



**MRC ConDuCT-II Hub for
Trials Methodology Research**

Newsletter

August 2017



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Updates from our themes



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

Trials that assess the cost-effectiveness of health technologies often rely on patient recall to measure healthcare use. However, the existing measures are characterised by inconsistency and a lack of validation. Theme 1, in collaboration with the MRC HTMR hubs in Oxford and the North West, have begun to develop a standardised resource-use measure (ISRUM) that could increase data quality, improve generalisability and reduce research burden in trials. We have used Delphi surveys to identify and reach agreement on a minimum set of core resource-use items that should be included in a standardised instrument for UK health economic evaluation (Thorn et al. in press). Initial findings demonstrate that it is feasible to develop a short, standardised resource-use instrument for use in RCTs. We are extending this work to develop and validate the ISRUM questionnaire through an MRC funded PhD studentship.

Theme 1 also has a work-package on Value of Information (VoI) methods to help identify whether a new trial is a good investment of research resources. VoI calculations are computationally demanding. Theme 1 members Howard Thom, Wei Fang, Jhenru Wang, and Nicky Welton are working in collaboration with Mike Giles (Oxford) on exploring the application of efficient methods from the field of financial mathematics to VoI calculations.

Following the success of the hub-network funded short course on Value of Information Methods held at UCL in London in June 2016, the course materials were integrated into a 5-day short course on “Bayesian Methods for Health Economics” held in Florence in June 2017, a collaboration between Nicky Welton (ConDuCT-II, Theme 1), Gianluca Baio and Anna Heath (UCL), Chris Jackson (Cambridge Biostatistics Unit), Mark Strong (Sheffield).

The course received very positive feedback, and will run again in June 2018. This dissemination activity is key to the adoption of VoI methods in practise. The theme also contributed to the development of a new short course “Introduction to Bayesian Data Analysis in WinBUGS”.

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

The QuinteT Recruitment intervention (QRI), pioneered by theme members in ConDuCT-I has been going through a process of extended and iterative development, considering how it may be tailored to particular contexts, from integration at the outset of an RCT, to involvement partway through RCTs encountering recruitment difficulties. In ConDuCT-II, theme 2 members have been involved in a number of studies where the QRI has been embedded in the RCT to understand and optimise recruitment. These include 12 ongoing

studies, four completed studies, three studies in the early stage of set up and a further four studies with embedded QRIs under review. An evaluation of the effectiveness of the QRI, which considers the components of a QRI and its implementation, is underway (Rooshenas et al, in progress).



Theme 2 members have continued to undertake qualitative synthesis across a range of RCTs with integrated QRIs, to understand the intricacies of the process of recruitment. Current areas of exploration include how surgeons present keyhole and open operations in the context of surgical trials (Paramasivan et al), the impact of recruiter's treatment biases on recruitment (Mills et al) and how recruiters describe the process (Jepson et al) and rationale (Conefrey et al) for randomisation. Research findings from this synthesis work have been translated into practical teaching material for recruiters, with team members running two very well received events this year to medical students (Granule) and surgical trainees (Bostic) (see below for more details). Watch this space for forthcoming publications and future training events!



Bostic 2017, in Oxford

The team have also been active in developing and refining innovative research methods aimed at improving trial recruitment processes, with publications on a measure of informed consent (Wade et al, 2017) and a framework for screening and approaching patients for recruitment (The SEAR framework, Wilson et al).

Follow the QuinteT team on Twitter: [@QuinteTBristol](https://twitter.com/QuinteTBristol)



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

In Autumn 2016, the FACT theme was successful in obtaining a HTMR small grant to conduct the ReSurgEnT (Research on Surgeons and Engagement in Trials) study. The aims of the study are: 1) To identify the key strategies leading to successful trial conduct within surgical trainee collaboratives; and 2) To use this to develop methods/recommendations to enhance clinician engagement in trials across clinical specialities and to inform the medical curriculum in training future clinicians to engage with research. Methods include non-participant observation of key trainee and trial meetings, and semi-structured interviews with key stakeholders. The study is now underway with Clare Clement being appointed as the study researcher. Thus far, three network meetings have been observed, and six interviews have been carried out. Further meeting observations and interviews are planned with trainee collaboratives across the country. If anyone is aware of any ongoing trials involving surgical trainees, please get in touch with

Clare: c.clement@bristol.ac.uk

Follow the study on twitter: [@ResurgentStudy](https://twitter.com/ResurgentStudy)



In other news, the first paper from the QuANTOC study (An ethnographic study of group decision-making and member roles to understand and improve how Trial Steering Committees and Trial Management Groups contribute to trial conduct) was published in 2016 in *Trials*.

