design & statistics.

Member	Prof. Chris Salisbury	C.Salisbury@bristol.ac.uk	Uni of Bristol / Prof in primary health care	My main interest is in pragmatic trials of organisational interventions in primary care. Specific methodological interests include (i) whether cost-effectiveness should more often be the primary outcome & methods to achieve that (ii) the relevance of the concept of a 'primary outcome' in pragmatic trials of organisational interventions (iii) what is the 'outcome' of good primary care & how can we measure it (iv) how best to conduct process evaluations.
Member	Dr. Jelena Savovic	J.Savovic@bristol.ac.uk	Uni of Bristol / Research fellow in evidence synthesis	Evidence synthesis & methodology.
Member	Prof. Kate Tilling	Kate.Tilling@bristol.ac.uk	Uni of Bristol / Prof of medical statistics	Implications of missing data on bias in RCTs, & in particular on using randomisation within RCTs to examine ways to minimise missing data, & on alternative ways to collect data (e.g. linkage, self-report). Other interests include analyses of longitudinal outcomes in RCTs.
Member	Prof Robert Hinchliffe	Robert.Hinchliffe@bristol.ac.uk	Uni of Bristol/Prof of vascular surgery	My general research lies in vascular disease and clinical trials. I have specific interests in disease of the aorta and diabetes related complications of the lower limb.
Research Fellow	Dr. Kerry Avery	Kerry.Avery@bristol.ac.uk	Uni of Bristol / Senior Lecturer	Methodological interests in RCTs: Improving the design of pilot work & developing guidance to evaluate the use & success of pilot work to optimally inform main trials.
Research Fellow	Dr Sian Cousins	Sian.cousins@bristol.ac.uk	Uni of Bristol / Research fellow in the MRC ConDuCT – II Hub for trials methodology research	Reducing bias in trials of invasive procedures through blinding of trial persons and placebo interventions.
Affiliate	Prof. Mel Calvert	m.calvert@bham.ac.uk	Uni of Birmingham / Prof of outcomes methodology	Developing best practice for PRO assessment and reporting in clinical trials.
Affiliate	Dr. Katy Chalmers	Katy.Chalmers@bristol.ac.uk	Uni of Bristol / Senior research associate in outcome methods for randomised controlled trials	
Affiliate	Dr Karen Coulman	Karen.Coulman@bristol.ac.uk	Uni of Bristol / Senior research assoc in randomised trials methodology and senior research assoc in outcome methods for randomised controlled trials	Core outcome sets & patient reported outcomes.
Affiliate	Mr. Angus McNair	Angus.Mcnair@bristol.ac.uk	Uni of Bristol / Clinical lecturer in academic surgery	My main methodological interest is in the selection, design & use of trial outcomes & particularly with patient reporting outcomes & involving patients in trial design.
Affiliate	Mr. Barry Main	B.G.Main@bristol.ac.uk	Uni of Bristol / Research fellow	PhD title: Developing a core information set for informed consent to surgery for oral & oropharyngeal cancer
Affiliate	Miss. Shelley Potter	Shelley.Potter@bristol.ac.uk	Uni of Bristol / Clinical lecturer	Selection of outcomes for use in trials. Use of qualitative research to explore issues surrounding participation & recruitment into trials.
Affiliate	Miss. Grace Young	grace.young@bristol.ac.uk	Uni of Bristol / Research assoc in medical statistics	Working within a trials unit, I am involved in a wide range of research areas including methods to reduce antibiotic consumption, neonatal interventions and treatment pathways for men with prostate cancer and bladder outlet obstruction. I have particular interests in over-diagnosis, over-treatment and the placebo effect.
Affiliate	Dr Debbi Caldwell	D.M.Caldwell@bristol.ac.uk	Uni of Bristol / Senior Lecturer in Public Health Research	Network meta-analysis of complex interventions; quantitative synthesis of public health RCTs and systematic review methodology
PhD student	Rachel Maishman	Rachel.Nash@bristol.ac.uk	Uni of Bristol (commenced Oct 2015)	PhD title: Improving measures of recovery after surgery for use in RCTs

Appendix 2: ConDuCT-II grants 2014-2018

i) Methodological

Grant dates	Funder	Title	Principal Investigator	Co-app(s)	Grant amount (£)
05/2016-02/2017	NIHR SPCR	A systematic review of the assessment of implementation fidelity in primary care trials	Barnes RK	Barnes RK, Huntley A, Heawood A, Mann C	£50,546.00
12/2016-07/2017	MRC HTMR	Advancing the integration of mixed methods in clinical trials: a two day summit	O'Cathain A	Young B, Horwood J, Richards D, Hill J	£9,950.00
04/2017-03/2022	NIHR	Bristol Biomedical Research Centre	Iredale J	Angelini G, Blazeby J, Davey Smith G, Gunnell D, Lawlor D, Ness A, Sterne JAC, Wynick D	£20,858,545.00
03/2016-08/2016	NICE Decision Support Unit	Calibration of absolute and relative treatment effects using individual patient data: Matching-adjusted Indirect Comparisons (MAIC) and Simulated Treatment Comparisons (STC) in Technology Appraisals.	Welton N	Welton N, Ades T, Phillippo D	£18,000.00
01/2017-12/2019	MRC-NIHR MRP	Calibration of multiple treatment comparisons using individual patient data. MRC Methodology Research Panel.	Welton N	Ades AE, Dias S, Phillippo DM	£308,461.00

