



MRC-NIHR Trials Methodology Research Partnership: Webinar recording

## **Trials methodology for global health trials**

*Presented by Lesley-Ann Erasmus and Mercy Chepkirui*

11 April 2022

On behalf of The Global Health Network



The slides are also available below.

For any queries, please contact [uktmn@nottingham.ac.uk](mailto:uktmn@nottingham.ac.uk)

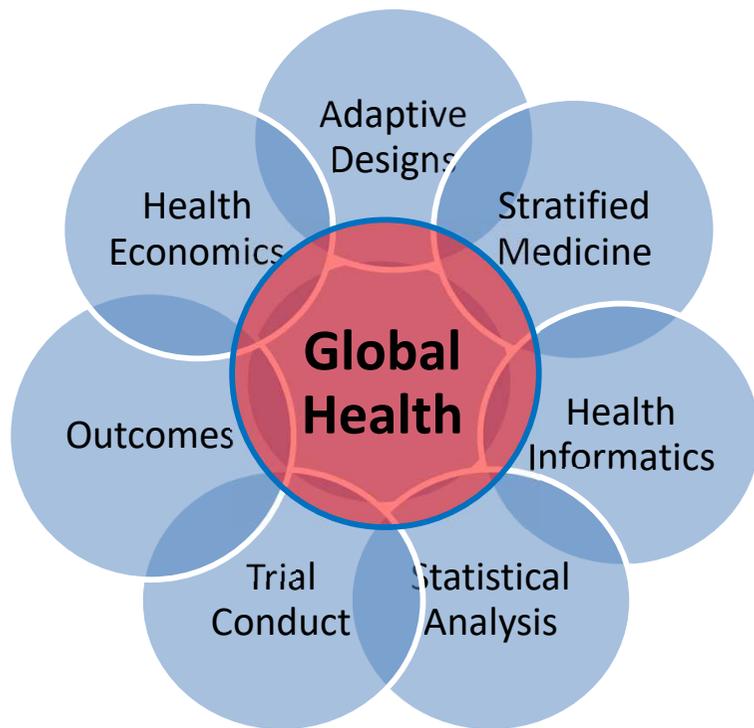
[https://www.youtube.com/watch?v=Wi0R2D\\_qpJQ](https://www.youtube.com/watch?v=Wi0R2D_qpJQ)

# 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





- Join any number of WGs & interact with a large, diverse membership
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[www.methodologyhubs.mrc.ac.uk](http://www.methodologyhubs.mrc.ac.uk)  
<https://globalresearchmethodstghn.org/>
- Hear about grant opportunities



Country	Title
Uganda	The practice of <b>pilot studies</b> in informing the conduct of HIV clinical trials in sub Saharan Africa: a review of study protocols
Kenya	Pilot implementation of <b>Short Message Service for randomisation</b> in a multisite pragmatic factorial clinical trial in Kenya (PRISMS Study)
Uganda	<b>Photovoice to explore community members perspectives</b> regarding health and healthcare challenges in Mukono District, Uganda
Tanzania	Assessment of the <b>challenges encountered in implementing vaccine clinical trial</b> methodologies in low income countries
UK/India	<b>Optimising Informed CONsent</b> in clinical trials in low- and middle-income settings: feasibility of an adapted QuinteT Recruitment Intervention (QRI) in India (OrION-I)
Thailand	Exploring <b>barriers to data reuse</b>
South Africa	<b>Cultural competence in trial design and conduct</b>

# The Global Health Network



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*Delivering equity to access to knowledge*  
*DOI numbers = recognition for sharing how-to*

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RAISING STANDARDS  
BRINGING EFFICIENCY

Member areas (58)

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This works as the barriers don't differ

A vast programme of in-person activities in the regions; connecting networks and teams

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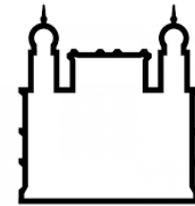
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3. Support the whole ecosystem for health research: embedding research everywhere

# Announcing The Global Health Network Conference 2022

Enabling Health Research in Every Healthcare Setting

*10 Years of addressing inequity in where research happens, who leads & who benefits.*

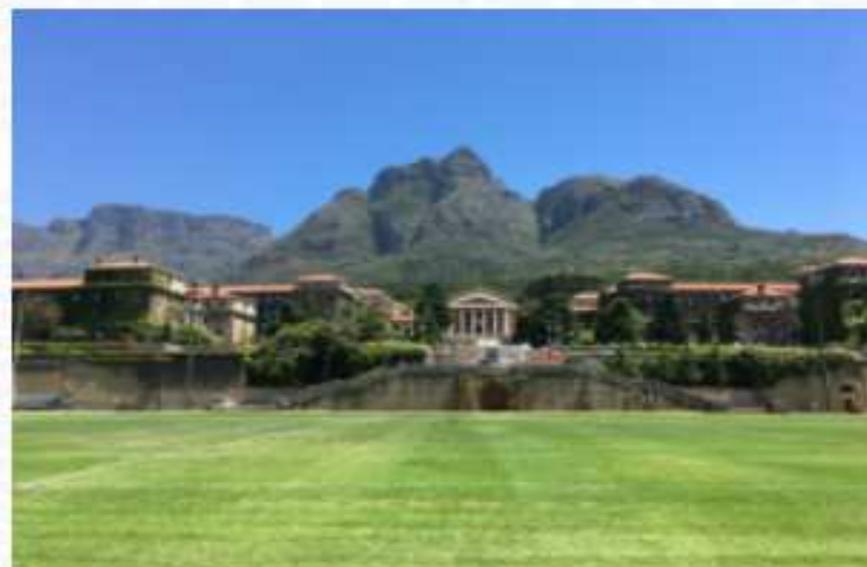
University of Cape Town, South Africa 24 – 25 November 2022

