



MRC-NIHR Trials Methodology Research Partnership: Webinar recording

Trials methodology: a community approach

Presented by Prof Paula Williamson

4 May 2022

On behalf of the TMRP

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

<https://www.youtube.com/watch?v=2tOpaxnJTFk>



Trials Methodology
TMRP
Research Partnership



@MRCNIHRTMRP

<http://www.methodologyhubs.mrc.ac.uk/>

Trials methodology: a community approach

Professor Paula Williamson
University of Liverpool
Lead, TMRP

Improving health by improving trials

What is trials methodology?



Health Research Board
TMRN
Trials Methodology Research Network



Trials Methodology
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2021 Cochrane-REWARD prize winners

This year was particularly competitive, with many very strong contenders for the prize committee to consider. Thank you to all who submitted nominations, and congratulations to the winners below:



Cochrane Connects REWARD Prize 1st...

Watch Later Share

COVID-END
COVID-19 Evidence Network to support Decision-making

Cochrane REWARD prize
28th February 2022

Jeremy Grimshaw, MBChB PhD, Co-PI, COVID-END in Canada:
Senior Scientist, Ottawa Hospital Research Institute, and Professor, University of Ottawa

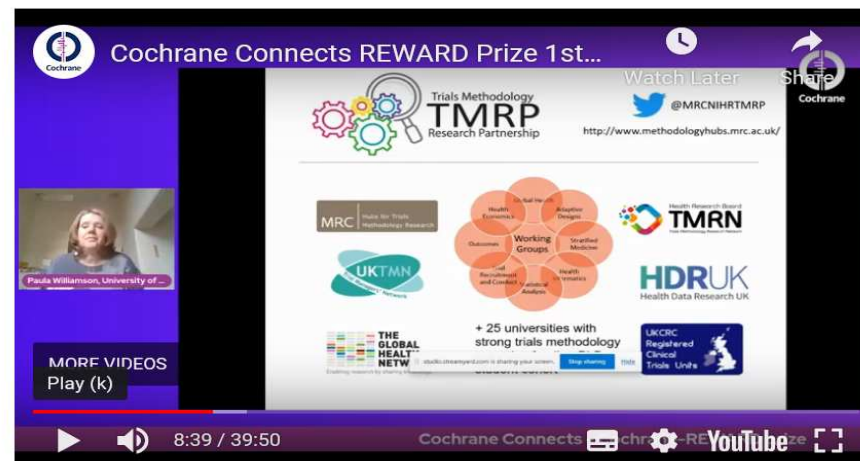
John N. Lavis, MD PhD, Co-PI, COVID-END in Canada:
Director, McMaster Health Forum, and Professor, McMaster University

Andrea Tricco, PhD, Co-PI, COVID-END in Canada:
PI, SPOR Evidence Alliance, Scientist, Unity Health Toronto, and Assoc Professor, University of Toronto

Nancy Santesso, PhD, Co-PI, COVID-END in Canada:
Deputy Director, Cochrane Canada; Assist Professor, McMaster University

1st prize winner: COVID-END

18:48 / 39:50



Cochrane Connects REWARD Prize 1st...

Watch Later Share

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<http://www.methodologyhubs.mrc.ac.uk/>

MRC Health, Trials, Methodology Research

UKTMN

Health Research Board (HRB)

Health Data Research UK (HDRUK)