Daykin et al. *Trials* (2016) 17:307
DOI 10.1186/s13063-016-1423-y

Trials

RESEARCH

Open Access



What are the roles and valued attributes of a Trial Steering Committee? Ethnographic study of eight clinical trials facing challenges

Anne Daykin^{1*}, Lucy E. Selman¹, Helen Cramer¹, Sharon McCann², Gillian W. Shorter^{3,4}, Matthew R. Sydes^{5,6}, Carrol Gamble⁷, Rhiannon Macefield¹, J. Athene Lane¹ and Alison Shaw¹

Read the article [here](#).

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



in collaboration with the COMET initiative, Theme 4 members have been involved in producing the COMET Handbook. The Handbook provides guidance on the development, implementation, evaluation and updating of core outcome sets and is based on an accumulation of the continued methodological work that has been going on in Theme 4 and other Hubs in recent years.

The Author(s) *Trials* 2017, **18**(Suppl 3):280
DOI 10.1186/s13063-017-1978-4

Trials

REVIEW

Open Access

The COMET Handbook: version 1.0



Paula R. Williamson^{1*}, Douglas G. Altman², Heather Bagley¹, Karen L. Barnes¹, Jane M. Blazeby³, Sara T. Brookes³, Mike Clarke^{4,5}, Elizabeth Gargon¹, Sarah Gorsl¹, Nicola Harman¹, Jamie J. Kirkham¹, Angus McNair³, Cecilia A. C. Prinsen⁶, Jochen Schmitt⁷, Caroline B. Terwee⁸ and Bridget Young¹

Read the article [here](#), and follow COMET on Twitter: [@COMETinitiative](#)



In other work, members of Theme 4 have developed a new outcome measure for assessing wounds after surgery for use in RCTs. One of the key features of the outcome measure is its design as a 'dual-completion' questionnaire – intended for completion by patients and/or observers (healthcare professionals). They have taken a novel approach to item construction and used plain language with medical terminology alongside. The rationale behind this method is that when there is a need to collect information from patients and professionals on the same outcome, the use of separate questionnaires with different items and wording may run the risk of measuring different issues. A 'dual-completion' questionnaire ensures that the same construct is being measured regardless of who is completing the questionnaire, making data amalgamation easier and outcome measurement more streamline for trials. Work so far has shown that combining plain language and medical terminology in items has advantages for content validity in the development of the questionnaire and ensures that items are interpreted as intended.

Plans are underway to use dual-completion questionnaires in other studies and settings where the views of patients and professionals are needed on the same issue (e.g. Delphi surveys for core outcome set development) and further validate the method.

As part of her NIHR Doctoral Research Fellowship project, Theme 4 affiliate Amber Young has started work on the development of a core outcome set for burns for use in RCTs. The project will include the views of patients including children and parents of children who have suffered from burns injuries. This is an area where there is much heterogeneity in outcome measurement and reporting and a core outcome set is much needed. Amber's study protocol was published in BMJ Open in July.

Open Access

Protocol

BMJ Open Agreement on what to measure in randomised controlled trials in burn care: study protocol for the development of a core outcome set

Amber Young,¹ Sara Brookes,¹ Nichola Rumsey,² Jane Blazeby¹

Read the article [here](#).



Recent successes



Grants

Congratulations to **Jonathan Rees** who has been awarded a Research Capacity Funding grant from the University Hospitals Bristol. The grant will be used to undertake pilot work entitled "*Developing consensus with health professionals and policy makers to define a core outcome set for emergency general surgery: preliminary work to inform an NIHR programme grant.*"



Nicky Welton, Tony Ades, Sofia Dias, and David Phillippo (Theme 1) have been awarded an MRC Methodology Research grant "*Calibration of multiple treatment comparisons using individual patient data*". This project aims to develop methods to adjust

for differences in population characteristics when making indirect and mixed treatment comparisons to inform decision making. The methods are developed for the situation where individual patient data is available from one (or more) RCT, but only aggregated summaries reported from the other RCTs relevant to the decision.



Professor Jo Coast (Theme 1) has been awarded a Wellcome Trust investigator award on developing “*A life-course approach to measuring capability for economic evaluation of health and social care interventions*”. This methodological work will include work to generate, value and validate new measures of capability wellbeing for children for use in economic evaluations of health services.