10/2018-10/2021	Scar Free Foundation	Core Outcomes for Burn Care Research: short-term outcomes and outcome measures for use in burn care efficacy trials	Young A	Blazeby J, Rumsey N	£140,000.00
12/2016-12/2017	MRC HTMR	Developing a medical work force to design and conduct trials to improve evidence-based practice: a case study of surgical Trainee Research Collaboratives and a stakeholder workshop (ReSurgEnT)	Lane A	Coulman K, Blencowe N, Blazeby JM, Daykin A, Cook J, Pinkney T, Bulbulia R, Marson T, Arenas-Pinto A	£49,969.00
09/2015-12/2016	NIHR Oxford BRC, MRC HTMR	Developing a patient and public involvement intervention to enhance recruitment and retention in surgical trials (PIRRIST)	Crocker J, Bulbulia R	Farrar N, Chant A, Bostock J, Locock L, Petit-Zeman S, Treweek S, Rees S, Woolfall K.	
03/2014-08/2016	MRC HTMR	Development of a central resource for research in recruitment in clinical trials (ORCCA database)	Gamble C	Williamson P, Clarke M, Mills N, Blazeby J, Bower P, Young B, Tudor-Smith C, Donovan J, Harman N, Treweek S	£90,261.00
06/2013-06/2016	MRC	Development of a method for adjusting trial results for biases in meta-analysis: combining generic evidence on bias with detailed trial assessment (COMBAT study)	Turner R	Turner R, Savovic J, Jones H, Stern JAC, Welton N, Higgins J	£274,851.00
08/2016-12/2017	MacMillan	Development of a SPIRIT-PRO Extension: Delphi survey consensus meeting and publication	Calvert M	Altman D, Blazeby J, Brown J, Brundage M, Coast J, Draper H, von Hildebrand M, Ives J, King M, Kyte D, Mercieca-Bebber R, Price G, Roberts L, Slade A.	£55,000.00

04/2016-03/2017	MRC HTMR	Efficient sample schemes for estimation of value of information of future research. MRC Network of Hubs for Trials Methodology Research.	Thom H	Thom H, Welton NJ, Jackson C.	£34,756.00
05/2017-05/2018	HRB-TMRN	Examining the influence of an informational video on participant retention in a randomised controlled trial.	Slattery B	McGuire B, McSharry J, Clement C, Molloy K, Haugh S, O'Connor L.	£9,051.96
03/2018-03/2020	Academy of Medical Sciences	Exploring strategies for implementing core information sets for informed consent to surgery for head and neck cancer: operationalising Montgomery	Main B		£30,000.00
01/2018-12/2018	MRC	Extending ORRCA to create a central resource for retention research within clinical trials (ORRCA 2)	Gamble C	Williamson P, Devane D, Kearney A, Harman N, Lane A, Cragg W, Snowdon C, Rogers C, Gillies K, Ananiadou S.	£40,830.00
03/2012-12/2014	Cochrane Collaboration	Extending the Cochrane Risk of Bias tool to assess risk of bias in randomised trials with non-parallel-group designs, and non-randomised studies	Sterne JAC	Savovic J, Reeves BC, Moher D, Turner L, Loke YK, Water E, Ramsay C, Tugwell P, Wells GA, Welch V	£69,967.00
04/2017-03/2019	MRC HTMR	Guidance to optimise pilot study design and conduct: A joint HTMR and NIHR HTA 'Research on Research' proposal.	Blazeby JM	Williamson P, Eldridge S, Gamble C, Blatch-Jones A, Avery K, O'Cathain A, Hoddinott P	£24,510.00

04/2017-03/2018	MRC HTMR	Health Economics Analysis Plans: developing content guidance through consensus	Thorn J	Thorn J, Hughes D, Ridyard C, Hollingworth W, Noble S, Wordsworth S, Mihaylova B, Brookes S, Wilson E.	£39,697.00
12/2015-02/2018	MRC-NIHR MRP	HOD: Assessing risk of bias in non-randomised studies of interventions	Higgins J		£365,652.00
04/2016-03/2018	MRC-NIHR MRP	Identifying and critiquing different approaches to developing complex interventions (INDEX study).	O’Cathain A	O’Cathain A, Turner K, Duncan E, Hoddinott P, Yardley L, Croot E	£380,463.00
04/2015-09/2015	NIHR SPCR	Identifying the Quality Indicators of a Patient-Centred Trial: obtaining expert consensus using the Delphi method	Bower P	Young B, Turner K, Planner C, Donnelly, Stephenson C, Gillies K, Knapp P	£11,208.00
09/2018-05/2019	MRC HTMR	IMPACT: Health Economics Analysis Plans: developing content guidance through consensus	Thorn J	Thorn J, Hughes D, Ridyard C, Hollingworth W, Noble S, Wordsworth S, Mihaylova B, Wilson E, Petrou S, Dritsaki M	£6,840.00
12/2018-11/2019	MRC HTMR	IMPACT: Identification of items for inclusion in a standardised resource-use measure	Thorn J	Hollingworth W, Noble S, Hughes D, Wordsworth S, Ridyard C, Garfield K	£4,286.50

01/2019	MRC-NIHR MRP	Inferring relative treatment effects from combined randomised and observational data.	Dias S	Dias S, Welton NJ, Ades AE, Phillippo D, Abrams KA, Sutton A, Bujkiewicz S, Gray L, Sheehan N	£725,176.00
2014-2016	MRC-NIHR MRP	Losing the losses: understanding the reasons for attrition in RCTs and developing the evidence to prevent it	Gamble C	Lane JA, Blazeby J, Heawood A, Kearney A	£216,000.00
01/2015-12/2017	Joint funded MRC and Pfizer	Model Based Network Meta-Analysis for Pharmacometrics and Drug-Development	Welton N	Ades T, Dias S	£327,555.00
04/2016-03/2021	NICE	NICE Clinical Guidelines Technical Support Unit.	Dias S	Dias S, Welton NJ, Keeney E, Ades AE.	£350,000.00
09/2017-02/2019	NIHR RfPB	Patient-centred trials: developing measures to improve the experience of people taking part in clinical trials	Bower P	Bower P, Sanders C, Young B, Turner K, Gillies K, Donnelly A	£149,827.00
01/2018-12/2020	European Union	ProgrammeE in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluations (PECUNIA)	Simon J	Thorn J, Hollingworth W, Noble S	£2,658,774.76
05/2015-10/2016	MRC HTMR	Refinement of and extension to the Cochrane Risk of Bias tool for Randomised trials.	Savović J	Higgins JPT, Clarke M, Kirkham J, Hróbjartsson A, Boutron I, Whiting P, Sterne JAC.	£50,000.00

