Adaptive platform trials: challenges, solutions and opportunities in trial conduct

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03-Oct-2024| Adaptive Platform Trials Scientific Meeting| Toronto, ON, Canada

Smarter Studies
Global Impact
Better Health

MRC CTU at UCL

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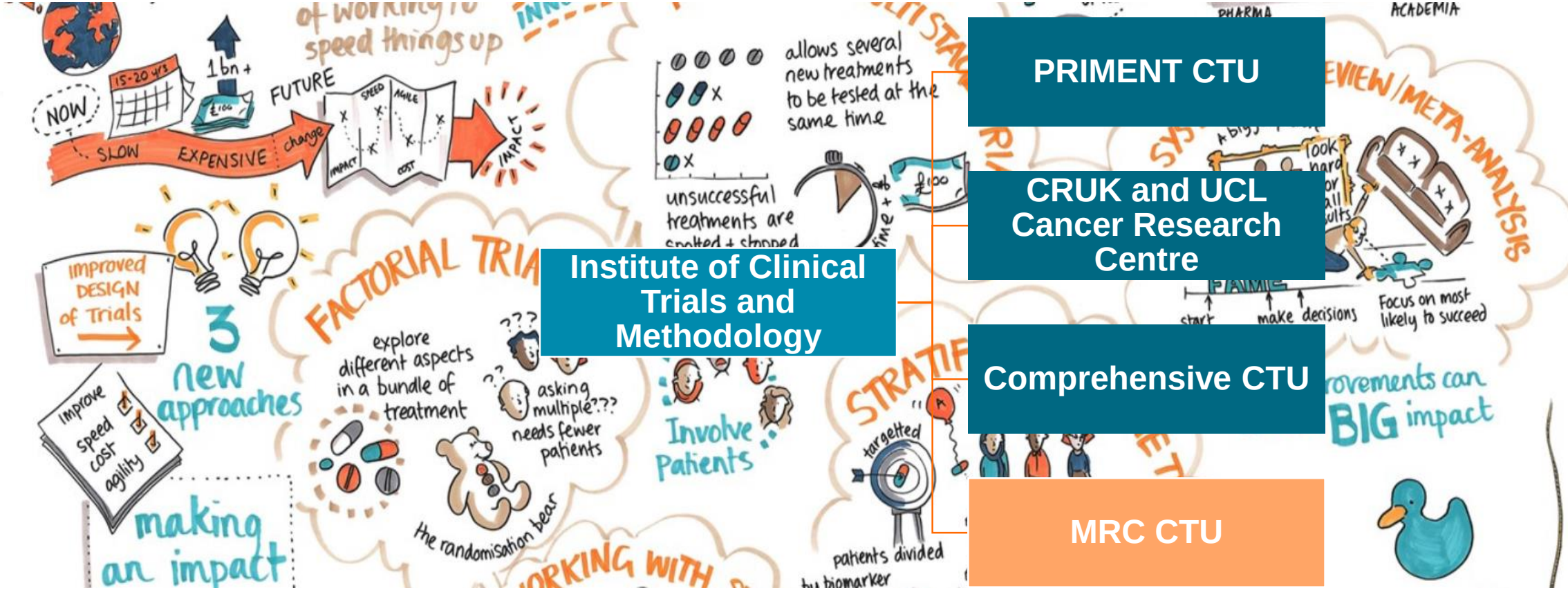

Institute of Clinical Trials and Methodology

PRIMENT CTU

CRUK and UCL Cancer Research Centre

Comprehensive CTU

MRC CTU

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Outline

Adaptive Platform trials

- Lessons learnt so far in trial conduct of adaptive trial designs
- New questions, new designs
- AMR challenge in resource-constrained settings
- Neglected tropical diseases: snakebite

STAMPEDE

FOCUS4

NeoSepI

SNIP-AFRICA

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Adaptive platform trials

Trial design

‘Traditional’ two-arm trial (blinded or unblinded)