UKCRC Registered Clinical Trials Unit

+ 25 universities with strong trials methodology

THE GLOBAL HEALTH NETW

8:39 / 39:50



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MRC

Hubs for Trials
Methodology Research



Health Research Board

TMRN

Trials Methodology Research Network



HDRUK
Health Data Research UK



Enabling research by sharing knowledge

UKCRC
Registered
Clinical
Trials Units



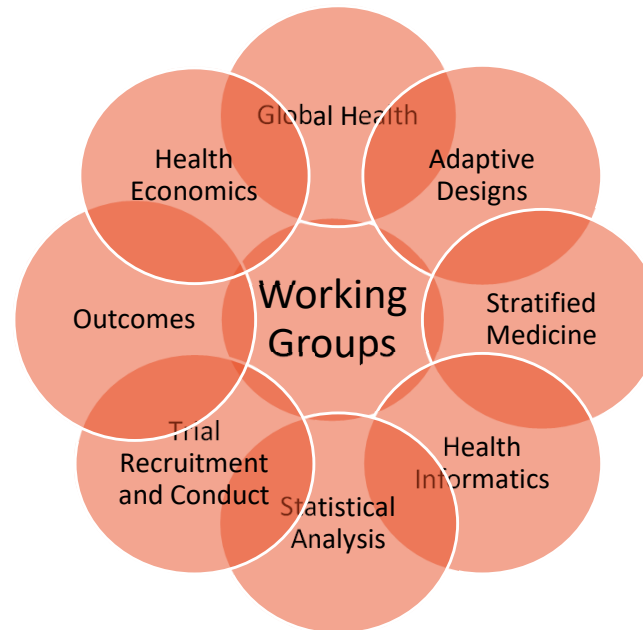


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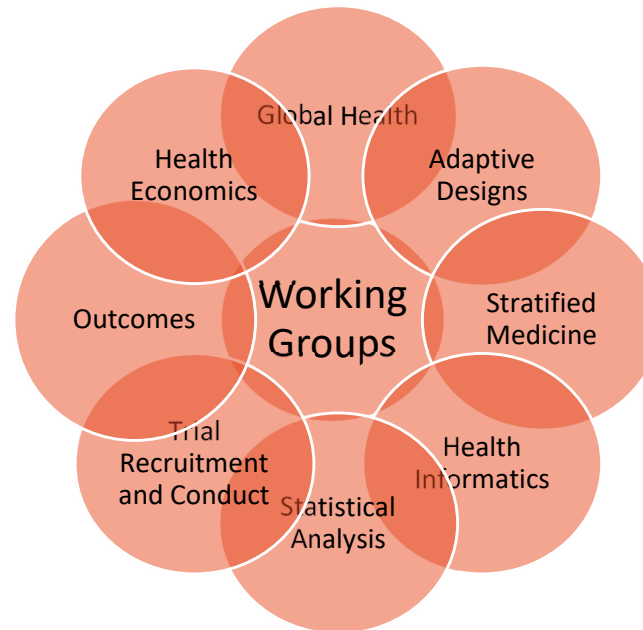


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Health Research Board
TMRN
Trials Methodology Research Network



+ 25 universities with strong trials methodology expertise funding PhD student cohort



A sense of community

“The TMRP has provided me with many opportunities to meet and work with researchers, including other PhD students, outside of my university. Not only has this widened my research experience beyond my PhD but it has also allowed me to meet and work with experts in this field at a time where networking can be particularly challenging in the virtual world. I have benefitted from training courses and other opportunities.”



“Academics are part of a community who happen to work at a particular institution. Institutional affiliation is only a part of our identity.”



What can a trials methodology network achieve?

- Better, more impactful research
- Less duplication of effort
- Value for money
- Increased knowledge exchange
- Agility - ability to pivot to COVID-19 projects

What have we done?

- Priority setting exercises – referenced in funding applications
- Small project awards (5-20K), unfunded projects, external grants
- Development and maintenance of online resources
- Open webinar series
- *'How to be a good CI', 'How to be a good TSC Chair', 'How to be a good TM'*

COVID-19 related activities 2020-2022

- **Adaptive Designs Working Group**

- Platform trials: RECOVERY, AGILE, HEAL-COVID

- **Statistical Analysis Working Group**

- Rapid, open reviews of protocols, preprints and publications on new COVID-19 treatments

- **Outcomes Working Group**

- COS: acute COVID-19, transmission prevention, Long COVID

- **Trial Conduct Working Group**

- Contributed to the NIHR INCLUDE Ethnicity Framework

- Advice
- Guidance pack
- Methodology advice
- Publications
- Top Tips

Home / Advice / Guidance pack

Guidance pack

Our overarching aim is Improving Health by Improving Trials. Since its inception in 2009, the HTMR Network has strived to undertake cutting edge research in areas important to trials methodology.

