MRC-NIHR Trials Methodology Research Partnership: Webinar recording

Data Integrity

*Presented by Liz Allen (Cape Town University), Philip Pallman (Cardiff University), Munya Dimairo (University of Sheffield), Alex Dmitrienko (Mediana)*

27 September 2022

On behalf of The Global Health Network

The slides are also available below.

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

https://www.youtube.com/watch?v=bfw9dzwC1HU
TMRP Webinar Series 5
The Global Health Network

Tools and resources for adaptive designs in clinical trials
Tuesday 27 September 2022
The Trials Methodology Research Partnership

- A global community of practice for improving the design, conduct, & analysis of trials everywhere
- The Global Health Working Group raises awareness of trials methodology research, signposting to technical working groups & training, facilitating collaborations & small methodology research grants for LMIC
- The Global Health Network joined the MRC-NIHR Trials Methodology Research Partnership to offer a gateway for researchers in LMICs to better contribute to & benefit from developments in this field
The practice of pilot/feasibility studies in informing the conduct of HIV related trials in sub-Saharan Africa: a scoping review

Sylvia Nalubega, Lawrence Obado Osuaw, Poku Brenda Agyeiwaa, John Bosco Matovu Junior
The Global Health Network enables easier, faster, and better research in the world’s most challenging settings.

Knowledge Sharing Hubs
Transferring knowledge and exchanging methods, processes and research findings between diseases, regions and organisations.

Capacity Development and Process Improvement
Regional and online training, resources and professional development to build skills and careers that deliver evidence to change practice.
Proud partner of the TMRP

Global Health Methodology Research

1. Photovoice to explore community members perspectives regarding health

PI: James O'Donovan and David Musoke, Makerere University School of Public Health

There have been calls for a greater number of clinical studies in low- and middle-income countries, ensuring they are contextually relevant. One useful approach towards this is Community Based Participatory Research (CBPR), which involves local stakeholders being central to the research process. CBPR is often research remains contextually relevant and better understand the lived experiences of individuals, suggesting it as a means of diversifying participation and increasing relevance at the local level. This method, aligned to CBPR, is photovoice, whereby cameras are given to individuals to document their lived experiences. In our project, the subject of interest is community health in the use of cameras and have undergone one round of photographic capture.

Conclusion

- The TMRP has contributed to equity in where research happens & who benefits.
- Any trial team member can explore optimal methods whatever their role
- Being part of this community can help with developing skills needed to answer questions about the way you design, operationalise, analyse & report your trials
- Including patients & participants in finding new & better trials methods is key
- Funders should consider investing in methods research within or alongside trials as a cost-effective way to sustain sites while improving the science of trials.
- It is also an excellent career development opportunity for early career researchers
- All diseases need an ecosystem of different types of research
- Each study requires a cycle of steps for accurate, safe & ethical data
- Findings should then be taken up into practice and policy

Steps & processes do not differ between diseases/type of research
Need to address gaps in evidence & tackle research inequity by sharing knowledge & know-how between diseases, organisations & settings
And embed research in every healthcare setting
A network of digital & physical spaces

A powerful mechanism for exchanging know-how & mobilising information

Research capacity development & knowledge exchange delivered through overlapping & interconnected focus areas

Not duplicating, but connecting excellence
Vast space for research organisations & networks to come together with research teams, health workers & policy makers

Research skills training, career development & knowledge mobilisation

- Online learning
- Webinars & workshops
- Regional capacity building programmes
- Resources & toolkits
- Process mapping
- Education & tacit learning
- Professional Development for researchers
- Essential Curriculum for health research

*Over 3 million courses taken*
*100,000’s documents shared*

Standards raised by providing access to tools, methods and how-to

*Delivering equity to access to knowledge*

Embedded with research capacity building mechanisms to develop lasting capable teams

Over 60 knowledge Hub exchanging how-to between diseases, regions & teams

This works as the barriers don’t differ
Communities of practice building lasting capable research teams
Myriad types of resources

- Courses = Training, strengthen skills base
- Webinars = Deliver, debate & share, lessons learnt, wider dissemination
- Project materials = Download, modify & re-use
- Apps & toolkits = Adapt & replicate
Certified open access eLearning:
130+ courses with 80+ translations

- Many different collaborators
- Open access, globally applicable
- Peer reviewed, regularly updated
- Certificate issued > 80% in quizzes
- > 500,000 people taken courses
Sharing expertise through webinars

**Workshops**

Workshops are a valuable and engaging way to learn, providing a fantastic opportunity for collective training sessions, skills transfer, networking and information sharing.