Grants

Congratulations to **Shelley Potter** for achieving an NIHR Clinician Scientist Award. She will be returning to Bristol in July 2017 and will be working closely with the ConDuCT-II Hub and Theme 4.



Dr **Barry Main** has been appointed to an NIHR academic clinical lecturer post in Oral and Maxillofacial Surgery. He started his post on 1st February 2017 and his work will include methods of the implementation of core information set for informed consent before surgery. The Hub and Theme 4 are delighted to have him back in the team.

Fellowship news

Nicky Welton and **Sofia Dias** (Theme 1) are collaborators on **David McAllister's** (Glasgow) 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*". David will be spending periods of time visiting Bristol during his fellowship.

Danya Bakhbaki will start an NIHR doctoral research fellowship in January 2018 and will be affiliated with Theme 4. Danya will be developing a core outcome set for interventions following stillbirth

Team news



Huge congratulations to:

Charlotte Murkin (MSc student and Theme 4 affiliate) who was awarded a prize for best oral presentation from a Young Investigator at the European Hernia Society conference for her work to develop a measure for parastomal hernia in the CIPHER study.

Howard Thom who has been appointed to a Research Fellow post on the Surgical Innovation theme of the NIHR Bristol Biomedical Research Unit. Howard will however continue to contribute to Theme 1 as a co-supervisor to his replacement on the theme. We wish Howard all the best in his new role.

Nicky Welton (Theme 1) who has been promoted to Professor.

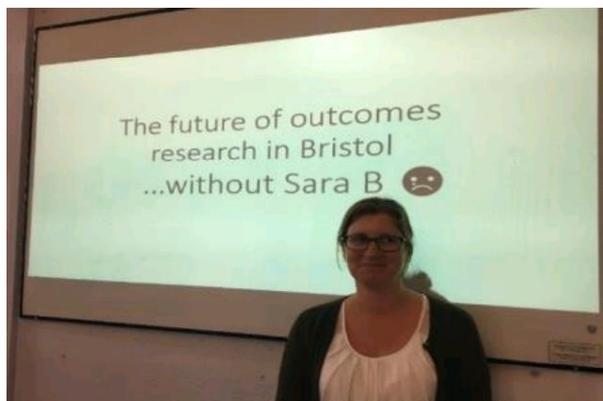


And some staff updates:

David Mawdsley (Theme 1) has left the University of Bristol to pursue his interests in computer programming at the University of Manchester.

We welcome **Hugo Pedder** (Theme 1) who replaces David Mawdsley on the joint MRC and Pfizer funder project on methods for model-based network meta-analysis to inform drug-development decisions.

We are very sad to be saying farewell to **Sara Brookes** as she moves from Bristol and starts a new post at the University of Birmingham in September. Sara has been 'core' to our Hub since its beginning and she will be sadly missed – we wish Sara all the best for her new job - the world of outcomes will not be the same without you!



 **PhD/MD news** 

We look forward to welcoming...

Nicola Fararr, who will be starting a PhD in October 2017. Nicola will join Theme 2 on trial recruitment, and will be undertaking a PhD exploring patient perspectives of recruitment in RCTs. She will be supervised by Leila Rooshenas, Daisy Elliott, Jenny Donovan (Theme 2) and Bridget Young (North West hub, University of Liverpool) .

Kirsty Garfield, who will start her MRC funded PhD in October 2027 on “Developing a modular resource-use questionnaire for use in RCTs”. Kirsty has worked with the Bristol Randomised Trials Collaboration (BRTC) trials unit for several years. She will join Theme 1 and is supervised by Jo Thorn, Sian Noble, Sam Husbands and Will Hollingworth.

Congratulations to...

Noah Howes, who successfully passed his MD viva in July 2017. His thesis was entitled “*Innovation in surgery – the evolution of evidence for a novel surgical procedure*”.

Sean Strong, who was recently awarded his PhD entitled "*Understanding the role of teamwork in recruitment to randomised controlled trials in surgical oncology: an exploratory study*".



Mairead Murphy, who was awarded her PhD entitled "*Developing a generic outcome measure for primary care*" in February 2017.

Workshops

Granule 2017

Jane Blazeby, Leila Rooshenas and **Nicola Mills** contributed to Granule (Generating student recruiters for randomised controlled trials) on the 19th June - an educational event aimed at medical students, which sought to raise awareness and understanding of the challenges of recruiting to RCTs. This is the second year that the ConDuCT-II Hub have collaborated with the Birmingham team to share their experiences from working on previous RCTs that were deemed 'difficult' to recruit to, and deliver a focused workshop on communicating the principles of randomisation to potential trial participants. Around 20 medical students attended, mostly near finalists but with a handful of keen first year students!