## Register your interest!

To tackle disease we need evidence to be generated through every type of health research study. This conference aims to bring together health research teams, organisations, health-workers, policy makers and practitioners to explore together how health research can be embedded into every healthcare setting.

The Global Health Network is also celebrating 10 years of mobilising research skills, know-how and methods to foster capable teams that generate new treatment strategies and prevention mechanisms that reduce the burden of disease within communities.

This is an opportunity to discover and share excellence in health research across disease areas, geographies and types of research and generate outputs that can be taken up and used by others.



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2. Pandemic preparedness through capacity development, knowledge sharing and stronger networks
3. Generating evidence from existing data and applying data science through data sharing and novel analytical approaches.
4. Engaging the community and building public trust in health research.
5. Developing research leadership, fostering team science and delivering evidence through equitable partnerships and networks.
6. Improving research processes and outputs by using digital technology, applying novel research methods and knowledge mobilisation.
7. Taking research findings into policy and practice through implementation, discoverability and connecting health research with public health.



# EVALUATION OF CULTURAL COMPETENCY IN AN AFRICAN SETTING: LESSONS LEARNED FOR TRIAL REPORTING STANDARDS

*Presenter:* Ms. Lesley-Ann Erasmus-Claassen (ATODRU)

Dr. Nandi Siegfried (PI)

Prof. Bronwyn Myers

Prof. Sally Hopewell

# BACKGROUND: CULTURAL COMPETENCY

- Cultural competence is a broad term used in trial design and conduct
- CC refers to the consideration of the cultural and linguistic diversity of a targeted populations
- By not considering relevant cultural, ethnic and diversity parameters during trial protocol development and trial conduct – recruitment, intervention development and delivery, adherence, and retention, might be negatively impacted and potentially reduce the overall internal validity of a study
- Lack of reporting of these parameters can further hamper the successful implementation of effective interventions post trial due to an inability for the reader to assess external validity (generalizability)

## BACKGROUND: GIBBS FRAMEWORK (2007)

Gibbs Framework Scoring	Reason
0	Culturally blind which describes methodological approaches underpinned by the belief that neither colour nor culture influence behaviour and that all people are the same
1	Culturally pre-competent describing approaches recognising that the dominant race or culture of a country is not universally applicable but fails to fully attend to cultural differences
2	Cultural competent describing approaches recognising the cultural diversity of the intended population
NM	Not Mentioned – if there was no reporting or no information provided relating to cultural competency considered

# BACKGROUND: GRIPP-2 (SF)

No	GRIPP-2SF Domain	GRIPP-2 questions
1	Aim	Is the aim of PPI reported in the study?
2	Methods	Is there a clear description of the methods used for PPI in the study?
3	Study results	Outcomes: Were the results of PPI in the study, including both positive and negative outcomes, reported?
4	Discussion and Conclusions	Outcomes: Did the investigators comment on the extent to which PPI influenced the study overall? Did they describe positive and negative effects?
5	Reflections/critical perspective	Did the investigators comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience?

PPI=patient and public involvement

- GRIPP2-Long Form and GRIPP2-Short Form are guidelines for the reporting of PPI in research
- The GRIPP-2(SF) is an abbreviated five-item checklist targeted to clinical trial reports