By funding various projects and initiatives, we have contributed to publications, guidance documents, resources and recommendations for trialists. The resources below constitute the current recommended "Guidance Pack"

- COMET: Core Outcome Measures in Effectiveness Trials
- DIRUM: Database of Instruments for Resource Use Measurement
- CONSORT PRO: Patient-Reported Outcomes
- ACE: Adaptive designs CONSORT Extension
- Monitoring trials efficiently: The role of central statistical monitoring

- Guidance
- Workshops
- Webinars
- Working Groups
- Publications

https://www.methodologyhubs.mrc.ac.uk/advice/network-guidance/

- Monitoring trials efficiently: The role of central statistical monitoring
- Sharing participant data: Good practice principles for sharing individual participant data from publicly funded clinical trials
- CONNECT: Consent methods in paediatric emergency and urgent care trials
- MAMS: Some recommendations for multi-arm multi-stage trials
- Qualitative research: Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers
- Surgical trials: Interventions in randomised controlled trials in surgery: issues to consider during trial design
- PIRRIST: Patient and public Involvement to enhance Recruitment and Retention In Surgical Trials
- SWATS: Online database for Studies Within A Trial (SWAT) and Studies Within A Review (SWAR)
- Doing trials within trials: A qualitative study of stakeholder views on barriers and facilitators to the routine adoption of methodology research in clinical trials

Network Hubs :: Guidance pack x +
https://www.methodologyhubs.mrc.ac.uk/advice/network-guidance/

- Rheumatoid Arthritis: Consensus Decision Models for Biologics in Rheumatoid and Psoriatic Arthritis: Recommendations of a Multidisciplinary Working Party
- Trial Steering Committees: Exploring the role and function of trial steering committees: results of an expert panel meeting.
- Why not to use A+B design: A discussion of appropriate design for phase I dose escalation studies.
- Optimising Recruitment: the Quintet Recruitment Intervention
- COS-STAR, COS-STAD and COS-STAP: Core Outcome Set-STAndards for Reporting, Core Outcome Set-STAndards for Development and Core Outcome Set - STAndardised Protocol items
- RoB 2.0: Revised Cochrane Risk of Bias tool 2.0 for randomised trials.
- ORBIT: Outcome Reporting Bias in Trials
- ORRCA and ORRCA II: Online Resource for Recruitment Research in Clinical Trials
- SOS: Search for Oversight Statisticians

Network Hubs :: Guidance pack x +
https://www.methodologyhubs.mrc.ac.uk/advice/network-guidance/

- SOS: Search for Oversight Statisticians
- SAPs: Guidelines for the Content of Statistical Analysis Plans in Clinical Trials
- BiGTeD: Biomarker-guided trial designs
- Internal pilot studies: developing progression criteria
- Pilot and feasibility studies: when to do an internal or external pilot
- MODEst Software: (MOdel-based Dose-Escalation Trials)
- HEAPs: Health Economics Analysis Plans
- MODRUM (ISRUM): Core Items for a Standardised Resource Use Measure
- Phase II Oncology Trials: Considerations and recommendations on using randomised designs

A list of some external resources of use to trialists can be found here.

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Planning – stratified medicine

Staff Intranet - University of Liv x Mail - prw@liverpool.ac.uk x Biomarker-guided trial designs x +

www.bigted.org

BiGTed

Biomarker-guided trial designs (BiGTed):
An online tool to help develop personalised medicine

Background



Personalized medicine is a growing area of research which aims to tailor the treatment given to a patient according to one or more personal characteristics. These characteristics can be demographic such as age or gender, or biological such as a genetic or other biomarker.