The Granule workshop, June 2017



Bostic 2017

Jane Blazeby, Leila Rooshenas and Marcus Jepson contributed to Bostic (Bristol and Oxford Surgical Trials Intervention Course) that was held from 17th-19th May as a collaboration between the Surgical Interventions Trials Unit in Oxford, and the ConDuCT-II Hub in Bristol. The course covers all aspects of designing and conducting RCTs. Similar to last year, this year's course included a session on the challenges of recruiting to surgical trials, with a specific focus on communicating equipoise to potential trial participants. The event was attended by 25 surgical trainees, all of whom provided very positive feedback on the event. We're looking forwards to hosting Bostic 2018 here in Bristol!



The Bostic workshop, May 2017



Selected publications



Theme 1:

Core items for a standardised resource-use measure (ISRUM): expert Delphi consensus survey. Joanna C Thorn, Colin Ridyard, Ruth Riley, Sara Brookes, Dyfrig Hughes, Sarah Wordsworth, Sian M Noble, Gail Thornton, William Hollingworth
Value in Health in press.

Resource-use measurement based on patient recall for cost-effectiveness studies is currently approached in an inconsistent manner. This study employed Delphi methodology to identify the key items of resource use that should be included in a standardised resource-use measure.

Thom HHZ, Jackson C, Welton NJ, Sharples L. Using Parameter Constraints to choose State-Structures in Cost-effectiveness Modelling. Pharmacoeconomics.

Published online 24th March 2017. Read the article [here](#)

Multi-state models are the most frequently used models in cost-effectiveness analyses. However, results can be sensitive to the choice of state-structure. In this paper we propose

a new method that allows us to test whether the costs and/or health consequences for a patient in two states are the same, and hence if the states can be merged.

Guyot PG, Ades AE, Beasley M, Pignon J-P, Beranger L, Welton NJ. Extrapolation of RCT-based survival curves using external information. Medical Decision Making.

Published online: September 28, 2016. Read the article [here](#)

Decision models need estimates of life-expectancy differences between treatment options. However, RCTs reporting survival outcomes only have a relatively short-term follow-up data available, and relative treatment benefits may be expected beyond that period. Extrapolation is therefore required. This paper proposes methods to combine RCT evidence with external data sources (registries, meta-analyses of similar treatments, expert opinion) to better inform extrapolations and evidence-based decision making.

Theme 2:

Understanding and Improving Recruitment to Randomised Controlled Trials: Qualitative Research Approaches. Elliott D, Husbands S, Hamdy F, Holmberg L & Donovan J. European Urology 2017 (in press). Read the article [here](#)

This review provides an introduction to the principles of qualitative research, and outlines the current literature on how this methodological approach can be used to understand - and subsequently improve - recruitment and informed consent to surgical RCTs.

Enabling recruitment success in bariatric surgical trials: Pilot phase of the By-Band-Sleeve study. Paramasivan S, Rogers C, Welbourn R, Byrne JP, Salter N, Mahon D, Noble H, Kelly J, Mazza G, Whybrow P, Andrews R, Wilson C, Blazeby J & Donovan J. International Journal of Obesity 2017 (in press). Read the article [here](#)

This paper outlines how the application of the QRI (QuinteT Recruitment Intervention) to the By-Band-Sleeve study enabled its move from the pilot to the main phase. The findings emphasise the importance of integrating the trial within clinical service provision.

Informed consent in randomised controlled trials: development and preliminary evaluation of a measure of participatory and informed consent (PIC). Wade J, Elliott D, Avery KNL, Gaunt D, Young G, Barnes R, Paramasivan S, Campbell B, Blazeby JM, Birtle A, Stein R, Beard D, Halliday A, Donovan JL. Trials 2017;

18:327. Read the article [here](#)

The paper outlines the development and formative evaluation of a measure to assess recruiter information provision and evidence of patient understanding in recorded recruitment appointments.

Conveying Equipoise during Recruitment for Clinical Trials: Qualitative Synthesis of Clinicians' Practices across Six Randomised Controlled Trials. Rooshenas L, Elliott D, Wade J, Jepson M, Paramasivan S, Strong S, Wilson C, Beard D, Blazeby JM, Birtle A, Halliday A, Rogers CA, Stein R & Donovan JL. PLoS Medicine 2016. 13, 10, 24 p., e1002147. Read the article [here](#)

This paper aimed to investigate how clinicians attempted to communicate equipoise to patients across six RCTs, by comparing clinicians' intentions with broad practices that support or hinder equipoise communication.

