

MRC

Hubs for Trials  
Methodology Research

MRC

Biostatistics Unit

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# The MRC Hubs for Trials Methodology Research Network

[www.methodologyhubs.mrc.ac.uk](http://www.methodologyhubs.mrc.ac.uk)



James Wason, MRC Biostatistics Unit

# Overview

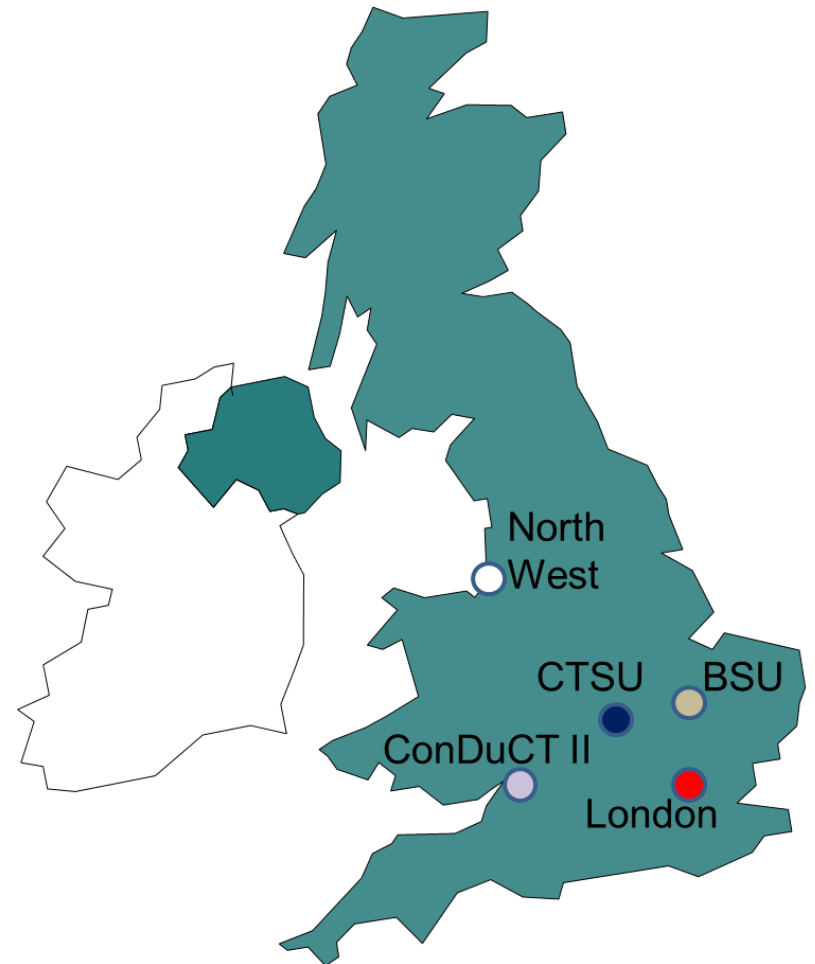
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1. Background to the HTMR network.
2. Some example projects.
3. Current interactions with NIHR statistics group.
4. Ideas for the future (discussion).