Prior to utilizing a patient's biomarker information in clinical practice, robust testing in terms of analytical validity, clinical validity and clinical utility is necessary. A number of clinical trial designs have been proposed for testing a biomarker's clinical utility, including Phase II and Phase III clinical trials which aim to test the effectiveness of a biomarker-guided approach to treatment; these designs can be broadly classified into **adaptive** and **non-adaptive**. While adaptive designs allow planned modifications based on accumulating information during a trial, non-adaptive designs are typically simpler but less flexible.

Antoniou et al, as members of the MRC Hubs for Trials Methodology Research's Stratified Medicine Working Group, have undertaken a comprehensive review of biomarker-guided trial designs based on an in-depth search strategy which identified 211 relevant papers, and the results of the review have been published in two separate papers, one focusing on adaptive trial designs and the other on non-adaptive trial designs. On this website, each of the trial designs identified in the review is represented graphically together with an overview of its key characteristics, methodology, and its pros and cons.

Adaptive Designs

Following a literature review we have identified eight distinct biomarker-guided adaptive designs, as follows:

Staff Intranet - University of Liv x Mail - prw@liverpool.ac.uk x Biomarker-guided trial designs x +

www.bigted.org

Adaptive Designs

Following a literature review we have identified eight distinct biomarker-guided adaptive designs, as follows:

Adaptive Signature design	Outcome-based adaptive randomization design	Adaptive threshold sample-enrichment design	Adaptive patient enrichment design
Adaptive parallel Simon two-stage design	Multi-arm multi-stage designs	Stratified adaptive design	Tandem two stage design

Non-Adaptive Designs

In the review, five distinct non-adaptive trial designs were identified, as follows:

Single Arm Designs	Enrichment Designs	Randomize-All Designs	Biomarker-Strategy Designs
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Planning – adaptive designs

Wilson *et al. BMC Medicine* (2021) 19:251
<https://doi.org/10.1186/s12916-021-02124-z>


BMC Medicine

RESEARCH ARTICLE

Open Access

Costs and staffing resource requirements for adaptive clinical trials: quantitative and qualitative results from the Costing Adaptive Trials project



Nina Wilson¹, Katie Biggs², Sarah Bowden³, Julia Brown⁴, Munyaradzi Dimairo², Laura Flight², Jamie Hall², Anna Hockaday⁴, Thomas Jaki^{5,6}, Rachel Lowe⁷, Caroline Murphy⁸, Philip Pallmann⁷, Mark A. Pilling⁹, Claire Snowdon¹⁰, Matthew R. Sydes¹¹, Sofia S. Villar⁵, Christopher J. Weir¹², Jessica Welburn², Christina Yap¹⁰, Rebecca Maier^{1,13}, Helen Hancock^{1,13} and James M. S. Wason^{1*} 

Abstract

Background: Adaptive designs offer great promise in improving the efficiency and patient-benefit of clinical trials. An important barrier to further increased use is a lack of understanding about which additional resources are required to conduct a high-quality adaptive clinical trial, compared to a traditional fixed design. The Costing Adaptive Trials (CAT) project investigated which additional resources may be required to support adaptive trials.

Planning – choosing the outcomes to measure

Network Hubs :: Guidance pack x COMET Initiative | Resources x

https://www.comet-initiative.org/Resources

Home Search the COMET Database **Resources** COS Endorsement COS Uptake Patients and the Public Events About us

COMET VIII

COMET INITIATIVE

Resources

This section of the website includes useful resources and tools. A trio of guidance for COS development now exists, in addition to the COMET Handbook. Click the links below for more information.