‘Innovative’ trial designs

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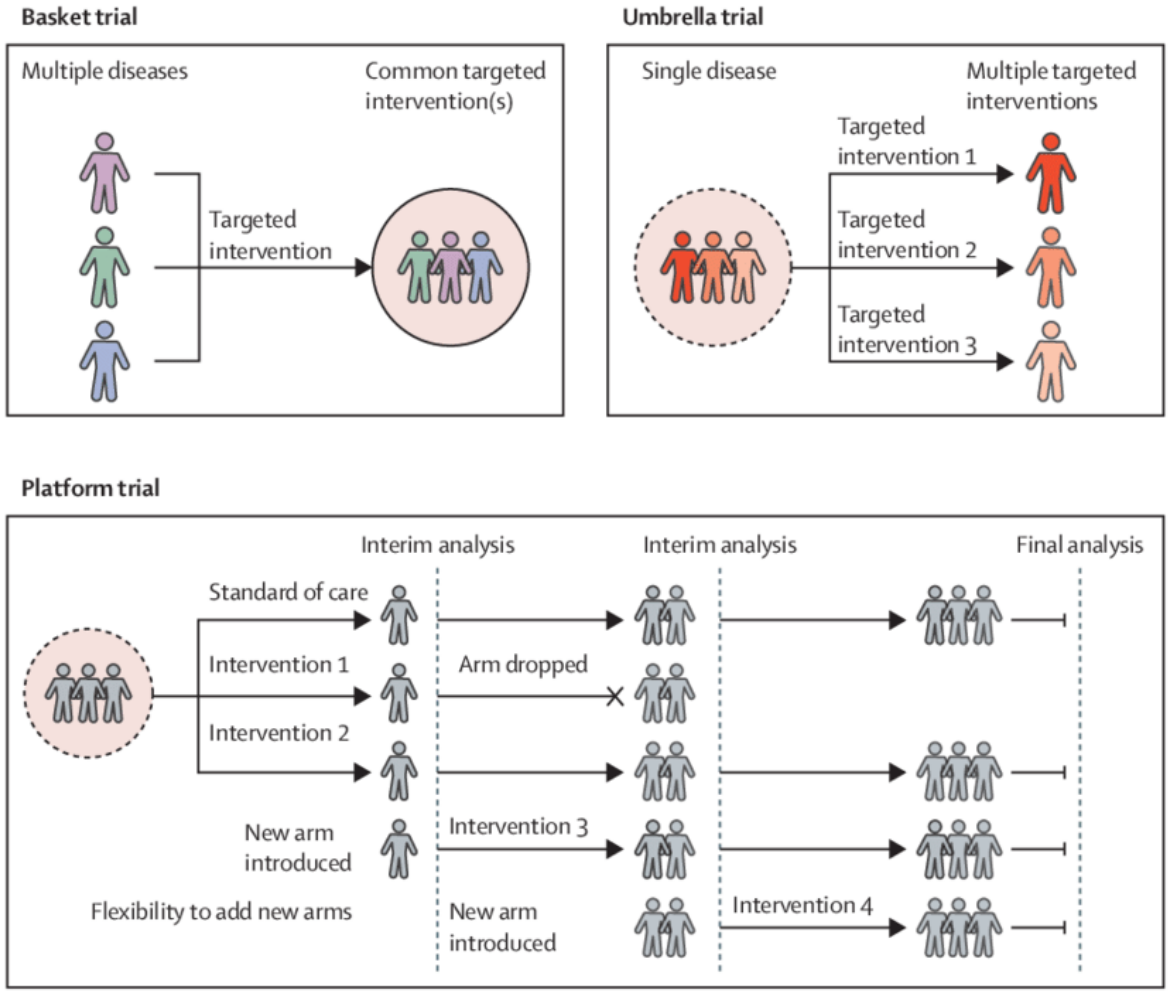
We don’t always have to use an adaptive platform trial design!

Innovative trials design

- Factorial (“domain”)
- Umbrellas
- Baskets
- Platform protocols
  - “Changing stuff”
  - Formalise approach of DMC…?!
- Multi-arm multi-stage (MAMS)
- MAMS-Selection
- MAMS-ROCI
- PRACTical
- Phase II/III seamless trial designs
- Etc etc



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What do we mean by “adaptive platforms”?