# History of the HTMR network

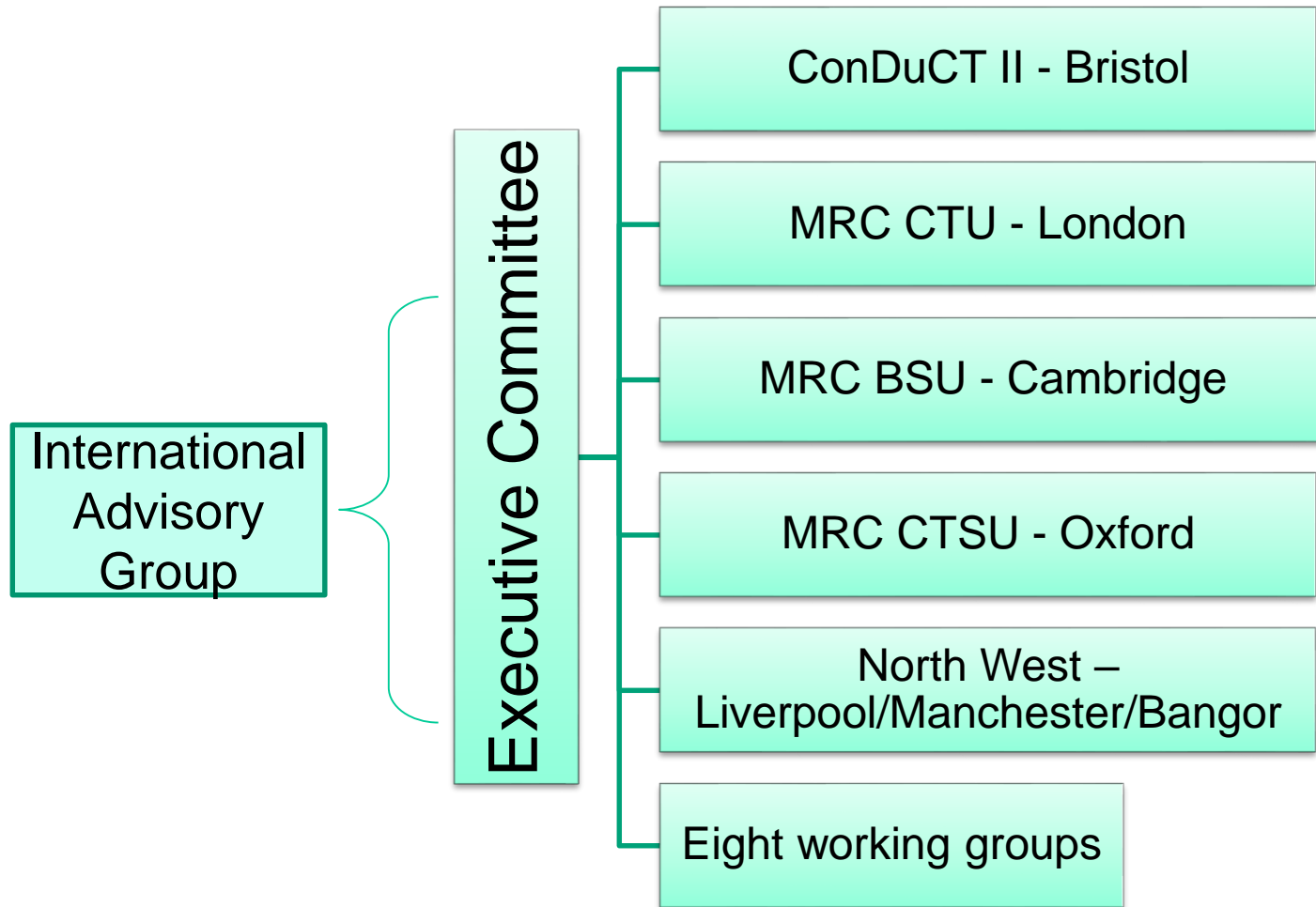
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- Started as a MRC-NIHR partnership in 2008 to develop a national platform for trials methodology research.
- Eight regional hubs were funded through a £12 million investment from the MRC.
- The network itself was funded with a £1.25 million grant.
- In 2014 the network was renewed for an additional five years, with five hubs forming the network.



# The HTMR Network today

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# Project funding



- Small investment projects
- Workshops
- Guidance
- Training

# Some examples of funded projects

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- Development of user-friendly web-based software for conducting Bayesian Phase I dose-escalation studies.
- Online tool for guidance on designing biomarker-guided randomised controlled trials.
- Clinical trials in small populations: methodological challenges and solutions.
- Development of guidance for statistical analysis plans for clinical trials.
- Full list on (together with final reports/publications): [www.methodologyhubs.mrc.ac.uk/research/network-projects](http://www.methodologyhubs.mrc.ac.uk/research/network-projects)

# Guidance on methodology

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**CONSORT PRO:** Patient-Reported Outcomes

**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

**NEW: Qualitative research:** Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers

**NEW: Surgical trials:** Interventions in randomised controlled trials in surgery: issues to consider during trial design

**NEW: SWATs:** Online database for Studies Within A Trial (SWAT) and Studies Within A Review (SWAR)

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

**NEW: Trial Steering Committees:** Exploring the role and function of trial steering committees: results of an expert panel meeting.

**NEW: Why not to use A+B design:** A discussion of appropriate design for phase I dose escalation studies.

A list of some external resources of use to trialists can be found [here](#).