04/2018-09/2020	MRC-NIHR MRP	Routinely embedding recruitment and retention interventions within randomised controlled trials.	Torgerson D	Parker A, Bower P, Cooper C, Beard D, Eldridge S, Emsley R, Montgomery A, Treweek S, Culliford L, Brocklehurst B, Hewitt C	£501,765.00
09/2016-08/2020	Wellcome Trust Intermediate Clinical Fellowship.	Treatment effectiveness in multimorbidity: Combining efficacy estimates from clinical trials with the natural history obtained from large routine healthcare databases to determine net overall treatment benefits.	McAllister D	McAllister D, Dias S, Welton NJ.	£709,000.00
01/2015-04/2015	CADTH	Use of Network Meta-analysis to Inform Clinical Parameters in Economic Evaluations.	Cooper NJ	Cooper NJ, Sutton AS, Welton NJ	£14,633.00
10/2017-09/2018	NIHR CTU Support Funding	User-focused research to identify the benefits of innovative digital recruitment and retention tools for more efficient conduct of randomised trials	Griffiths G	Cook A, Nuttall J, Lane A, Clement C, Wyatt J, Peveler R, Falk S, Mullee M.	£74,689.00
09/2016-08/2016	MRC HTMR	What might a Global Health Trials Methodology Research Agenda look like?	Williamson P	Lang R, Bowman L, Sydes M, Blazeby JM, Clarke M, Wang D, Bhangu A	£14,436.00
05/2015-01/2016	MRC HTMR	Workshop: Mapping current usage of Health Economic Analysis Plans (HEAPs)	Thorn J	Thorn J, Hughes D, Ridyard C, Hollingworth W, Noble S, Wordsworth S, Mihaylova B	£9,630.00

ii) RCTs with applied Hub methods and/or integrated methodological projects

Grant dates	Funder	Title	Principal Investigator	Co-app(s)	Grant amount (£)
2017-2020	NIHR HTA	A clinical effectiveness investigation of a multi-faceted intervention (incorporating a prognostic algorithm) to improve management of antibiotics for CHildren presenting to primary care with acute COugh and respiratory tract infection (CHICO): an efficient cluster RCT informed by a feasibility RCT.	Blair P	Hay A, Francis N, Ingram J, Beech E, Horwood J, Dixon P, Cabral C, Creavin S, Lucas P, Lane JA.	£826,831.23
04/2014-07/2016	NIHR HTA	A feasibility study and pilot RCT to establish methods for assessing the acceptability, and clinical and cost-effectiveness of enhanced psychological care (EPC) in cardiac rehabilitation services for patients with new onset depression compared with treatment as usual: CADENCE	Campbell J	Richards S, Dickens C, Richards D, Taylor R, Gandhi M, Turner KM, Ukoumunne O, Anderson R, Kessler D, Kuyken W, Chawner R, Gibson A	£448,291.00
10/2017-12/2021	NIHR HTA	A phase 3 trial of Rivastigmine to prevent falls in Parkinson's Disease	Henderson E	Ben-Shlomo Y, Hollingworth W, Metcalfe C, Steeds D, Whone A, Sterne J	£2,545,636.00
2018 - 2022	NIHR HTA	A pragmatic multicentre randomised controlled trial to assess the clinical and cost effectiveness of negative pressure wound therapy versus usual care for surgical wounds healing by secondary intention (SWHSI 2)	Chetter I	K Lamb, J Dumville, R Macefield, D Torgensen, Hewitt, Henderson, T Pinkney, Blazeby JM	£1,653,552.18

04/2016-04/2021	NIHR HTA	A randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of laparoscopic cholecystectomy compared with observation/conservative management for preventing recurrent symptoms and complications in adults with uncomplicated symptomatic gallstones (C-Gall)	Ahmed I	Avenell A, Blazeby J, Croal B, Hernández R, Murchie P, Norrie J, Ramsay C, Gillies K, Brazzelli M	£1,397,962.00
01/2015-01/2017	NIHR HTA	A randomised controlled trial of Partial prostate Ablation versus Radical prostatectomy (PART) in intermediate risk unilateral clinically localised prostate cancer a feasibility study	Hamdy F	Ahmed H, Donovan JL, Gillatt D, Gray R, Leslie T, Wolstenholme J, Rosario D, Brewster S, Emberton M	£655,011.00
10/2016-09/2018	NIHR SPCR	A randomised controlled trial on the effectiveness of GP promotion of e-cigarettes in supporting reduced smoking and abstinence in hardcore smokers with smoking-related chronic disease (ERASE).	Begh R	Aveyard P, Coleman T, Naughton F, Gilbert H, Barnes R	£308,980.00
06/2018-05/2024	NIHR HTA	A randomised controlled trial to establish the clinical and cost effectiveness of expectant management versus pre-operative imaging with MRCP in patients with symptomatic gallstones undergoing laparoscopic cholecystectomy at low or moderate risk of common bile duct stones: The Sunflower Study.	Toogood G	Beckingham I, Vohra R, Reeves B, Rogers C, Albasaz R, Jepson M, Avery K (PPI lead), Blazeby J, Guthrie J, Booth E, Hollingworth W, Hanna T, Blencowe N, Jennings N, Culliford L, Gaunt C, Hiles T, Johnstone D, Griffiths E, Revesai S, Mikulski A.	£2.9m

01/2019-12/2020	NIHR HTA	A Randomised Controlled Trial to investigate the clinical and cost-effectiveness of Paravertebral Blockade compared with Thoracic Epidural Blockade in reducing Chronic Post-Thoracotomy Pain (TOPIC2)	Gao F	Gao Smith F, Naidu B, Goebel A, Wilson M, Jarrett H, Melody T, Yeung J, Kerr A, Small C, Middleton L, Jepson M, Shelley B, Marczin N, Jackson L,	
07/2016-09/2016	CRUK	A Randomised Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC)	Paramasivan S	Donovan J	£15,693.00
01/2016-08/2018	NIHR PHR	A woman-centred, tailored SMS-delivered multi-component intervention for weight loss and maintenance of weight loss in the postpartum period: intervention adaptation and pilot RCT	McKinley M	Hoddinott P, Kee F, Free C, Anderson A, McIntosh E, Dombrowski S, Young I, Holmes V, Cardwell C, Woodside J	£483,040.00
04/2017-09/2017	NIHR PHR	ACTION 330: A cluster randomised feasibility trial evaluation of a teaching assistant led, extracurricular physical activity intervention for 8 to 10 year olds.	Jago R	Gillet D, Powell J, Metcalfe C, Sebire S	£507,782.00
2016-2019	NIHR HTA	Antidepressants to prevent relapse in depression.	Lewis G	Lewis G, Freemantle N, Gilbody S, Hunter R, Kendrick A, Kessler D, King M, Moore M, Nazareth I, Wiles N	£1,668,027.00
11/2014-2017	NIHR HTA	Aspirin for Venous Ulcers: Randomised Trial (AVURT)	Hinchliffe R	Torgerson D, McDaid C, Gabe R, Bland M, Dumville J, Chetter I, Harding K, Moffatt C, Standsby G, Lindsay E, Rolfe D, Philips C, Tilbrook H, Clark L	£500,000.00