# AIM

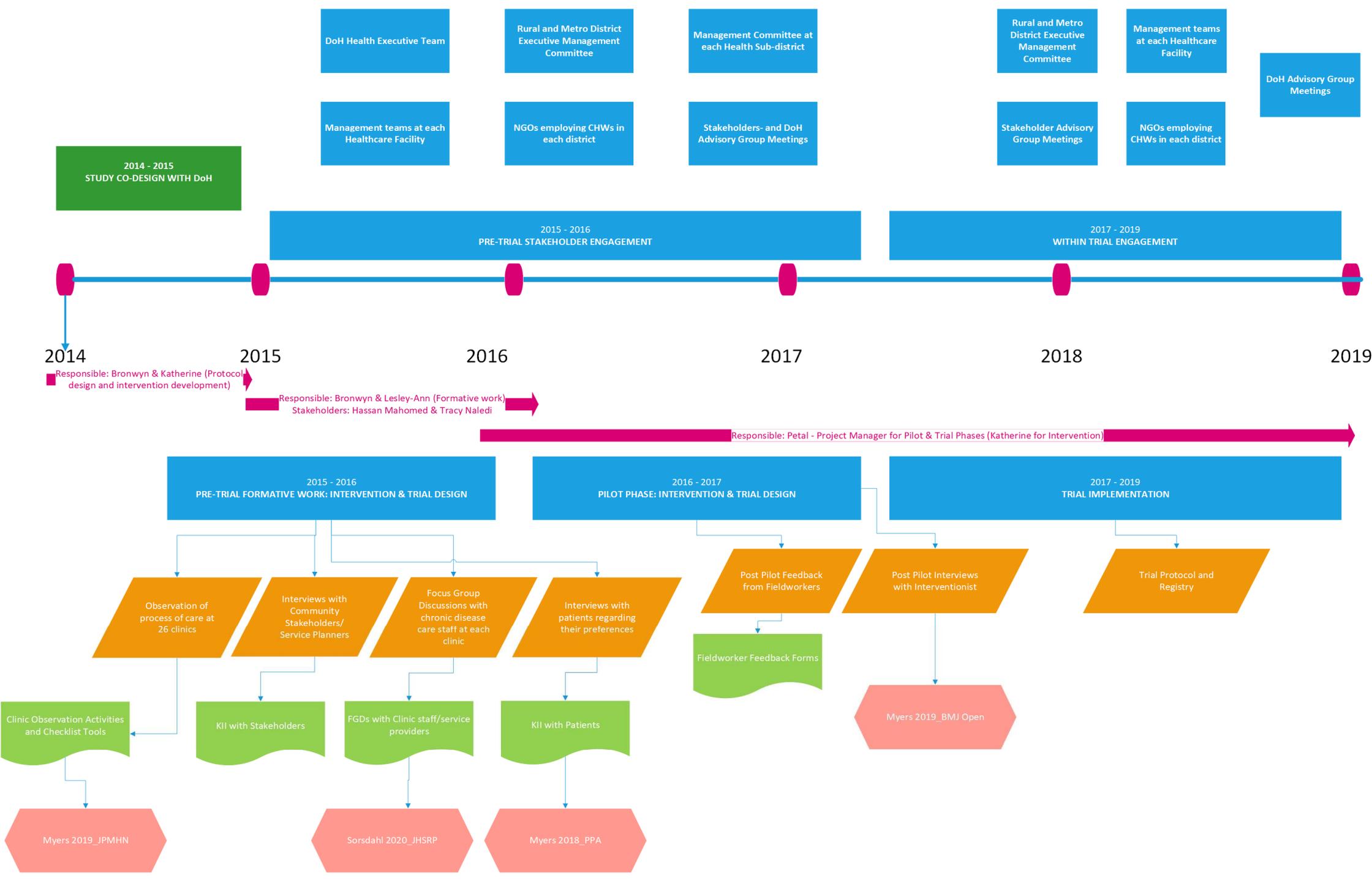
- Study evaluating *utility* and *comparability* between the Gibbs and GRIPP-2 tools to measure cultural competency when applied in a complex trial conducted within an African setting, i.e. Project MIND



# METHODS (1)

- Secondary data analysis:
  - 1) identified and collated all relevant publications, source and procedural data related to the trial
  - 2) prepared a trial process diagram specific to Project Mind with the responsible investigator linked to each stage\*

\* As an additional component of the study, we explored the use of MS Visio to assist with integrating data sources into one shared environment, for easier accessibility of data sources and enhancing our ability to conceptualize all the stages of the Project MIND trial



# METHODS (2)

## STEP 1:

- Two independent investigators applied and scored both Gibbs and GRIPP-2(SF) tools to the four published manuscripts arising from the trial
- Prepared a decision-making matrix to identify where no judgement could be made due to inadequate reporting, or where scores were '0' or '1'

## STEP 2:

- Third investigator independently and systematically scrutinised all procedural and source data to establish whether cultural competency had been met
- Consensus for final score reached between discussion of all investigators

# FINDINGS: APPLICATION IN PROJECT MIND

	<b>Gibbs Domain</b>	<b>Gibbs score following publication analysis</b>	<b>Additional source or procedural data analysis</b>	<b>Gibbs final Score</b>
1	Forming partnerships	2	Not required	2
2	Defining research questions	1	No	1
3	Identifying data sources and target populations	2	Not required	2
4	Appointing staff	1	Yes	2
5	Recruitment of sample	2	Not required	2
6	Data collection	2	Not required	2
7	Development of intervention	1	Yes	1
8	Analysis/evaluation	2	Not required	2
9	Reporting/disseminating findings	2	Not required	2