# Webinars

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Methodology Research

## Resources

[Training Courses](#)[Workshops and events](#)[Webinars](#)[Webinars 2014](#)[Webinars 2015](#)[Guidance pack](#)[Publications](#)[Working Groups](#)[Jobs](#)[Studies Within a Trial](#)[Trials Change Lives](#)[External resource sites](#)[Home](#) / [Resources](#) / [Webinars](#)

## Trial Conduct Webinars 2016

The Trials Conduct Working Group host regular webinar talks on topics pertinent to their research. You can access recordings of previous websites through the links below.

### Next webinar

11 May 2016

"You have to keep your nerve on a DMC." Challenges for Data Monitoring Committees in neonatal intensive care trials: qualitative accounts from the BRACELET Study

Dr Claire Snowdon, Lecturer at the Department of Medical Statistics, London School of Hygiene & Tropical Medicine

Register to hear live. Or visit us later to listen to the recording.

### Recordings 2016

11 February 2016 'Clinical trials safety and regulation: application of risk-based methodological approaches'. Christina Reith, Clinical Research Fellow, CTSU, University of Oxford

### Older webinars

[2015](#)[2014](#)[Guidance](#)[Workshops](#)[Webinars](#)[Working Groups](#)[Publications](#)



# Methodology Advisory Service for trials (MAST)

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## Network advice on trials methodology

The individual Hubs for Trials Methodology Research provide extensive support and advice to researchers with questions about the use of non-standard methods in trials, both individually and collectively through the Network and its Working Groups. The Hubs also help colleagues in Clinical Trials Units and the Research Design Service when they receive enquiries, and the Network itself can act as a clearing house for queries that cannot be resolved by an individual Hub.

The Methodology Advisory Service for Trials (MAST) provides additional support to colleagues based in a Clinical Trials Unit or Research Design Service with non-standard methods queries who are unsure about which Hub to approach for advice. In these cases please feel free to contact the Network directly and we will connect you to one of our team. You should send an email to us at [enquiries@methodologyhubs.mrc.ac.uk](mailto:enquiries@methodologyhubs.mrc.ac.uk) including:

- Your name, email address and telephone number
- The name of your Clinical Trials Unit or Research Design Service
- The nature and context of your query
- The name and current status of the relevant trial

Researchers or principal investigators who wish to avail of this Network service should first approach their local Hub, Clinical Trials Unit or Research Design Service, if known. The links at the bottom of this page will help you to find the one closest to you.

### What advice can we offer?

The Hubs and the Network support researchers, statisticians and other methodologists in the 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 (Study Within A Trial) to help resolve uncertainties.

Useful links:

- [About the HTMR Network](#)
- [UKCRC CTU Network](#)
- [NIHR Research Design Service](#)