05/2014-04/2021	NIHR HTA	BASIL-2: Bypass vs. Angioplasty in Severe Ischaemia of the Leg-2	Bradbury A	Shearman, Odurny, Hinchliffe, Belli, Davies, Burfitt, Perkins, Uberoi, Claridge, Ganeshan, Naylor, Adair, Chetter, Ettles, Scott, Patel, Beard, Cleveland, Stansby, Jackson, Brittenden, Yadavaldi, Stuart, Moss, Robertson	£2,004,572.00
10/2015-2021	NIHR HTA	Basil-3: BALloon vs Stenting in Severe Ischaemia of the Leg-3	Bradbury A	Shearman, Odurny, Hinchliffe, Belli, Davies, Burfitt, Perkins, Uberoi, Claridge, Ganeshan, Naylor, Adair, Chetter, Ettles, Scott, Patel, Beard, Cleveland, Stansby, Jackson, Brittenden, Yadavaldi, Stuart, Moss, Robertson	£1,938,633.00
2017-2020	NIHR HTA	BEE: best emollient for childhood eczema.	Ridd M	Santer M, Thomas K, MacNeill S, Heawood A, Banks J, Roberts A, Garfield K, Baxter H, Barrett T, Lane JA, Williams H, Hay A.	£1400000 / £1,384,969?

09/2017-08/2020	CRUK, CSO, HSCNI, NICHS, The Lullaby Trust, Scottish Cot Death Trust	Cessation in Pregnancy Incentives Trial: A multi-centre phase III randomised controlled trial.	Tappin D	Bauld L, Coleman T, Cooper S, Ussher M, Kee F, Torgerson D, Adamson J, Hoddinott P, Sinclair L	£1,413,973.00
01/2015-12/2018	NIHR HTA	Children's drops for ear pain in acute otitis media: the CEDAR randomised controlled trial	Hay A	HayA, Nunez D, Fletcher M, Hollingworth W, Horwood J, Novak C, Stoddart P, Lyttle M, Williamson I, Little P, Harman K, Francis N, Whitman B, Dunn N, Jones J, Blair P, Hartland J, Mikulski A	£1,377,900.00
10/2013-06/2015	NIHR RfPB	Choice of moisturiser for eczema (COMET).	Ridd M	Ridd M, Montgomery A, Shaw L, Ball N, Hollinghurst S, Redmond N, Guy R, Purdy S.	£435,403.00
2018-2021	MRC/Wellcome Trust Joint Global Health Trials Initiative and FAPESP.	Cluster randomised controlled trial (RCT) for late life depression in socioeconomically deprived areas of Sao Paulo, Brazil (PROACTIVE).	Araya R	Scazufca M, Peters TJ, Hollingworth W.	Total £1,104,894 (comprising £513,569 from MRC/Wellcome Trust and £591,325 from FAPESP).

07/2016-05/2019	NIHR HTA	CONservative TRreatment of Appendicitis in Children a randomised controlled Trial CONTRACT (Feasibility study)	Hall N	Blazeby JM, Crawley E, Beasant L, Eaton S, Young B, Corbett H, Wood W, Stanton M, Reading I, Giuliana S, Chorozoglou M, Grist S, Walker E	£482,881.60
07/2015 – 08/2016	NIHR RfPB	Does Laryngeal Reinnervation or Type I Thyroplasty give better voice results for patients with Unilateral Vocal Fold Paralysis (VOCALIST): a feasibility study	Birchall M	Jepson M, Donovan JL	£309,667.00
04/2019-09/2020	NIHR HTA	Effectiveness and cost-effectiveness of INSPIRatory muscle training (IMT) for reducing postoperative pulmonary complications (PPC): a sham-controlled randomised controlled trial (RCT) (INSPIRE)	Pufulete M	Pufulete M, Rogers C, Reeves B, Mills G, Jack S, Harris J, Benedetto U, Wordsworth S, Jepson M & Richardson K.	
06/2017-06/2021	NIHR HTA	Effectiveness, cost effectiveness and safety of gabapentin versus placebo as an adjunct to multimodal pain regimens in surgical patients: A placebo controlled randomised controlled trial with blinding (The GAP study)	Gibbison B (non-clinical lead - Rogers C)	Angelini G, Culliford L, Grocott M, Pufulete M, Reeves B, Wordsworth S, Wynick D, Al-Ghnaniem Abbadi R, Edwards M, Gibbison B, Casali G, Chauhan N, Joyce B, Molyneux M, Alzetani A	£1,139,565.13
10/2016-01/2017	NIHR HTA	Embedded QRI - Multi-centre randomised controlled trial to compare the clinical and cost-effectiveness of a 'vein bypass first' with a 'best endovascular treatment first' revascularisation strategy for severe limb	Jepson M	Donovan J	£11,573.00