# FINDINGS: APPLICATION IN PROJECT MIND

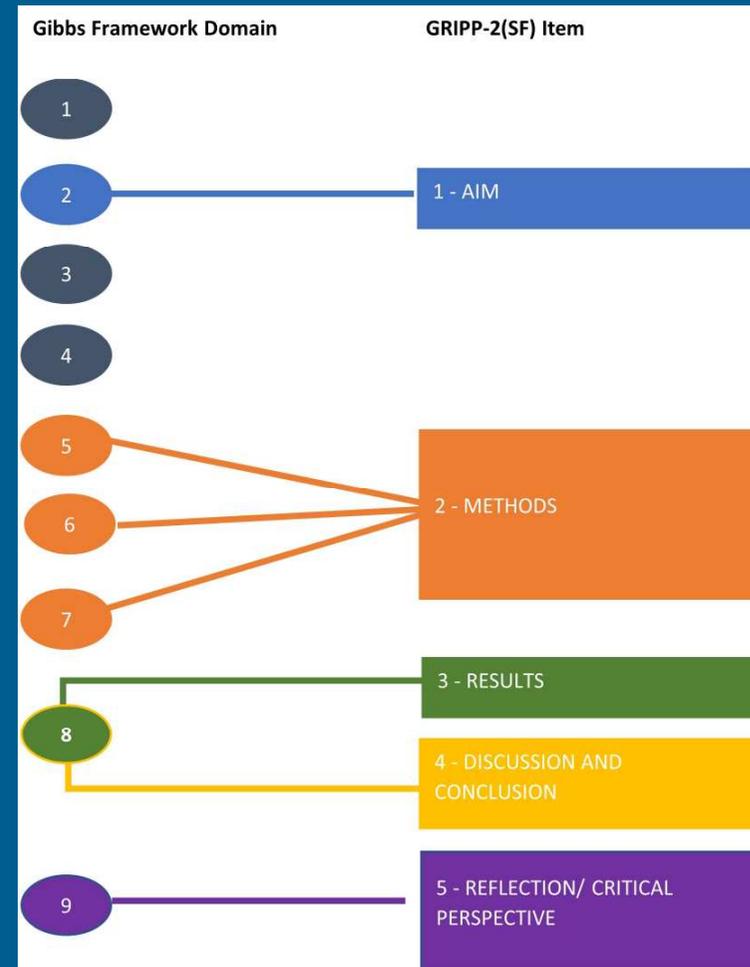
- The application of the Gibbs Framework indicated that the Project MIND trial was highly culturally competent, fully meeting all but two of the nine Gibbs criteria
- The Gibbs Framework revealed that the trial research question was not driven by the articulated needs of patients (question 2), and neither were patients, caregivers and clinical providers involved in the development of the intervention (question 7)

# FINDINGS: UTILITY OF GIBBS FRAMEWORK

- The Gibbs Framework includes:
  - evaluation of partnerships forged before the start of the trial
  - assessment of the awareness of the investigators' cultural framework and its influence on their research approach
- Self-reflection of a researcher's own cultural bias:
  - is a key research attribute but is rarely considered in the conduct or reporting of a clinical trial
  - important for trialists working in countries and cultural settings different from their own
  - failure to consider the lens of the trialist, how it may differ to those of the trial participants and trial clinical staff, may *impact successful recruitment, participation, and ultimately the robustness of findings if attrition is high*
- Challenges in coding and operationalizing the guidance due to lack of definitions, glossary and examples

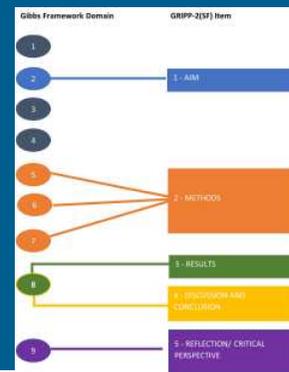
# FINDINGS

## COMPARABILITY BETWEEN THE GIBBS FRAMEWORK AND GRIPP-2 (SF)



# COMPARABILITY BETWEEN THE GIBBS FRAMEWORK AND GRIPP-2 (SF)

- **Gibbs framework** can be used to guide all stages of framing the trial research question, protocol development and final analysis before and during trial conduct with reference to cultural competency
- **GRIPP-2 (SF)** more applicable when reporting PPI retrospectively and as a quality assurance step in the writing up of PPI in trial publications and reports



## CONCLUSIONS (1)

- We operationalized secondary data analytical methods in the application of the Gibbs Framework to a LMIC trial which was judged to be culturally competent in seven of nine domains
- We recommend that an updated version of the Gibbs Framework tool consider inclusion of a user glossary and worked examples
- Consideration should be given to whether “cultural competency” as a term is fit for purpose (othering)

## CONCLUSIONS (2)

- Further evaluation of the Gibbs Framework may take the form of retrospective application to completed trials or prospective application in planned and ongoing trials while monitoring the utility of its use
- Comprehensive evaluation of the trial's cultural competency required scrutiny of both published manuscripts and source and procedural data, suggesting that there is a gap in current trial reporting standards with respect to cultural competence

# KEY MESSAGE

- Identification of the key components of the Gibbs Framework to incorporate into the current CONSORT Statement and SPIRIT Statement which guide reporting standards for trial conduct and protocol development respectively, will clearly require further interrogation, development, and collaboration among trialists.
- However, we believe the Gibbs Framework is a reasonable starting point.

ANY QUESTION OR COMMENTS?