“Planning to be flexible”

Pallmann et al. BMC Medicine (2018) 16:29
https://doi.org/10.1186/s12916-018-1017-7

Testing multiple primary questions within one protocol

Operational complexities

Addition of new comparisons

Early stopping

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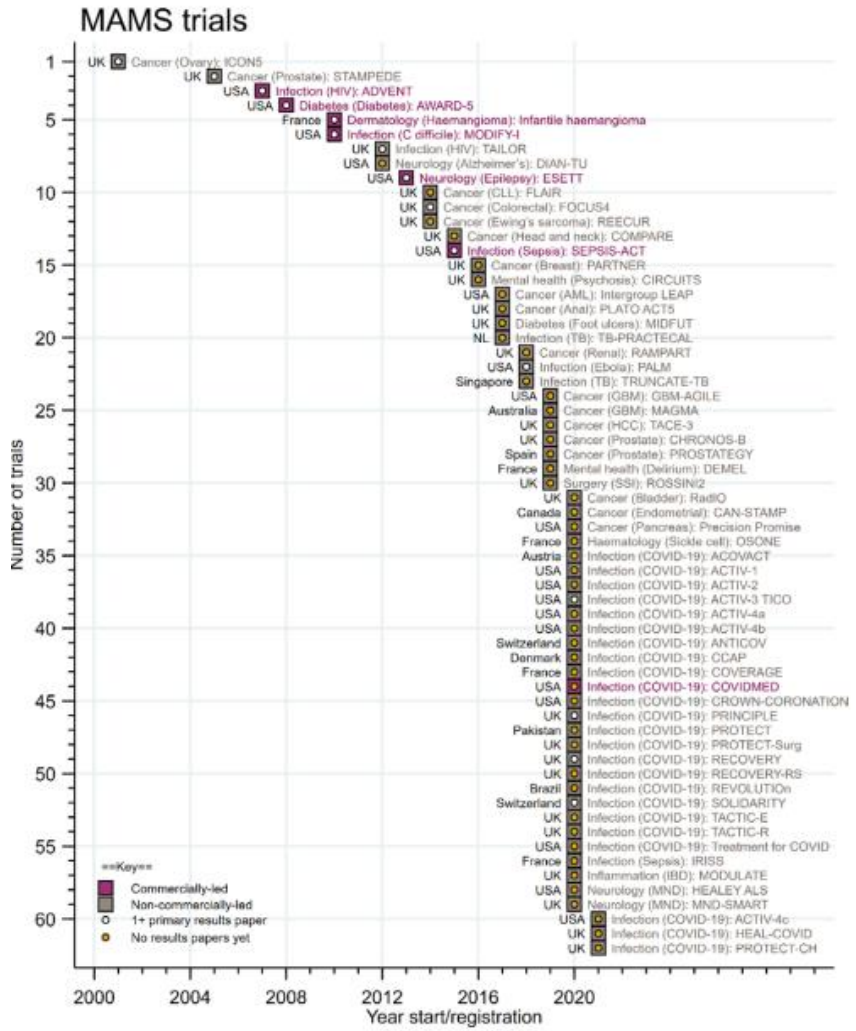
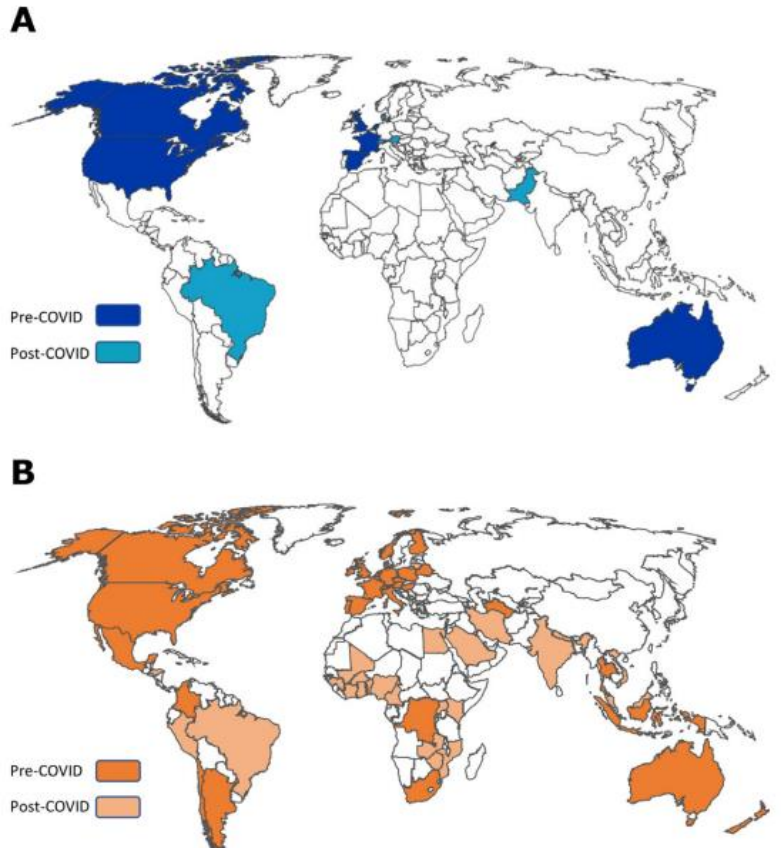
Conduct of adaptive platform trials