The range of workshops and format for delivering these sessions can be creatively designed to best serve the context of the learning, initiatives such as these help to support and strengthen capacity at both an individual and institutional level. We set-up and facilitate a wide range of practical workshops in close collaboration with coordinators and study teams in diverse settings. Please do review the variety of workshops hosted across the regions that cover a breadth of topics, which have generated rich outputs from these sessions to benefit researchers globally.

**AFRICA**

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**Workshop Details**

- **Migrant Communities and the COVID-19 Pandemic: Ethical considerations**
  - Mon 6th Jan 11:00-12:00pm (BST)
  - During the COVID-19 pandemic, migrants have often been denied rights and placed in situations which put them at heightened risk of disease. This webinar looks at migrant communities' explicit and implicit...

- **Richard T Johnson Lecture | Neurologic morbidity from pediatric cerebral malaria—Looking Beyond the Body Count**
  - Tue 14th Jan 3:00-4:00pm (BST)
  - Neurological infectious diseases pose some of the greatest challenges to clinicians. The presenting clinical syndromes are often elusive, determining the causative organism can be problematic, and th...

- **Indigenous communities, ‘vulnerability’, and the COVID-19 pandemic**
  - Mon 20th Jan 1:00-2:00pm (BST)
  - Indigenous populations around the world have historically experienced—and continue to experience—both social and economic marginalisation, and as a result are at disproportionate risk during public...

- **Introduction to Research for nurses and midwives**
  - Thu 23rd Jan 12:00-1:00pm (BST)
  - Global Research Nurses mentor is to empower nurses and midwives to get involved in research, no matter where they work or the role they undertake. This webinar will inspire you to get started in research...

- **Global Brain Health Clinical Exchange Platform – Critical Care of the Neurologic System in COVID-19**
  - Fri 24th Jan 3:00-4:00pm (BST)
  - In this interactive workshop, Dr. Ayesha Batra will cover critical care of the neurologic system during acute COVID-19. Cerebrovascular and infectious disease, the role of neurointervention, and th...

- **Communicating Science to Facilitate the Uptake of Research Findings into Policy and Practice**
  - Thu 30th Jan 1:00-2:00pm (BST)
  - Part 2: How to write a policy brief. Speaker: Dr. Sohina Shafique. A stakeholder mapping exercise conducted in March 2020 by the Applying Research to Policy and Practice for Health (ARPH) programme at th...
Supporting career development

- Professional Development Scheme (PDS) created by The Global Health Network & WHO-TDR
- Records, tracks and guides professional development using *core competencies*
- Can aggregate data across teams = track and measure development over time
Increasing findability & attributing effort

Resources

Resources actively guide, teach and train researchers in setting up and running high-quality studies

A range of resources exist to truly provide active and detailed support for implementing health research studies. This includes the provision of openly accessible study documentation presented in study profiles, which can be downloaded and adapted to suit various study designs and settings. Structured guidance is available through the process map to methodically walk researchers through the various steps in the design and operational set-up of a study. Free elearning courses afford the opportunity to engage in wider skills-based training, including the fundamental basics, and more specialist modules.

Study Profiles  Process Map  eLearning Courses
Methodology research: mixed methods → data from 7000+ individuals in 153 countries

Understanding the barriers and enablers to the implementation of clinical trial conduct in Ethiopia, Cameroon and Sri Lanka

Using The Global Health Network Community and Data to Assess Capacity for Regulatory Standard Clinical Research in LMICs

The Global Health Network
February 2018
Clinical trials: foundational & core, need to be informative

• Program to help B&MGF grantees optimise studies for informativeness & impact
• Evidence-based catalogue of best practices, open-source simulation software, & other tools
• Now publicly available, translatable across trials, implementation research

The DAC Assessment Tool (DAT)

The DAT is a questionnaire which may be used or completed by the study PI and her/his team covering design, analyze, and communicate topics important to consider when designing informative studies. While not all points are relevant to all studies, in general they are intended to promote sound and proven scientific methodology combined with the use of recent innovations in trial design.

For example, in addition to supporting PI teams as they plan their study, fully completed DATs can serve as diagnostic guides to help study stakeholders assess whether a proposed study is likely to provide definitive answers and lead to implementable results. Completed DATs help identify gaps in study planning that need to be addressed with:

Clinical Trial Simulation

Efficient power and sample size calculations for late-phase clinical trials.

Target Policy Profile Overview

A tool to facilitate dialogue around evidence needed to effect a change in policy.

TARGET POLICY PROFILE TEMPLATE - AVAILABLE IN 6 LANGUAGES
The next five years

1. Shift leadership to the Global South through three regional leadership centres
2. Take mechanisms for knowledge mobilisation, capacity building & connecting excellence to scale with out partners
3. Support the whole ecosystem for health research: embedding research everywhere

WHO Collaborating Center for research information sharing, e-learning and capacity development
Thank you!