		ischaemia due to infra-popliteal arterial disease (BASIL-2)			
2018-2023	NIHR PGfAR	Evaluating the Population Impact of Hepatitis C Direct Acting Antiviral Treatment as Prevention for People Who Inject Drugs - EPIToPe.	Hickman M, Hutchinson S (co-PIs)	Dillon J, De Angelis D, Elliott L, Foster G, Goldberg D, Martin N, Eriksen A, Donnan P, Mandal S, Vickerman P, Hollingworth W, Liddell D, Flowers P, Ijaz S, Harris M, Lane JA	£2,775,497.00.
04/2018-03/2020	NIHR RfPB	Fatigue - Reducing its Effects through individualised support Episodes in Inflammatory Arthritis (FREE-IA): A Feasibility Study for a Randomised Controlled Trial	Dures E		£248,039.00
04/2014-02/2020	NIHR HTA	Full Randomised Controlled Trial of Arthroscopic Surgery for Hip Impingement versus best Conventional care UK FASHIoN 2	Griffin D	Donovan JL, Realpe A, Jepson M, Petrou S, Parsons NR, Achten J, Wall PD, Costa M, Gates S.	£1,727,557.00
07/2015-07/2018	NIHR HTA	Gastric Bypass, adjustable gastric Banding or Sleeve gastrectomy surgery to treat severe and complex obesity: a multi-centre randomised controlled trial	Blazeby JM	Donovan JL, Welbourn R, Andrews R, Wordsworth S, Thompson J, Perkins M	£3,939,934.00
12/2015-12/2018	NIHR HTA	Guided self-help for depression in adults with autism spectrum disorder (ADEPT)	Russell A, Rai D	Russell AJ, Wiles N, Kessler D, Rai D, Ensum I, Barton S, Ingham B, Parr J, Horwood J	£418,442.00

2017-2022	NIHR HTA	H4RT: The High-volume Haemodiafiltration vs High-flux Haemodialysis Registry Trial.	Caskey F	MacNeill S, May M, Lane JA, Hollingworth W, Ben-Shlomo Y, Donovan J, Rooshenas L, Abbott D, Farrington K, Davenport A, Wheeler D, Power A, Mitra S.	£1,738,554.00
03/2014-09/2017	NIHR HS&DR	Improving the management of patients with multimorbidity in general practice (3D).	Salisbury C	Guthrie B, Bower P, Mercer S, Brookes S, Hollinghurst S, Heawood A, Gjini A, Rafi I.	£1,789,589
2014-2018	NIHR PGfAR	Infection: Orthopaedic management (INFORM)	Blom A	Whitehouse M, McGowan A, Goberman-Hill R, Noble S, Lenguerrand E, Burston.	£2,012,256.00
05/2016-10/2021	NIHR HTA	Investigating the effectiveness and cost effectiveness of using FITNET to treat paediatric CFS/ME in the UK	Crawley E	Crawley E, Bleijenberg G, Hollingworth W, Kessler D, Knoop H, Macleod J, Metcalf C, Mills N, Nijhof S, Price S, Stallard P, Van de Putte E, Willows MJ	£999,977.80

03/2013-08/2014	NIHR HTA	Long term follow up of patients in the COBALT (CBT for treatment resistant depression) trial	Wiles N	Wiles N, Lewis G, Peters T, Thomas L, Hollinghurst S, Campbell J.	£162,230.00
04/2018-12/2019	NIHR RfPB	Low intensity interventions for antenatal depression: A feasibility study of an RCT of Interpersonal Counselling compared to Cognitive Behavioural Therapy.	J Evans	Evans J, Ingram J, Taylor H, Egan K, Cramer H, O'Mahen H, Law T, Round Kessler J, Culpin D, Ford J.	£241,934.00
10/2015-01/16 & 09/2016-11/2016	NIHR HTA	Male synthetic sling versus Artificial urinary Sphincter Trial: Evaluation by Randomised controlled trial (MASTER)	Jepson M	Donovan J	£9,347.00
01/2017	NIHR HTA	Mesothelioma and Radical Surgery 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma (MARS 2)	Lim E	Elliott D, Edwards JG, Darlson L, Popat S, Waller D, Fox-Rushby J, Fennell DA, Rogers C	£1,725,924.
09/2014-11/2017	NIHR PHR	NAP SACC UK: A feasibility cluster randomised controlled trial in child care settings to increase physical activity and healthy eating in 2-4 year olds	Kipping R	Hollingworth W, Jago R, Metcalfe C, Moore L, White J, Ward D, Papadaki A, Campbell R	£431,495.00
2017-2020	NIHR HTA	Nasal Airway Obstruction Study (Nairos)	Carrie S	Drinnan M, O'Hara J, Morrison J, Rousseau N, Rooshenas L, Stocken D, Wilson J, Hall L, Ternent L.	£1,158,487.32

08/2015-04/2017	NIHR RfPB	Needle fasciotomy versus limited fasciectomy for the treatment of Dupuytren's contractures of the fingers: a study which investigates the feasibility, acceptability and design of a multicentre randomised trial (HAND-1).	Davis T	Hollingworth W, Blazeby J, Mills N, Duley L, Montgomery A	£259,754.00
10/2015-04/2024	NIHR HTA	Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis	Stein R	Dunn J, Bartlett J, Cameron D, Donovan JL, Earl H, Francis A, Hall P, Hughes-Davies L, Hulme C, Marshall A, McCabe C, Morgan A, Pinder S, Poole C, Rea D, Stallard N, Makris A, Rooshenas L, MacPherson I, Harmer V	£3,373,808.00
04/2017-07/2020	NIHR PHR	Optimisation, feasibility testing and pilot randomised trial of Positive Choices: a school based social marketing intervention to promote sexual health, prevent unintended teenage pregnancies and address health inequalities in England	Bonell C	Mercer C, Allen E, Young H, Coyle K, Carrera M, Hadley A, Wells C, Hillier J, Fletcher A, Elbourne D, Hastings G, Lohan M, Campbell R, Morris S	£595,368.33
04/2012-06/2015	NIHR School for Primary Care Research	OSAC (Oral Steroids for Acute Cough) Trial.	Hay A	Hay A, Little P, Moore M, Kendrick D, Orton E, Thompson M, Harnden A, Wang K, Hollinghurst S, Horwood J, Downing H, Sterne J	£1,506,076.00

