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=2tOpaxnJT FK
Trials methodology: a community approach

Professor Paula Williamson
University of Liverpool
Lead, TMRP
Improving health by improving trials
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:
+ 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
Guidance pack

Our overarching aim is Improving Health by Improving Trials. Since its inception in 2009, the HTM5 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

Rheumatoid Arthritis: Consensus Decision Models for Biologics in Rheumatoid and Psoriatic Arthritis: Recommendations of a Multidisciplinary Working Party

Trial Steering Committee: 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-STAR and COS-STAP: Core Outcome Set-STDAnds for Reporting, Core Outcome Set-STDAnds for Development and Core Outcome Set - STDAndised Protocol items

RoB 2.0: Revised Cochrane Risk of Bias tool 2.0 for randomised trials.

ORRCA and ORRCA II: Online Resource for Recruitment Research in Clinical Trials

SOS: Search for Oversight Statistics

SAPA: Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

BMTEd: Biomarker-guided trial designs

Internal pilot studies: developing progression criteria

Pilot and feasibility studies: when to do an internal or external pilot

MEPSEX: Interim evaluation of evidence on mechanisms of informed consent

HEAP: Health economic analysis plans

MIDIRUM (DIRUM): Care Items for a Standardised Reasons 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.
Planning – stratified medicine

**BiGTeD**
Biomarker-guided trial designs (BiGTeD):
An online tool to help develop personalized 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 using a biomarker’s clinical utility, including those used in phase I and phase II 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:

- 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
Planning – adaptive designs

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 Jaki⁵,⁶, 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 Maier¹¹,¹³, Helen Hancock¹¹,¹³ and James M. S. Wason¹¹

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
Conduct – recruitment and retention research
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
“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”
### Citation Analysis for JAMA article

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

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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/](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 2022

6th International Clinical Trials Methodology Conference
Narrogate, UK
3 - 6 October

Register Now!

E: ICTMC@in-conference.org.uk
T: +44 (0) 131 336 4203
W: www.ICTMC.org
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

Contact:
sinead.holden@ucd.ie

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?