**Gibbs Domain 1: Forming Partnerships**

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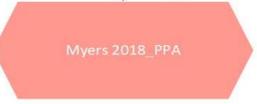
2014 - 2015  
STUDY CO-DESIGN WITH DoH



2014  
Responsible: PI & Co-I (Protocol design and intervention development)

2015  
**Gibbs Domain 4: Appointing staff**  
Responsible: PI & Research Assistant (Formative work)  
Stakeholders: WCDoH Co-I & Collaborator

2016  
2017  
2018  
2019  
Responsible: Trial Manager for Pilot & Trial Phases (Co-I)  
**Gibbs Domain 8: Analysis / Evaluation**



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# Pilot implementation of a mobile text message-based solution for randomization in clinical trials.

Mercy Chepkirui

**KEMRI** | Wellcome Trust





# Outline

- Background & rationale
- Objectives
- Methodology
- Results
- Live demonstration
- The present & further work
- Conclusions

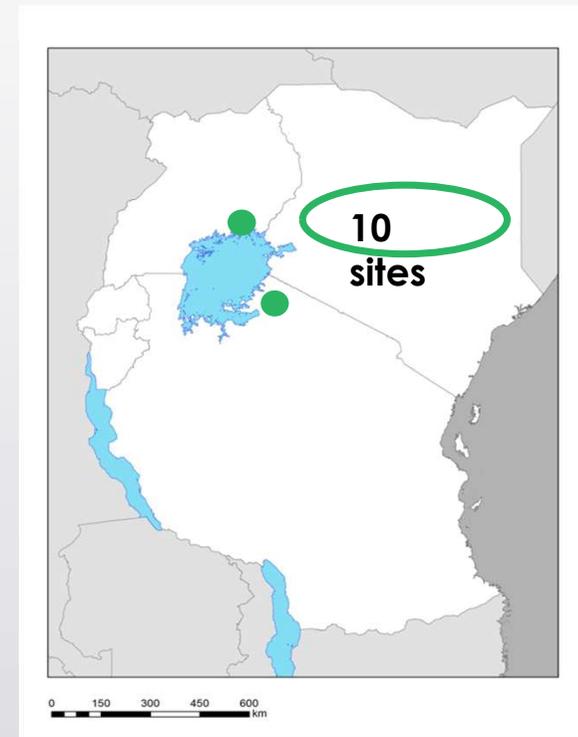
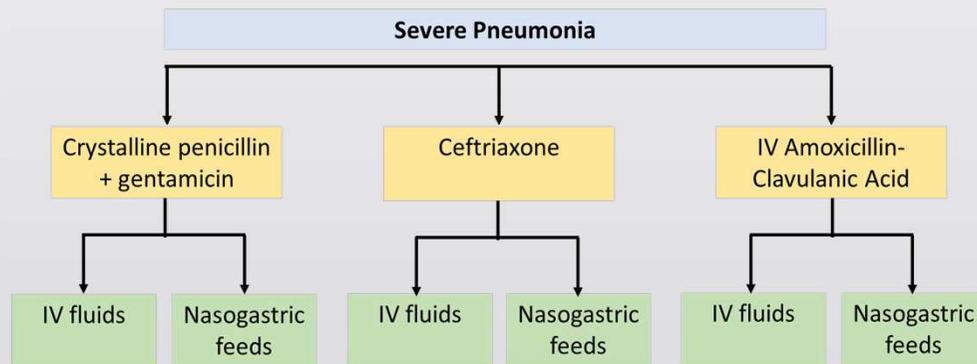


# Background

- Randomization - the standard method of experimental control
- Randomization involves two steps
  - Generating an unpredictable random sequence,
  - Implementing the sequence in a way that conceals the treatment until the participant have been **assigned** the treatment .
- Impact of improper randomization
  - Biased estimates of treatment effects
- Traditional methods for concealment
  - The use of sequentially numbered opaque sealed envelopes is prone to manipulation, can get easily damaged during shipping and filling and concealing is time-consuming which is prone to human-error.

# Supportive Care and Antibiotics for Severe Pneumonia among Hospitalized Children (SEARCH)

- Randomized pragmatic 3x2 factorial clinical trial
- Sample size: 4392 children in 12 sites – CIN platform
- Primary endpoint: Mortality at Day 5
- Secondary outcomes: length of hospitalisation, time to full volume oral feeds, mortality at Day 30



# Rationale

- Centrally-administered web-based/telephone randomization is an option.
- Weak communication infrastructure and poor internet connectivity in low resource settings is a limitation.
- An affordable, auditable, and suitable for low-resource settings is the use of mobile phone-based Short Messaging Service (SMS).
- SMS used in clinical trials
  - To reduce missed appointments (Perron, N. J., 2013)
  - To improve clinic attendance (Chen, Z. W., 2008)
  - As a cost-effective intervention for managing patients with chronic illnesses (Islam, S. M.S., 2019; Finitsis, D. J., 2014; Thakkar, 2016; Park, L.G., 2014).
  - SMS reminder trial for malaria case management (Zurovac et al., 2011) to improve adherence to treatment guidelines.
- Rapidly expanding mobile phone technology in developing countries.