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TGHN Strategic Partnerships Lead
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www.methodologyhubs.mrc.ac.uk
https://tghn.org/
https://dac-trials.tghn.org/
Work with stakeholders

Link with trialists, methodologists, medical professionals, patients, academics, industry, regulators, funders, publishers

Methodology

Statistical methods development
Software development
Applied trials research

Implementation

Tutorial and guidance papers
Educational resources
Conference sessions and webinars
CTU visits and collaborations

MRC-NIHR TMRP
Adaptive Designs Working Group

Outreach project

Selected current projects:
- sample size simulation
- patient information sheets
- estimands
- bias-adjusted point and confidence intervals estimation
- early phase reporting guidance

>30 active members from across the UK and Ireland
Find out more

http://www.methodologyhubs.mrc.ac.uk/about/working-groups/

Get in touch

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PANDA: A Practical Adaptive & Novel Designs and Analysis toolkit

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On behalf of PANDA team: Philip Pallmann, Graham Wheeler, Thomas Jaki, Mike Bradburn, Laura Flight, and Cindy Cooper

TMRP series - Global Health/Adaptive Designs Working Groups, 27th Sept 2022

https://panda.shef.ac.uk/
Funding declaration and disclaimer

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The views or opinions expressed during this talk are mine and do not necessarily reflect those of the National Health Service (NHS), the National Institute for Health Research (NIHR), or the Department of Health and Social Care.

https://panda.shef.ac.uk/
Outline

• Brief background and the birth of PANDA
• Intended purpose and target audience
• PANDA platform features
• Wishes and the future
• Take a few questions

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Where we are coming from …

• Adaptive designs can be very efficient when used appropriately

• Their use in practice is steadily increasing

• Lack of practical knowledge among diverse stakeholders is still a persisting barrier

• A lot is being done and things are improving … but more still needs to be done!

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Back then … and the birth of PANDA

- Very limited practical training on adaptive designs
- Face-to-face tends to be expensive and inconvenient
- Training tends to target statisticians; other key stakeholders are left behind (clinicians, trial managers, proposal developers, etc)
- Extra burden on leading statisticians to educate trial teams throughout the trial cycle

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Purpose of PANDA and target audience

- To bridge the practical knowledge gap in adaptive trial designs
- Offers self-paced practical learning
- Easily accessible to anyone involved in clinical trials research interested in learning about issues around adaptive trials
- Less technical language
- One-stop shop repository (e.g., guidance on specific topics)

PANADA

https://panda.shef.ac.uk/
Accessing PANDA: [https://panda.shef.ac.uk/](https://panda.shef.ac.uk/)

- Linear structure
- Linked content
- Easy of navigation and to find content
- Defined technical terms
- Key references for further reading
- Link to related resources (e.g., Mediana)
I want to learn about an adaptive design...

In an adaptive clinical trial design (see Figure 2), researchers start from the same place by making assumptions on design parameters. However, they can't stick by these assumptions rigidly, as long as they are aware of the uncertainties around these assumptions. This allows them to have flexibility to make necessary changes to parts of the trial once they gain more knowledge over the course of the study. These changes are informed by what they learn from outcome data or information gathered from a group of patients already recruited as the trial progresses (interim data).

Thus, there are potentially multiple paths the trial can take depending on what the emerging data are telling them. Similar to driving a car with your eyes open using real-time travel information available to you (e.g., road signs and traffic navigation system) — you stuck at a red traffic light, take the quickest route to reach your destination, change the route when there is a diversion on the current route, or abandon your journey when all routes are blocked.

It's important to note that researchers do not make things up as they go along! While flexibility has advantages, unplanned changes impact on both the validity of statistical inference and the practicalities of doing the trial and may undermine the credibility of the results. This type of change, trial adaptations, and the criteria for making them need to be considered in advance. Changing a trial part-way through needs thought. More specifically, the criteria and timing of possible adaptations are decided at the design stage and specified in trial documents (e.g., the trial protocol and statistical analysis plans). Researchers should not compromise the scientific rigor in running the trial to produce reliable and valid results to influence practice.

In summary, the overall goal of an adaptive design is to address research questions that are relevant to clinical practice quickly and efficiently, while balancing ethical and scientific interests.

Figure 2.
I want to learn about general considerations ...

- Specific topic (e.g., data management, costing in grant applications,
- Reporting guidance
- Resources (tutorial papers, easy-to-read books, etc)

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I want to learn more about a specific adaptive design ...