# Capacity Building

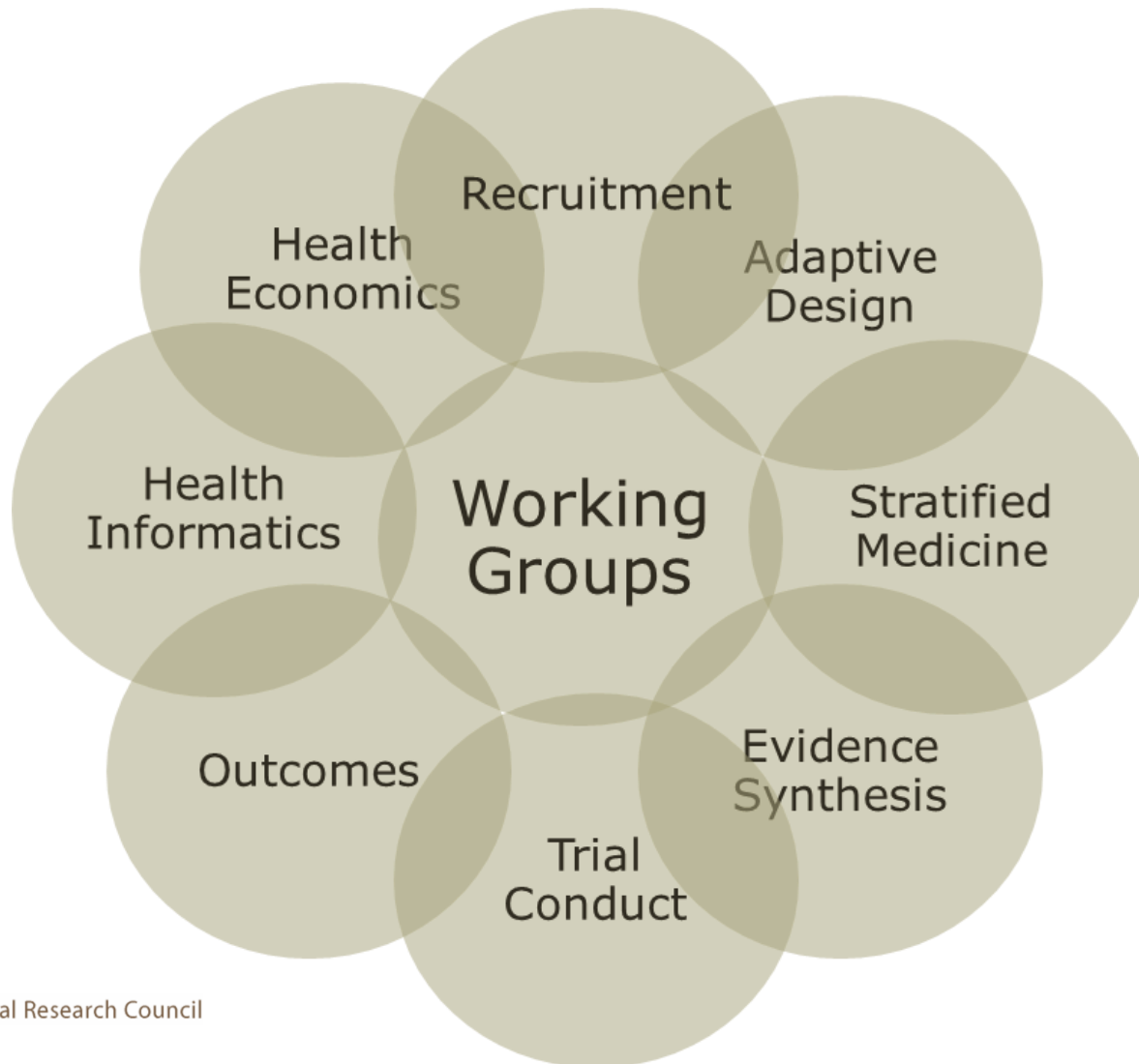
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- Doctoral students
- Training workshops
- Conferences



# Working Groups include HTMR members & others

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# Some current statistical focuses

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- Stratified/personalised/precision medicine
- Platform trials
- Adaptive designs

# BiGTed (**B**iomarker **G**uided **T**rial **D**esigns)

– [www.bigted.org](http://www.bigted.org)

- User-friendly online tool to inform on different trial designs.
- Easy to navigate graphical display to aid understanding and planning.
- Based on extensive literature reviews<sup>1,2</sup>.
- Final version launch later this year.

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

### Outcome-based adaptive randomization design

In the context of personalized medicine, this design is used when the biomarkers are only putative or not known at the beginning of a Phase II trial and is also useful when there are multiple targeted treatments and biomarkers to be considered. It aims to test simultaneously both biomarkers and treatments while providing more patients with effective therapies according to their biomarker profiles. Outcome-adaptive randomization is sometimes included under the umbrella of "Bayesian clinical trials" but as criticized by Korn and Freidlin (2011), there is nothing inherently Bayesian about it.

**Alternative names:** Adaptive randomization, Bayesian Adaptive, Bayesian Adaptive randomization, Combined dynamic multi-arm, Outcome-Adaptive randomization, Outcome-based Bayesian Adaptive Randomization