# Objectives

## **Overall objective**

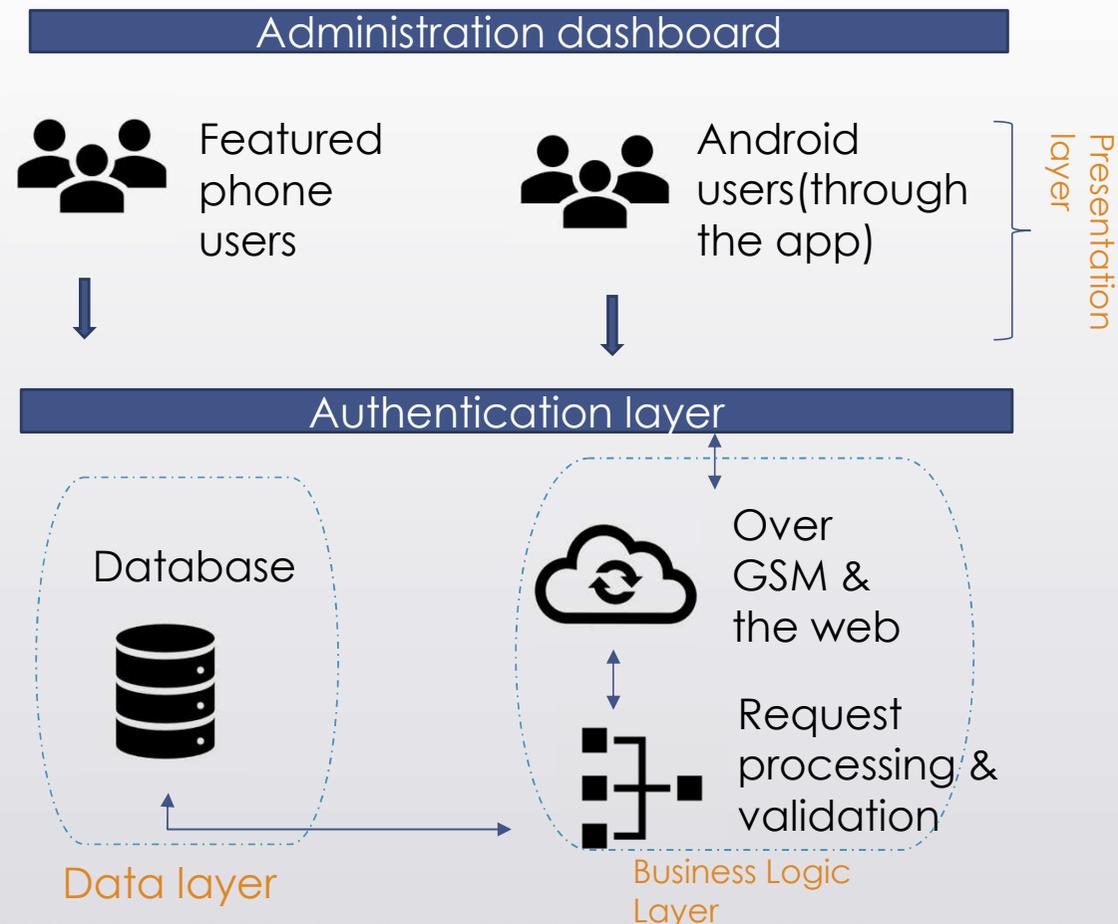
To evaluate the feasibility and accuracy of randomization using text messaging through response time and correct treatment allocation.

## **Specific objectives:**

- Estimate response time of SMS delivery for every randomization request across different networks.
- To determine allocation sequence concordance for both approaches
- Assess user experience for both approaches.