2013-2018	NIHR HTA	Palliative radiotherapy in addition to self-expanding metal stent for improving outcomes of dysphagia and survival in advanced oesophageal cancer: ROCS (Radiotherapy after Oesophageal Cancer Stenting) Study	Adamson D	Blazeby JM, Byrne A, Crosby T, Staffurth J, Griffiths G, Cohen D, Nelson A, Fitzgibbon J.	£1,576,136.00
11/2014-11/2022	CRUK	Phase III randomised controlled trial Comparing Alternative Regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer (Compare).	Mehann H	Jepson M, Donovan JL, Foran B, Gaunt P, Paleri V, Miles E, Bowden S, McCaul J, Robinson C, Hartley A, Sanghera P, Forster M, Harrington K, Dunn J, Billingham L, Chester J, Nutting C, Sen M	£1,706,972.00
03/2017-12/2018	NIHR PHR	Pilot randomised trial of Project Respect: a school-based intervention to prevent dating and relationship violence and address health inequalities among young people	Bonell C	Campbell, R, Barter C, Fletcher A, Young H, Allen E, Elbourne D, Hillier J, Jamal F, Morris, S, Gough D	£483,064.56
2017-2020	NIHR HTA	Pragmatic, primary care, multi -centre, individually randomised superiority trial of four emollients in children with eczema, with internal pilot, nested economic evaluation and qualitative study	Ridd M.	Ridd M, Thomas K, Santer M, Williams H, Hay A, Heawood A, Banks J, MacNeill S, Hollinghurst S, Lane A, Roberts A, Garfield K, Barrett T, Baxter H	£1,394,969
01/2017-12/2021	NIHR HTA	Prepare for Kidney Care: a randomised controlled trial of preparing for responsive management versus preparing for renal dialysis in advanced kidney disease	Caskey F	Lane JA, Donovan J, Abbott B, Rooshenas L, Murtagh F, Salisbury C, Murphy E, Chilcot J, Roderick	£2,538,968.92

				P, Ben-Shlomo Y, Farrington K, Rayner H, Burns A, Davies S, Coast J, Huxtable R, MacNeill S, Gibson A.	
05/2017-10/2017	NIHR HTA	Qualitative Ancillary Study: Understanding and optimising recruitment to the TARVA trial TARVA: Total Ankle Replacement Versus Arthrodesis	Griffin D	Realpe A	£14,515.27
12/2015-12/2021	NIHR HTA	Randomised Oesophagectomy: Minimally Invasive or Open: Definitive trial (ROMIO)	Barham P	Berrisford R, Blazeby J, Donovan JL, Hollinghurst S, Metcalfe C, Rogers C, Avery K, Wong N, Howes B, Elliot J.	£2,119,632.00
2018-2029	NIHR HTA	SMALL: A Phase III, randomised, multi-centre trial addressing overtreatment of small, screen-detected breast cancer by comparing standard surgery with minimally invasive vacuum-assisted excision	McIntosh SA	Coles C, Dodwell D, Gaunt C, Lyburn I, Paramasivan S , Pinder S, Pirrie S, Potter S, Rea D, Roberts T, Sharma N, Stobart H, Taylor-Phillips S, Wallis M, Wilcox M	£2,395,249.50
01/2017-11/2018	PCF Young Investigator Award	Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone: a randomised controlled feasibility trial	Sooriakumaran P	Hamdy F, Eden C, Kelly, J, Wilson C	£183,000.00

06/2014-06/2016	NIHR HTA	The Bluebelle study: a feasibility study of three wound dressing strategies in elective and unplanned surgery	Blazeby JM	Andronis L, Coast J, Donovan JL, Draycott T, Gooberman-Hill R, Magill L, Mathers J, Reeves B, Rogers C, Calvert M, Pinkney T, Longman R, Woodward M, Blencowe N, Hurley K, Torrance A, Young T	£444,264.00
2018-2020	NIHR School for primary care research	The TEST (Trial of Eczema allergy Screening Tests) Study: feasibility randomised controlled trial with economic scoping and nested qualitative study	Ridd M	Ridd M, Santer M, Boyle B, Chalmers J, Blair P, Heawood A (qualitative methods lead), Coast J, Garfield K, Marriage D, Grimshaw K, Muller I, Kai J, Jameson K, Bolton H	£438,692.00
01/2015-04/2021	NIHR HTA	The VIOLET trial - Video assisted thoracoscopic lobectomy versus conventional Open Lobectomy for lung cancer, a multi-centre randomised controlled trial with an internal pilot	Lim E	Blazeby JM, Nicholson A, Rogers C, Shackcloth M, Wordsworth S, Batchelor T, Paramasivan S	£1,642,978.00
2017-2020	NIHR HTA	Treating Urinary symptoms in Men in Primary Healthcare using non-pharmacological and non-surgical interventions (TRIUMPH)	Drake M	Lane JA, Hashim H, Fader M, Ridd M, Rees J, Cotterill N, Noble S, MacNeill S, Hackshaw-McGeagh L, Robles L, Taylor G.	£992,103.00

2014-2018	NIHR HTA	UNBLOCS: laser or saline/bipolar surgery.	Drake M	Lane JA, Noble S, Brookes S, Abrams P, Page T, Swami S.	£1,100,000.00
10/2014-03/2018	NIHR HTA	Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men	Drake M	Drake M, Abrams P, Glazener C, Blair P, Horwood J, Lane J, McGrath J, Noble S, Pickard R, Taylor G, Roy P, Smith B, Costley J, Williams N, Hashim H, Chapple C	£1,708,002.00

iii) Non-RCT studies with applied Hub methods and/or integrated methodological projects

Grant dates	Funder	Title	Principal Investigator	Co-app(s)	Grant amount (£)
07/2016-06/2018	NIHR PHR	A network meta-analysis of complex interventions to prevent mental-ill-health in children and young people: evaluation of effective and cost-effective intervention components	Caldwell D	Caldwell DM, Welton NJ, Campbell R, Gunnell D, Kidger J, Thomas J, Hetrick S	£350,079.00
1/2015-12/2017	NIHR RfPB	A prospective multicentre cohort study to inform the feasibility and conduct of a pragmatic randomised clinical trial comparing new techniques of implant based breast reconstruction (iBRA study)	Potter S	Holcombe C, Conroy B, Jain A, Gardiner M, Mills N, Cutress R, Teasdale L, Blazeby J, Williamson P	221363