Database

- Systematic reviews of COS
- Newsletter
- Plain language summaries
- Patients and the Public
- Downloadable slide set

COS-STAD

PLOS MEDICINE BROWSE PUBLISH ABOUT

OPEN ACCESS
GUIDELINES AND GUIDANCE

Core Outcome Set-STAndards for Development: The COS-STAD recommendations

Jamie J. Kirkham, Katherine Davis, Douglas G. Altman, Jane M. Blazeby, Mike Clarke, Sean Tunis, Paula R. Williamson

Published: November 16, 2017 • <https://doi.org/10.1371/journal.pmed.1002447>

Article	Authors	Metrics	Comments	Media Coverage
v				

COS-STAP

Trials

Home About Articles In Review Submission Guidelines News

Research | Open Access | Open Peer Review | Published: 11 February 2019

Core Outcome Set-STANDARDISED Protocol Items: the COS-STAP Statement

Jamie J. Kirkham, Sarah Goost, Douglas G. Altman, Jane M. Blazeby, Mike Clarke, Sean Tunis, Paula R. Williamson & for the COS-STAP Group

Trials 20, Article number: 116 (2019) | [Cite this article](#)

1511 Accesses | 15 Altmetric | [Metrics](#)

COS-STAR

PLOS MEDICINE BROWSE PUBLISH ABOUT

OPEN ACCESS
GUIDELINES AND GUIDANCE

Core Outcome Set-STAndards for Reporting: The COS-STAR Statement

Jamie J. Kirkham, Sarah Goost, Douglas G. Altman, Jane M. Blazeby, Mike Clarke, Declan Devane, Elizabeth Gargan, David Mihov, Jochen Schmitt, Peter Tugwell, Sean Tunis, Paula R. Williamson

Published: October 18, 2018 • <https://doi.org/10.1371/journal.pmed.1002148>

Article	Authors	Metrics	Comments	Media Coverage
v				

Type here to search

11°C 23/04/2022 11:58

Conduct – recruitment and retention research

The screenshot shows the ORRCA website homepage. At the top, there is a navigation bar with the ORRCA logo and buttons for Home, About, Search, Join the team, Ongoing Research, and Contact. Below the navigation bar, the main content area features a 'Welcome to ORRCA' section with a paragraph describing the project's aim to bring together published and ongoing work in recruitment and retention research. A second paragraph provides updates on the recruitment and retention databases. To the right, there is a 'Sign up here to receive newsletters' button and a 'Social' section with a 'Follow @ORRCA_rct' button and a tweet from @ORRCA_rct. At the bottom, there is a search bar and two statistics boxes: '4,452 Articles in recruitment database' and '1,338 Articles in retention database'. The Windows taskbar is visible at the bottom of the screen.

Network Hubs :: Guidance pack x ORRCA :: Home x +

← → ↻ 🏠 <https://www.orrca.org.uk/#> ☆ 📁 ☰

ORRCA Home About Search Join the team Ongoing Research Contact

Welcome to ORRCA

The ORRCA project (Online Resource for Research in Clinical triAls) aims to bring together published and ongoing work in the field of recruitment and retention research into searchable databases.

We are still updating the recruitment database with publications from 2018 and 2019 due to the large volume of literature in this field. Articles will be added periodically throughout the review process. An update of the retention database for 2020 and 2021 publications will be starting shortly. Authors are welcome to submit papers as soon as they are published. *Retention database last update: 09/02/2022. Recruitment database last update 31/03/2022*

Search

4,452
Articles in recruitment database

1,338
Articles in retention database

Search studies

ORRCA Newsletter

✉ Sign up here to receive newsletters

Social

🐦 Follow @ORRCA_rct

Tweets by @ORRCA_rct

orrca
@ORRCA_rct

So many people involved in this... see the the paper / Orrca.org.uk/jointheteam for the full list of reviewers and collaborators. https://twitter.com/ORRCA_rct/status/1452543463875035141

📅 Oct 25, 2021

Windows taskbar: Type here to search, 11°C, 23/04/2022, 12:00

Trial Conduct Working Group - Funding Awards



INITIAL: Involving patients and the public In sTatistical Analysis pLans

Determining the most important methodological areas requiring methodological research for routine data in trials: a consensus