# Methodology

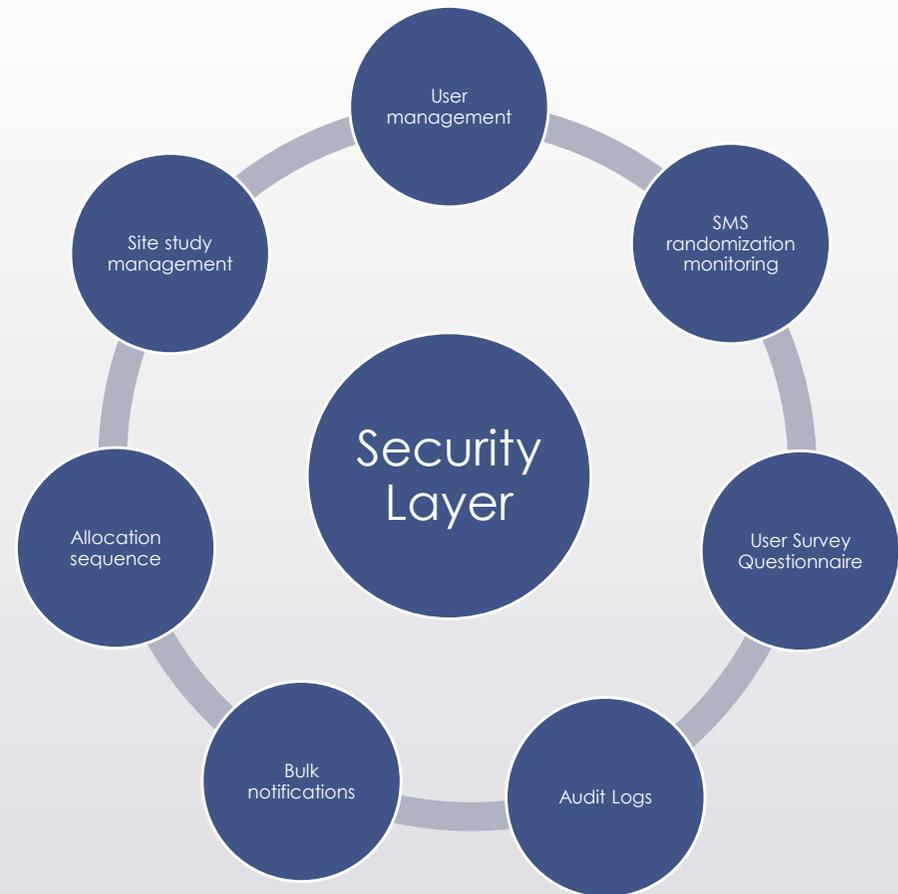
- SMS platform development (3-tiers)
- SMS implementation mode: IPNOs and site names
  - Syntax "Randomize [ipno] to [studynome][sitename]"
- Sample size: 200 eligible participants in SEARCH clinical trial.
- 2 study sites in Nairobi
- A pair-wise randomization: A participant will be randomized using 2 methods. The existing envelope method & SMS method.
- Carry out user surveys(Clinical trial team).



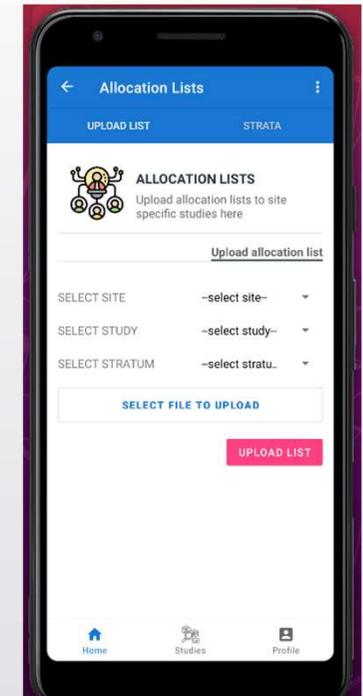
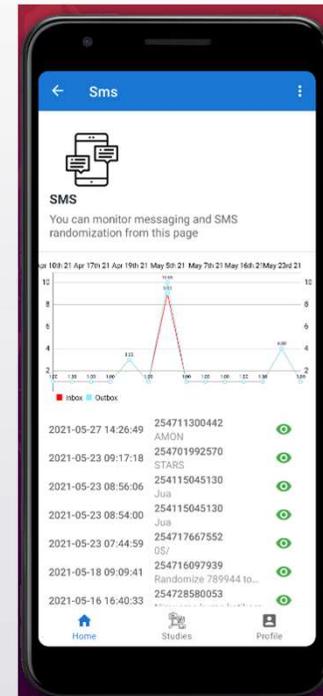
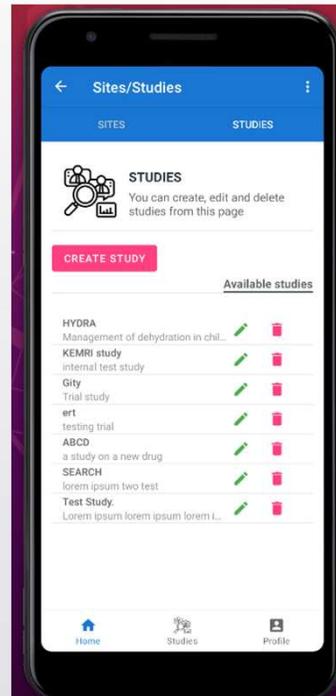
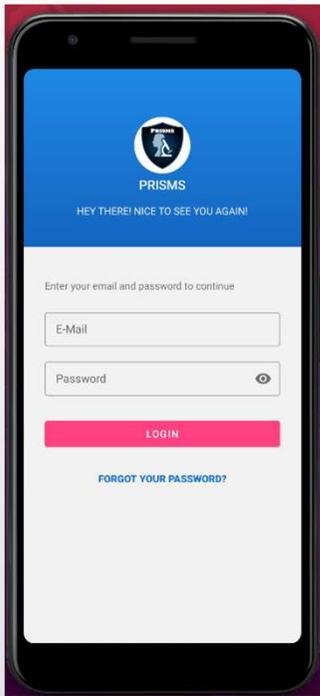
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## Results: Apps

- Randomization application: SMS integration, Android application & Administrative dashboard
- Administrative dashboard  
<https://prisms.kemri-wellcome.org>