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Noor NM, et al. BMJ Open 2022;12:e055615. doi:10.1136/bmjopen-2021-055615

MAMS trials in COVID research

- RECOVERY trial (UK)
  - Started as a four-arm trial with other arms added later
  - Three research questions were answered - with over 12,000 participants recruited – in just over 100 days
  - Provided convincing results to influence changes in clinical practice
- SOLIDARITY (advocated by WHO; multiple countries)

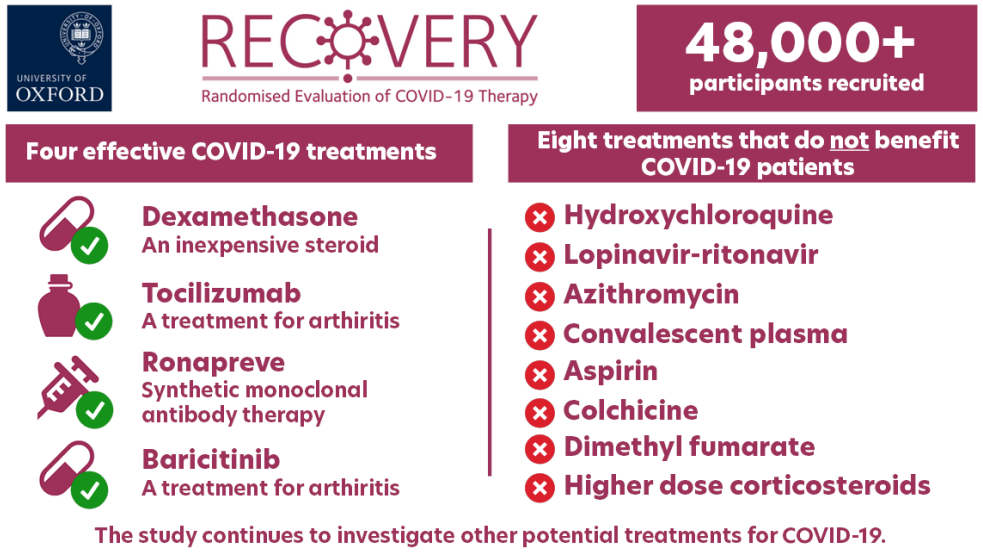
F1000Research F1000Research 2020, 9:1109 Last updated: 23 NOV 2020

Check for updates

OPINION ARTICLE

REVISED **Adaptive platform trials using multi-arm, multi-stage protocols: getting fast answers in pandemic settings [version 2; peer review: 2 approved]**

Nurulamin M. Noor, Sarah L. Pett, Hanif Esmail, Angela M. Crook, Claire L. Vale, Matthew R. Sydes, Mahesh K.B. Parmar