Minority ExpeRIences In Trials (MERIT): Understanding why ethnic minority groups are under-represented in trials through a rapid qualitative evidence synthesis, and mapping evidence to find solutions

Beyond “must speak English”: In search of a fairer way to operationalise patient screening for language proficiency in trial recruitment



Analysis

BMJ

RESEARCH

Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists

“When I take a look at the data I see what best advances the story, and if you include too much data the reader doesn’t get the actual important message, so sometimes you get data that is either not significant or doesn’t show anything, and so you, we, just didn’t include that”

JAMA Network
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This Issue Views 67,150 | Citations 32 | Altmetric 280

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Special Communication FREE
December 19, 2017

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD¹; Ashma Krishan, BSc²; Deborah Stocken, PhD^{3,4}; Steff Lewis, PhD⁵; Edmund Juszcak, MSc⁶; Caroline Doré, BSc⁷; Paula R. Williamson, PhD¹; Douglas G. Altman, DSc⁸; Alan Montgomery, PhD⁹; Pilar Lim, PhD¹⁰; Jesse Berlin, ScD¹¹; Stephen Senn, PhD¹²; Simon Day, PhD¹³; Yolanda Barbachano, PhD¹⁴; Elizabeth Loder, MD, MPH¹⁵

» Author Affiliations | Article Information
JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

Editorial Comment Related Articles

Abstract

Importance While guidance on statistical principles for clinical trials exists, there is an absence of guidance covering the required content of statistical analysis plans (SAPs) to support transparency and reproducibility.

Objective To develop recommendations for a minimum set of items that should be addressed in SAPs for clinical trials, developed with input from statisticians, previous guideline authors, journal editors, regulators, and funders.

Design Funders and regulators (n=39) of randomized trials were contacted and the literature was searched to identify existing guidance; a survey of current practice was conducted across the network of UK Clinical Research Collaboration-registered



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Home > Library > Reporting guideline > Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Search for reporting guidelines

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Guidelines for the Content of Statistical Analysis Plans in Clinical Trials



Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions
Observational studies	STROBE	Extensions
Systematic reviews	PRISMA	Extensions
Study protocols	SPIRIT	PRISMA-P

Citation Analysis for JAMA article

November 2020: viewed 80K times with >22K downloads, 124 citations

Primary reason for citation	2018	2019	2020	Grand Total	Country of first author	
Guidance used as a template	6	8	28	42	UK	15
Reporting and transparency	7	8	11	26	Denmark	6
Recommending use of guidance	1		9	10	Australia	4
Future SAP will follow guidelines	1	4	3	8	USA	4
Discussion of statistical methods	2	2	2	6	Canada	3
Justification for a SAP element	1	3	2	6	Netherlands	2
Other guideline development	1	1	2	4	unknown	2
Other		1	2	3	Saudi Arabia	1
Application outside RCT		2		2	China	1
Data sharing methods		1		1	Chile	1
Cross referencing guidelines			1	1	Italy	1
Grand Total	19	30	60	109*	Finland	1
					Germany	1


15 citations excluded (7 duplicates, 4 awaiting access, 1 citation could not be confirmed, 3 editorial /letters associated with the original publication)

Analysis

“Subgroup analyses in randomised controlled trials frequently categorise continuous subgroup information”
(Faye Williamson et al, submitted)



**Ensuring clinical trials answer the questions of interest:
Implementation of the estimand framework**



28th April 2022, 9.30-12.30, Online meeting
What are estimands and why should we be using them?

Want to know what an estimand is? What an intercurrent event is? The principles of the estimand framework and why we should be following this?

29th April 2022, 9.30-13.45, Online workshop
How to implement the estimand framework

Also want to learn how to apply the estimand framework through case studies?