**Adaptations:** Change in randomization ratio

**Variations:** i) Bayesian covariate adjusted response-adaptive randomization

**Methodology**

**Statistical/Practical considerations**

**Key references**

BIGTED is funded by the Medical Research Council

To find out more please contact us by E-Mailing

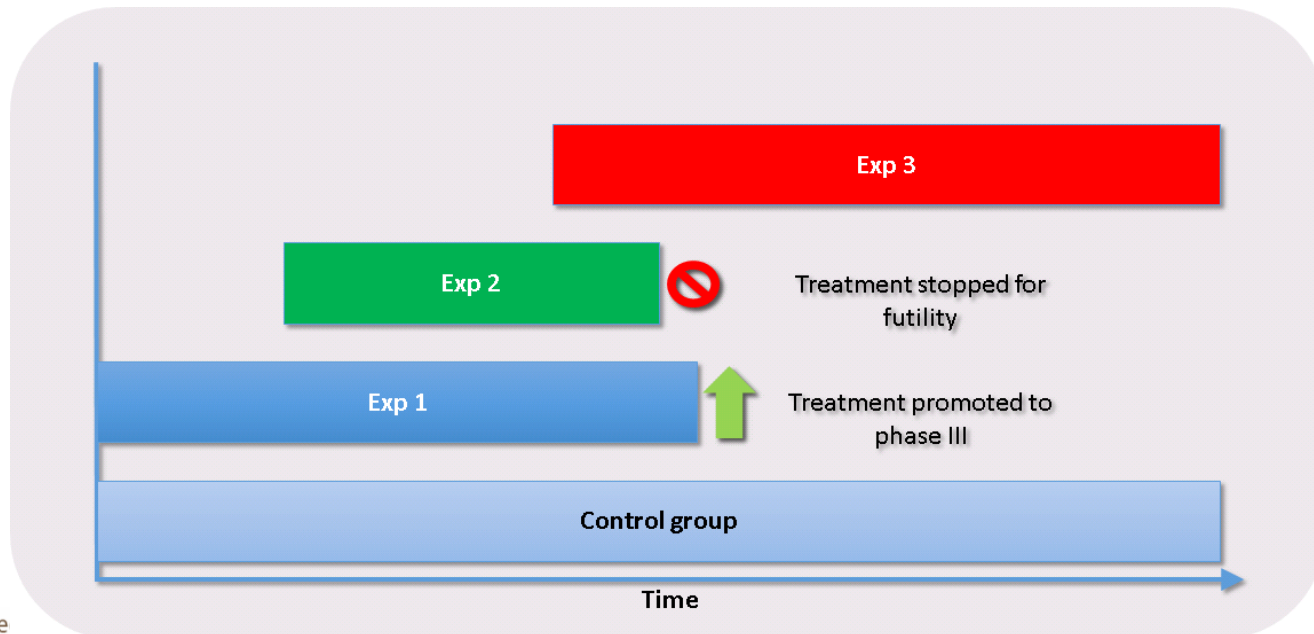
- Miranta Antoniou
- Andrea Jorgensen
- Ruwanthi Kolumunnage-Dona

**MRC** Medical Research Council

1. Antoniou M, Jorgensen AL, Kolumunnage-Dona R. Biomarker-Guided Adaptive Trial Designs in Phase II and Phase III: A Methodological Review. PLoS ONE. 2016;11(2).
2. Antoniou M, Kolumunnage-Dona R, Jorgensen AL. Biomarker-Guided Non-Adaptive Trial Designs in Phase II and Phase III: A methodological Review. J.Pers.Med. 2017; 7(1), 1.

# Perpetual platform trials

- **Perpetual platform trials** can continue adding in new treatments and biomarkers as they become available.
- Initial funding application can be done to test available treatments.
- New funding applications can be made to add new targeted treatments and linked biomarkers in.



# Adaptive designs

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- Adaptive designs have a lot of potential to improve efficiency of trials.
- However they are complicated and many more methodological approaches available than have actually been used in practice.
- The HTMR network has part-funded an ‘adaptive designs outreach officer’, Philip Pallmann (p.pallmann@lancaster.ac.uk).
- Aim of this role is to help encourage the use of suitable adaptive trial approaches.

# Some current interactions

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- In 2014 a meeting on early phase dose-finding trials was held, organised by Simon Bond.
- Since then considerable interaction between NIHR Statistics group early phase group and HTMR adaptive designs working group.
- Will hear more about this in Simon's talk later on.



# Some current interactions

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- ACE project to develop CONSORT extension for adaptive designs reporting.
- Led by Munya Dimairo (Sheffield).
- Funded by NIHR CTU support scheme and MRC HTMR.

# Potential for more interactions with NIHR Statistics group?

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- More contact between relevant subgroups?
- New groups to address challenges in trials?
- Joint events?

# More general questions (to you)

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- How can methodologists better work with NIHR statisticians?
  - to motivate new methodological work
  - to help support use of new methods in practice
- What about other (non-trials) methodology work?
- How to encourage applied statisticians to get involved in more methodology work?