06/2018-05/2020	MRC-NIHR MRP	Adaptation of evidence-informed complex population health interventions for implementation and/or re-evaluation in new contexts: New guidance.	Moore G	Littlecott H, Murphy S, Segrott J, Rehfuess E, Pfadenhauer LM, Craig P, Moore L, Hoddinott P, Evans R, O’Cathain A	£273,907.00
11/2016-10/2018	NIHR PHR	Assets-based feeding help Before and After birth (ABA): feasibility study for improving breastfeeding initiation and continuation.	Jolly K	McArthur C, Hoddinott P, Dykes F, Thomson G, Ingram J, Sitch A, Trickey H, Robert T, Dombrowski S	£328,980.00
09/2015-2020	NIHR PGfAR	Chronic pain after total knee replacement: better post-operative prevention and management (the STAR Programme)	Gooberman-Hill R	Dieppe P, Arden N, Baker P, Beswick A, Blom A, Bruce J, Eccleston C, Judge A, MacKichan F, McCabe C, Noble S, Peters T, Price A, Roper C, Wylde V.	£100,937.00
10/2017-10/2020	NIHR HTA	Embedded QRI - ETAA: a cohort study of effective treatments for thoracic aortic aneurysms	Rooshenas L		£11,036.00
10/2016-01/2017	NIHR HTA	Embedded QRI - Multi-centre randomised controlled trial to compare the clinical and cost-effectiveness of a ‘vein bypass first’ with a ‘best endovascular treatment first’ revascularisation strategy for severe limb ischaemia due to infra-popliteal arterial disease (BASIL-2)	Jepson M	Donovan J	£11,573.00
10/2015-01/16 & 09/2016-11/2016	NIHR HTA	Embedded QRI - Male synthetic sling versus Artificial urinary Sphincter Trial: Evaluation by Randomised controlled trial (MASTER)	Jepson M	Donovan J	£9,347.00

06/2018-11/2019	Linbury and Ashden Trust	Exploring the mechanisms of action of the Lightning Process and applying for funding to replicate a treatment trial for children with CFS/ME.	Crawley E	Anderson E, Beasant L, Barnes R, Mills N	£49,538.00
06/2016-8/2018	NIHR PHR	Feasibility study of how best to engage obese men in narrative SMS (short message system) and incentive interventions for weight loss, to inform a future effectiveness and cost-effectiveness trial	Hoddinott P/Dombrowski S	Avenell A, Elders A, Gray C, Grindle M, Jones C, Kee F, McKinley M, Men's Health Forum Charities, Van Der Pol M, Williams B	£490,970.00
05/2015-04/2016	BAPRAS; BSSH	Feasibility work to inform a multicentre randomised controlled trial of splint duration for mallet injuries (MALIT)	Blazeby JM	Henderson J	£23,140.00
09/2016-08/2018	NIHR HTA	How do smoking cessation medicines compare with respect to their neuropsychiatric safety: a systematic review, network meta-analysis and cost effectiveness analysis	Thomas K	Caldwell D, Welton N, Stevenson M, Gunnell D, Munafo M	£261,107.00
03/2017-02/2018	NIHR SPCR	Identifying the most appropriate treatment for IAPT attendees with depression and co-morbid personality difficulties.	Turner K	Moran P, French L, Kessler D, Wiles N	£53,629.00
2018-2020	Health Foundation	Impact of health on social and economic outcome: qualitative study.	Howe L	Davies A, Davies N, Dickson M, Heawood A, Jones H, Rice F.	£449,973.00

2018-2022	NIHR HS&DR	Improving medicines use in people with polypharmacy in primary care (IMPPP)	Payne R	Salisbury C, Round J, Heawood A, Morris R, Dreischulte T, Guthrie B, Chew-Graham C, Jameson C.	£1,872,267.31
04/2016-03/2022	NIHR PGfAR	Integrated therapist and online CBT for depression in primary care.	Wiles N	Kessler D, Welton N, Wevill C, Coyle D, Turner K , Churchill R, Parrott S, Williams C, Lewis G, Nazareth I, Shafran R, Gilbody S, Peters T, Macleod U, Lanham P	£2,233,801.00
04/2019-04/2021	NIHR RfPB	KNe Implant Prosthesis Study (KNIPS) - The choice between implants in total knee replacement: evidence synthesis and economic decision model to determine the effectiveness and cost-effectiveness of knee implants for NHS patients	Marques E	Marques E, Blom AW, Welton N, Higgins JPT, Beswick A, Thom H, Hunt L, Denis J, Whitehouse M, Burston A,	£ 253,626
2016-2018	NIHR HTA	Monitoring for neovascular AMD Reactivation at Home: the MONARCH study	Hogg R	Burton B, Chakravarthy U, Donnelly M, Goverdham S, Knox P, Lotery J, Reeves B, Rogers CA, Sivprasad S, Tunde P	£1,139,565.00

05/2017-05/2020	Bowel Disease Research Foundation	Optimising management of fistulating perianal Crohn's disease	Adegbola S	Tozer P, Sahnan K, Adegbola S, Allin B, McNair A, Lee M, Heywood N, Blackwell S, Verjee A, Fearnhead N, Sagar P, Brown S, Bach S, Hart A, Lobo A, Sebastian S, Hind D	£56,589.00
04/2014-06/2015	NIHR SPCR	Primary care patients' views and experiences of treatments for depression: a secondary analysis of qualitative data.	Turner KM	Donovan JL, Kessler D	£79,542.50
01/2016-02/2022	NIHR PGfAR	REPROVIDE (Reaching Everyone Programme of Research On Violence in diverse Domestic Environments).	Feder G	Feder G, Williamson E, Szilassy E, Gilchrist G, Cramer H, Bailey J, Hollinghurst S, Carey J, Hegarty K, Howard L, Hester M, Ziebland S, Peters T	£2,529,230.00
10/2018-09/2023	NIHR	Research Design Service South West (RDS SW) Infrastructure grant	Taylor G	Barton A, Blair P, Cabral C, Green C, Greenwood R, Hapeshi J, Hollingworth W, Powell R, Smith P, Thomas P, Thomas X	£5,182,323.00