Theme 3:

Daykin A, Selman LE, Cramer H, McCann S, Shorter GW, Sydes MR, Gamble C, Macefield R, Lane JA, Shaw A. What are the roles and valued attributes of a Trial Steering Committee? Ethnographic study of eight clinical trials facing challenges. Trials (2016) 17:307. Read the article [here](#)

This study aimed to explore the role and valued attributes of trial steering committees using a multi-perspective ethnographic design.

Avery KNL, Williamson PR, Gamble C, Francischetto EO, Metcalfe C, Davidson, P, Williams H, Blazeby JM. Informing efficient randomised trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open (2017) 7: e013537. Read the article [here](#)

This paper outlines the key issues to consider in the optimal development and review of operational progression criteria for RCTs with an internal pilot phase.

Theme 3 was well-represented at the joint International Clinical Trials Methodology Conference (ICTMC)/Society for Clinical Trials meeting in Liverpool in May 2017. Some of

the oral presentations included:

Daykin A , Selman LE , Cramer H, McCann S, Shorter GW, Sydes MR, Gamble C , Macefield R, Shaw A, Lane JA. Changing roles and relationships within trial oversight: an ethnographic study of eight clinical trials facing challenges. 5 May 2017 Trials 18(Suppl 1).

Gravani A, Jepson M, Wilson C, Lane A, Rogers C. Analysis of trial-specific training during the site initiation phase: the ATLAS study 5 May 2017 Trials 18 (Suppl 1).

Theme 4:

Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB, Young B. (2017). [The COMET Handbook: version](#)

[1.0. Trials;18\(Suppl 3\):280.](#) Read the article [here](#)

The COMET initiative have produced the COMET Handbook to bring together the latest thinking around core set development and consensus methods.

Macefield, R. C., Reeves, B. C., Milne, T. K., Nicholson, A., Blencowe, N. S., Calvert, M., et al. (2017). Development of a single, practical measure of surgical site infection (SSI) for patient report or observer completion. *Journal of Infection Prevention; 18(4): 170-179. doi:10.1177/1757177416689724.* Read the article [here](#)

In conjunction with the Bluebelle Study Group, theme 4 researchers have developed a new outcome measure for assessing wound healing after surgery. This "dual-completion" questionnaire (designed for use by patients and/or healthcare professionals) is a novel approach to outcome assessment that can be applied to other settings.

Development of a Core Outcome Set for Clinical Effectiveness Trials in Esophageal Cancer Resection Surgery. Avery KN, Chalmers KA, Brookes ST, Blencowe NS, Coulman K, Whale K, Metcalfe C, Blazeby JM; ROMIO Study Group; CONSENSUS Esophageal Cancer Working Group. (2017). *Annals of Surgery.* [Epub ahead of [print](#)] Read the article [here](#)

A Delphi study and consensus meetings with patients and professionals was completed to determine a core outcome set for trials in oesophageal cancer surgery.

Collaborating with industry

Theme 1 has two MRC-funded projects in collaboration with industry:

1. Model Based Network Meta-Analysis for Pharmacometrics and Drug-Development. This project is jointly funded by the MRC and Pfizer, and aims to develop methods for network-meta-analysis that account for dose-response and time-course information from phase-II and phase-III RCTs, and allow exploration of model fit and inconsistency.
2. Calibration of multiple treatment comparisons using individual patient data. This project is fully funded by the MRC, but includes collaboration with 2 pharmaceutical companies to access datasets that illustrate the methods with (or based upon) real health technology appraisals.



Upcoming courses



Watch out for training workshops for surgeons and research nurses on the **hidden challenges of RCT recruitment in Winter 2017/8**. Dates will be advertised on the [QuinteT website](#) as soon as they have been finalised.

On November 21st 2017, we will host a workshop on **Economic evaluation alongside surgical trials**. Health economists working on surgical RCTs, CIs of surgical RCTs, trialists and those interested in economic evaluations of surgical interventions are invited to attend this event. Please email htmr-conduct@bristol.ac.uk for further details.



Dates for your diary



The **Recruitment Working Group** are holding a face to face meeting on 5th October 2017. With two important recruitment projects nearing completion (the [ORRCA](#) project and the [PRioRiTy study](#)), members will meet to identify gaps in the current knowledge and develop a collaborative bid to address these gaps.



Find out more about the ConDuCT-II Hub



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