- Motivation
- When is it appropriate
- Design concept
- Statistical methods
- Case studies
- Statistical software
- etc

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Show me how to do it …

• Snippets of statistical code

https://panda.shef.ac.uk/
Easy access to statistical implementation resources

https://panda.shef.ac.uk/
Search facility

- Subject of interest
- In specific sections or topics
- Tag specific

https://panda.shef.ac.uk/
Wishes and the future

- It is a community resource
- Work in progress (videos, content, … )
- Help us to improve the content in PANDA
  - Feedback
  - Practical related content (e.g., lessons learned from implementing adaptive trials)
- The field is growing so we need to keep PANDA up to date
  - Content relating to new adaptive designs (e.g., adaptive platform designs, etc)
- Can this be expanded to early phase trials?

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Acknowledgements

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• Andrew Tattersall for video content
• Platform developers (epiGenesys)
• ADWG
• Many people who have contributed in several ways

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Open-access clinical trial simulation software

Alex Dmitrienko | Sep 27, 2022
Outline

• Clinical trial simulation
• Software tool
  • R package (MedianaDesigner package)
  • Power/sample size calculations for adaptive and other trials
  • Documentation and case studies
  • Online training
Clinical Trial Simulation
Clinical trial simulation

• Clinical trial simulation
  • Only reliable approach for designing modern trials with complex designs and analysis strategies
  • Simulation-based approaches free trial sponsors from artificial restrictions

• Clinical trial optimization
  • Facilitates a disciplined simulation-based evaluation of candidate trial designs to transition from traditionally used designs to optimal designs
  • *Clinical Trial Optimization Using R* (Edited by Dmitrienko and Pulkstenis, 2017)
Open-source software tools

• Mediana package
  • R package released in 2015 to streamline the process of designing clinical trials and general research studies
  • It has become very popular in the clinical trial and general research community (downloaded over 35,000 times)

• MedianaDesigner package
  • Extended Mediana to adaptive trial designs and other trial designs
Software Tool
Software tool

• Open-source software tool
  • R package (MedianaDesigner package)

• Power/sample size calculations
  • Support for simulation-based power/sample size calculations in late-stage trials, including a broad class of adaptive trials
  • User-friendly interface with emphasis on most commonly used features and design parameters
  • Efficient clinical trial simulation engine
Two deployment options

• Desktop deployment
  • Software tool is deployed as an R package (aimed at expert users with R programming experience)
  • Available on CRAN web site
    • https://cran.r-project.org/web/packages/MedianaDesigner/index.html

• Cloud deployment
  • Software tool is available as a web application running in the cloud (aimed at beginners and casual users)
  • Web applications available on Mediana’s cloud platform
    • https://cloud.mediana.us
Power/Sample Size Calculations
Supported trial designs

- Adaptive designs
  - Phase II (proof-of-concept) designs
    - Response-adaptive designs
  - Phase III (confirmatory) designs
    - Adaptive designs with sample size or event count re-estimation
    - Adaptive treatment selection designs
    - Adaptive population selection designs

- Related components
  - Optimal selection of a futility stopping rule
  - Blinded event prediction in event-driven trials
Supported trial designs

• Traditional designs
  • Traditional trials with multiple objectives
    • Support for all popular traditional multiplicity adjustments and advanced multiplicity adjustments (gatekeeping procedures)
  • Cluster-randomized trials
Documentation and Case Studies
Documentation

• Technical manuals
  • Detailed description of statistical methodology with examples
    • https://mediana.us/medianadesigner/

• Online user manual
  • Multiple case studies to help users come up to speed with the software tool
    • https://medianasoft.github.io/MedianaDesigner

• English and French versions
Online Training
Online training

• Ten-part training course
  • Adaptive designs and clinical trial simulation
  • Available on Mediana’s YouTube channel
    • https://medianasoft.github.io/AdaptiveDesignTraining

• Introductory modules
  • First two videos (Parts 1 and 2) are aimed at a broad audience

• Technical modules
  • Remaining videos (Parts 3 through 10) are more technical and assume a statistical background
Online training

• Adaptive designs
  • Phase II (proof-of-concept) designs: Response-adaptive designs
  • Phase III (confirmatory) designs: Designs with sample size re-estimation, treatment selection and population selection

• Methodology and case studies
  • Two videos for each class of adaptive designs
  • Underlying statistical methodology and regulatory considerations
  • Case study with a detailed software demonstration
Summary
Open-access software

• Software tool
  • Open-source software tool to facilitate power/sample size calculations for traditional and adaptive trials
  • Documentation, case studies and online training

• Feedback
  • Feedback and suggestions are welcome
    • https://github.com/medianasoft/MedianaDesigner/issues
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