12/2016-12/2018	Bristol Hospitals Charitable Fund - David Telling Award	Studies to inform clinical aortic aneurysm research (including the development of an aortic aneurysm patient focus group and pilot studies in emergency surgery)	Hinchliffe R	Mouton R	£176,000.00
11/2014-05/2017	NIHR RfPB	Testing the feasibility of a consultation-level intervention for frequent attenders with clinically inexplicable symptoms in primary care	Barnes R	Cramer H, Salisbury C, Kessler D, Hollinghurst S, Metcalfe C	£249,940.00
2019-2021	NIHR RfPB	The BRighteR study–Breast Reconstruction: Investigating long-term clinical and cost-effectiveness in the National Mastectomy and Breast Reconstruction Audit cohort	Potter S	Holcombe C, Hollingworth W, O’Donoghue J, Mouhiddin S, Gulliver-Clarke C, Jeevan R, Browne J, McKenzie M, Fairbrother P	£349,001
07/2014-06/2016	NIHR RfPB	The choice between hip prosthetic bearing surfaces in total hip replacement: evidence synthesis, statistical analysis and decision modelling to evaluate the effectiveness and cost-effectiveness of prosthetic implants for the NHS.	Marques E	Marques E, Blom A, Hollingworth W, Welton NJ, Beswick A, Hunt L, Davies P, Burston A.	£230,304.00
06/2015-05/2018	NIHR RfPB	The iBRA (implant Breast Reconstruction evaluation) study – A prospective multicentre cohort study to inform the feasibility and conduct a pragmatic randomised clinical trial comparing new techniques of implant-based breast reconstruction	Potter S	Holcombe C, Conroy B, Jain A, Gardiner M, Mills N, Cutress R, Teasdale L, Blazeby J, Williamson P	£243,418.00

2017-2018	The Association of Breast Surgery	The Pre-BRA (Pre-pectoral Breast Reconstruction Evaluation) Study. An IDEAL 2a/2b prospective cohort study to determine the safety and effectiveness of pre-pectoral implant based breast reconstruction	Potter S	Holcombe C, Jackson R	£10,000.00
2015-2016	Avon Primary Care Research Collaborative	To develop a cluster randomised controlled trial to evaluate a consultation-level intervention for frequently attending patients in primary care: The Footprints in Primary Care Study.	Barnes R	Barnes R, Cramer H, Thomas C.	£22,266.00
2013-2018	NIHR PGfAR	Towards safer delivery and monitoring of cancer treatments. Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID).	Velikova G	Potrata B, Hulme C, Franks K, Hall G, Brown J, Hewison J, Selby P, Kozłowska K, Waugh M, Blazeby JM, Jones R, Ajayi F, Harley C, Davidson S, Morris C.	£1,969,062.00
09/2016-02/2018	Glasgow Children's Hospital Charity/NHS Health Scotland	Use of breast pumps to improve breastfeeding outcomes: development and feasibility testing of a novel incentive intervention (BABI 1)	McInnes R	Hoddinott P, Gillespie N, Elders A, Currie S	£42,669.00
05/2014-05/2017	NIHR PGfAR	What are the indications for prescribing antidepressants that will lead to clinical benefit? (PANDA)	Lewis G	Araya R, Churchill R, Hollingworth W, Kessler D, Peters TJ, Welton N, Wiles NJ, Ades T, Malpass A, Dowrick C, Robinson J, Kendrick T, Gilbody S, Croudace T	£1,999,968.00

Appendix 3: ConDuCT-II publications 2014-2018

i) Methodological

Albarqouni LN, López-López JA, Higgins JPT. Indirect evidence of reporting biases was found in a survey of medical research studies. *J Clin Epidemiol*. 2017; 83:57-64 doi:10.1016/j.jclinepi.2016.11.013

Al-Janabi H, Flynn TN, Peters TJ, Bryan S, Coast J. Test-retest reliability of capability measurement in the UK general population. *Health Econ*. 2015; 24(5):625-30 (doi:10.1002/hec.3100)

Al-Janabi H, van Exel J, Brouwer W, Coast J. A Framework for Including Family Health Spillovers in Economic Evaluation. *Med Decis Making*. 2015; 36(2):176-86 (doi:10.1177/0272989X15605094)

Alkhaffaf B, Blazeby J, Williamson P, Bruce I, Glenny A-M. Reporting of outcomes in gastric cancer surgery trials: A systematic review. *BMJ Open*. 2018; 8:e021796 (doi:10.1136/bmjopen-2018-021796)

Alkhaffaf B, Glenny A, Blazeby JM, Williamson P, Bruce IA. Standardising the reporting of outcomes in gastric cancer surgery trials: protocol for the development of a core outcome set and accompanying outcome measurement instrument set (the GASTROS study). *Trials*. 2017; 18:370
<https://doi.org/10.1186/s13063-017-2100-7>

Anker SD, Agewall S, Borggrefe M, Calvert M, Caro JJ, Cowie MR, Ford I, Paty JA, Riley JP, Swedberg K, Tavazzi L, Wiklund I, Kirchhof P. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. *Eur Heart J*. 2014; 30:2001
<http://dx.doi.org/10.1093/eurheartj/ehu205>

Avery KN, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson C, Williams H, Blazeby JM, members of the Internal Pilot Trials Workshop supported by the Hubs for Trials Methodology Research. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open*. 2017; 7:e13537
doi:10.1136/bmjopen-2016-013537

Avery KNL, Chalmers KA, Brookes ST, Blencowe NS, Coulman K, Whale K, Metcalfe C, Blazeby JM, the ROMIO Study Group. Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. *Ann Surg*. 2018; 267(4):700-10

Bailey C, Orlando R, Kinghorn P, Armour K, Perry R, Jones L, Coast J. "The ICECAP-SCM tells you more about what I'm going through" - Measuring quality of life amongst patients receiving supportive and palliative care. *Palliat Med*. 2016; 30(7):642-52 (doi:10.1177/0269216315624890)

Banghu A, Singh P, Pinkney T, Blazeby JM. A detailed analysis of outcome reporting from randomised controlled trials and meta-analyses of inguinal hernia repair. *Hernia*. 2015; 19(1):65-75
(doi:10.1007/s10029-014-1299-4)

Beard D, Hamilton D, Davies L, Cook J, Hirst A, McCulloch P, Paez A. Evidence-Based Evaluation of Practice and Innovation in Physical Therapy Using the IDEAL-Physio Framework. *Phys Ther* 2018; 1;98(2):108-121 (doi:10.1093/ptj/pzx103)

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