Reporting and sharing findings

- CONSORT-PRO
- CONSORT-Adaptive Design
- CONSORT- and SPIRIT-Surrogate
- SPIRIT-Routine

- Tool to assess outcome reporting bias, <http://www.outcome-reporting-bias.org/>

- Data sharing guidance

- Recommendations for sharing qualitative data in trials

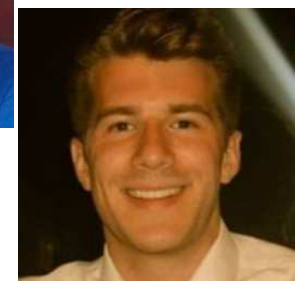
Global Health project awards

- **Sylvia Nalubega**, Soroti University, Uganda: *The practice of pilot studies in informing the conduct of HIV clinical trials in sub Saharan Africa: a review of study protocols*
- **Naomi Waithira**, MORU Tropical Health Network, University of Oxford, UK: *Exploring barriers to data reuse*
- **Nandi Siegfried**, MRC Alcohol, Tobacco and Other Drug Research Unit, South Africa: *Cultural competence in trial design and conduct*
- **Mercy Chepkirui Terer**, KEMRI-Wellcome Trust Research Programme, Kenya: *Pilot implementation of Short Message Service for randomisation in a multisite pragmatic factorial clinical trial in Kenya (PRISMS Study)*



Global Health project awards

- **Sangeetha Paramasivan**, University of Bristol, UK: *Optimising Informed CONsent in clinical trials in low- and middle-income settings: feasibility of an adapted QuinteT Recruitment Intervention (QRI) in India (OrION-I)*
- **Wigilya Mikomangwa**, Muhimbili University of Health and Allied Sciences, Tanzania: *Assessment of the challenges encountered in implementing vaccine clinical trial methodologies in low income countries*
- **David Musoke and James O'Donovan**, Makerere University, Uganda: *Photovoice to explore community members perspectives regarding health and healthcare challenges in Mukono District, Uganda*



MRC Doctoral Training Programme in Trials Methodology, 2021-2028



Statistics

Computer science

Data science

Health informatics

Health economics

Psychology

Social science

Behavioural science

Bioethics

International Clinical Trials Methodology Conference



ICTMC
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Harrogate, UK
5 - 6 October

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THE TRIALS METHODS RESEARCH AGENDA: A PRIORITY SETTING EXERCISE, 2022

Inviting input from:

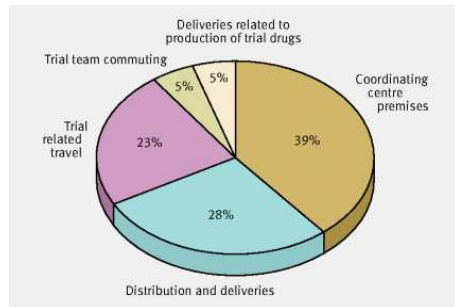
- members of the public
- patients
- researchers involved in clinical trials and/or trials methodology research
- clinicians and health professionals
- funders
- research ethics organisations
- those involved in the conduct of clinical trials (including investigators, research nurses, trials operations staff, statisticians, health economists, clinical trial pharmacists, regulators)
- editorial board members of journals that publish clinical trial protocols, clinical trials results and trials-relevant methodology

Collaborating countries:

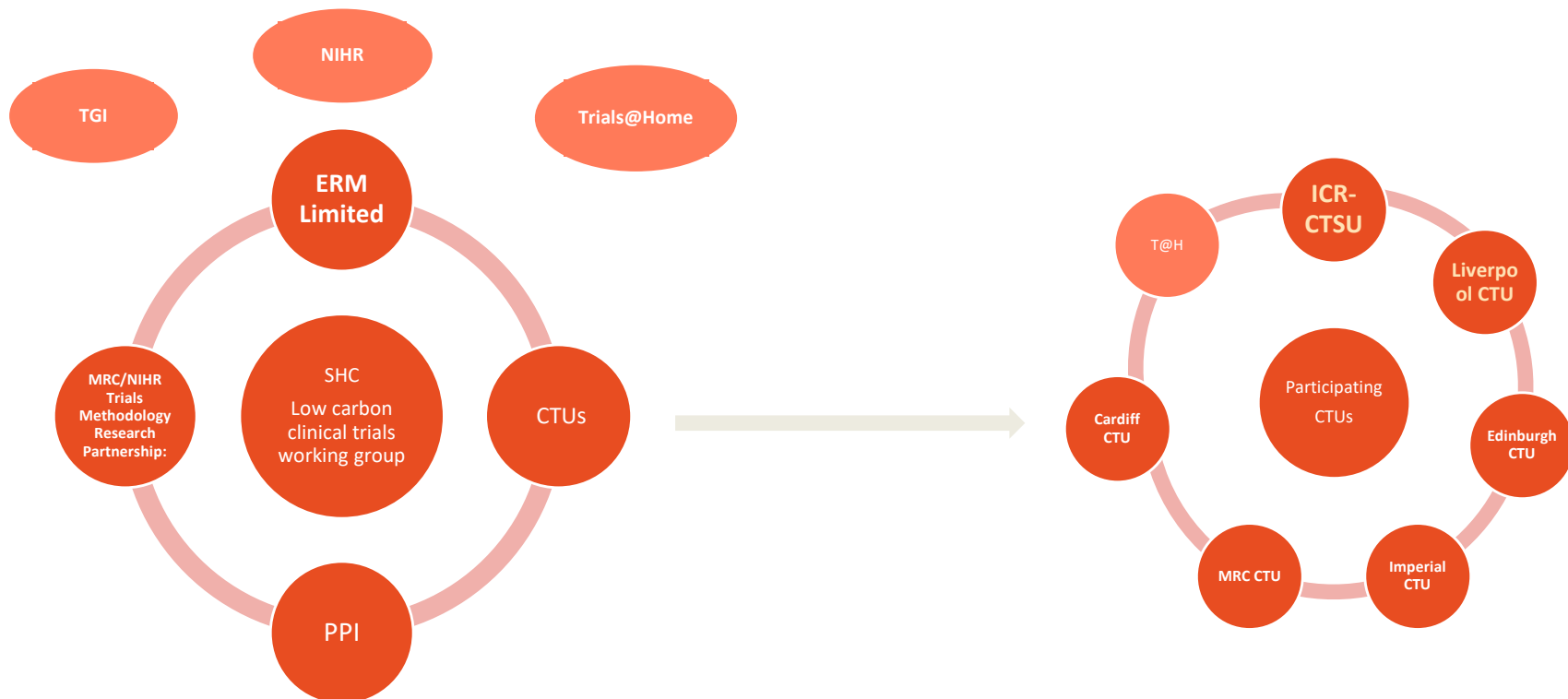
UK
IRELAND
SWITZERLAND
FRANCE
AUSTRALIA

Contact:
sinead.holden@ucd.ie

Enabling lower carbon clinical trials: *Development and prototype testing of a method to quantify the carbon footprint of current clinical trials to inform future lower carbon clinical trial design*



Proportions of greenhouse gas emissions in CRASH Trial Case study
BMJ 2007;334:671



TMRP – the future

- Partner organisations and Working Group Co-Leads
- Funding:
 - TMRP Coordinator
 - DTP 2021-2028
 - Re-investment from ICTMC 2022



- Strengthening collaborations with: international organisations, Patient Research Partners, industry
- Future funding applications – for TMRP and for specific projects
- ICTMC 2024 😊
- Delivering impact of work to date

Impact of/KT for methods research

- *What's been the most impactful methods research or guidance you are aware of, and why?*
- What do we mean by 'impact'?
- Who or what do we want to be 'impacted'?
- Is there a translational gap?
- How can we achieve impact?
- How can we demonstrate impact?