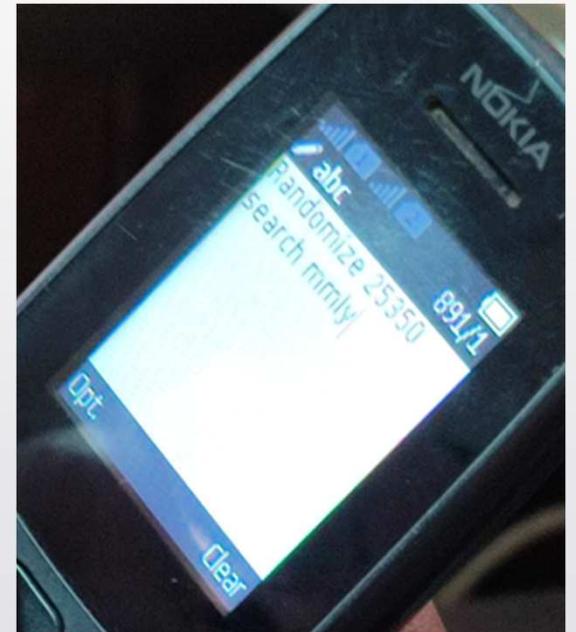
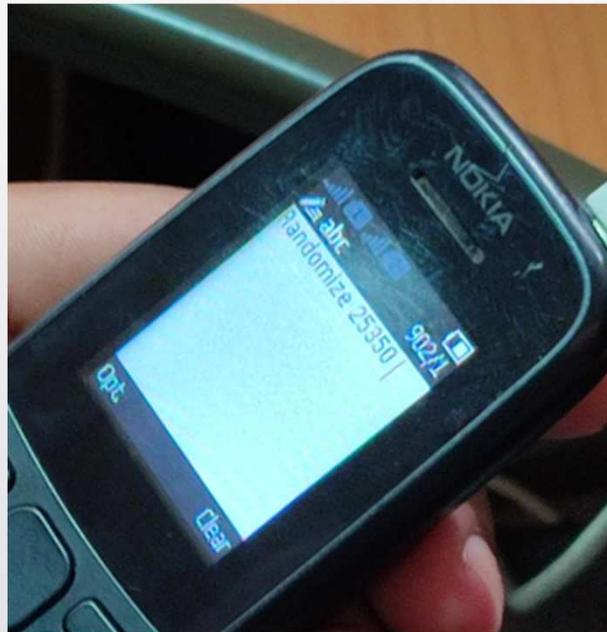


# Android app



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# Featured phone randomization

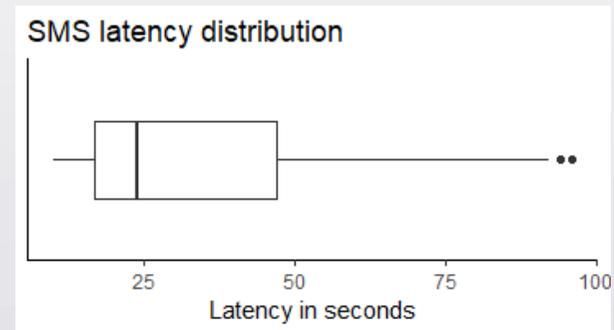


# SMS Latency

- 530 SMS runs of latency processed

Success Randomizations	Invalid requests	Non-authorized	Unregistered users	Exhausted sequence	Duplicated attempts
399(75%)	106(20%)	2(0.38%)	2(0.38%)	1(0.19%)	20(3.77%)

- Average latency summary
  - Less than 100 sec(508 – 96%)
  - Outliers (22 – 4%)
    - 4 hours after(invalid message) - 1 sms
    - Later than 100 secs – 22 SMS (9 SR, 13 IVD)
  - Latency rate(medium) – 25 secs



Min.	1st Qu	Median	Mean	3rd Qu.	Max.
10	17	25	89.17	51	14805



# Latency & Concordance

- Number of allocations requests – 2 sites

Total	Single step	2 step
217	179	38

- Concordance (Envelop/text)



## Live demonstration

- Randomize a participant using a text
- Randomize through the app
- Check the log on the dashboard



## Present & Further work

- SMS randomization in a clinical trial targeting 200 participants
  - Comparative real-world SMS randomization (SEARCH Clinical trial)
- User surveys
  - 15<sup>th</sup> April 2022
- Final analysis and reporting
  - May 2022



## Conclusions

- We have developed SMS based solution based on a multi-site factorial design.(web app & mobile app)
- Early findings performs very well in controlled settings
- The findings can inform randomization approach in future studies in low resource settings.
- SMS is a potential alternative approach for randomization in large and complex clinical trials.



# Acknowledgements

- The team
  - Ambrose Agweyu
  - Charles Opondo
  - Dennis Kimego – lead developer
  - SEARCH trial clinicians
- Institutions
  - KEMRI –Wellcome Trust
  - The global health network
  - Trials Methodology Research Partnership (TMRP)
  - Department of Medical Statistics, London School of Hygiene and Tropical Medicine, UK
  - SEARCH trial participating hospitals.



Q & A