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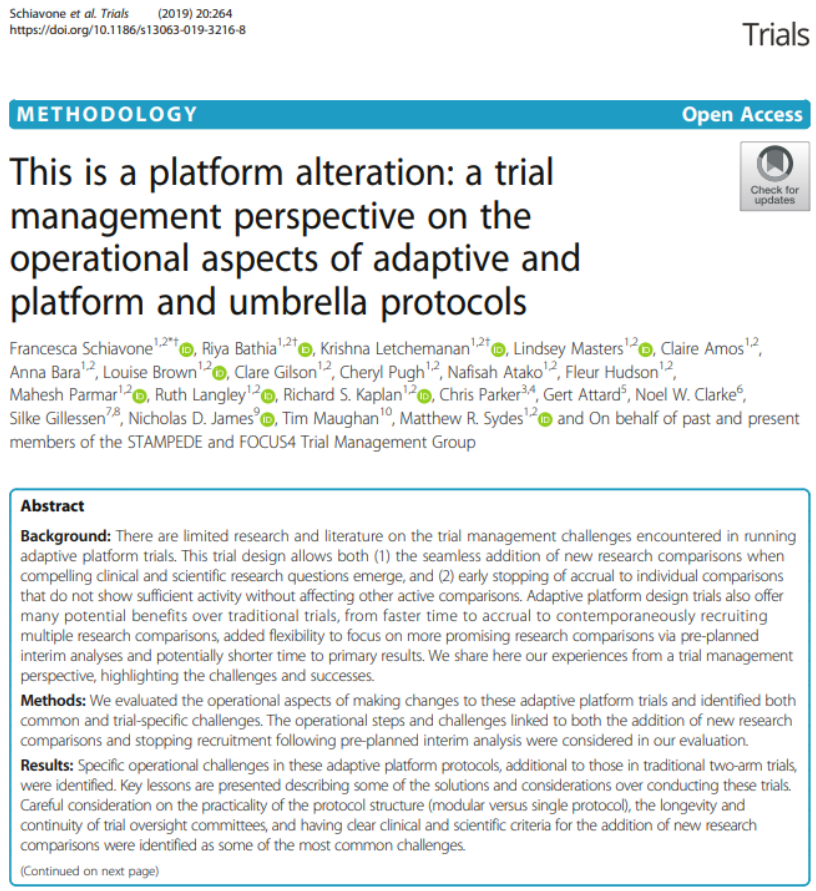
MAMS in late phase oncology trials



Schiavone *et al. Trials* (2019) 20:264
https://doi.org/10.1186/s13063-019-3216-8

Trials

METHODOLOGY Open Access

This is a platform alteration: a trial management perspective on the operational aspects of adaptive and platform and umbrella protocols

Francesca Schiavone[1,2*†], Riya Bathia[1,2†], Krishna Letchemanan[1,2†], Lindsey Masters[1,2], Claire Amos[1,2], Anna Bara[1,2], Louise Brown[1,2], Clare Gilson[1,2], Cheryl Pugh[1,2], Nafisah Atako[1,2], Fleur Hudson[1,2], Mahesh Parmar[1,2], Ruth Langley[1,2], Richard S. Kaplan[1,2], Chris Parker[3,4], Gert Attard[5], Noel W. Clarke[6], Silke Gillessen[7,8], Nicholas D. James[9], Tim Maughan[10], Matthew R. Sydes[1,2] and On behalf of past and present members of the STAMPEDE and FOCUS4 Trial Management Group

Abstract

Background: There are limited research and literature on the trial management challenges encountered in running adaptive platform trials. This trial design allows both (1) the seamless addition of new research comparisons when compelling clinical and scientific research questions emerge, and (2) early stopping of accrual to individual comparisons that do not show sufficient activity without affecting other active comparisons. Adaptive platform design trials also offer many potential benefits over traditional trials, from faster time to accrual to contemporaneously recruiting multiple research comparisons, added flexibility to focus on more promising research comparisons via pre-planned interim analyses and potentially shorter time to primary results. We share here our experiences from a trial management perspective, highlighting the challenges and successes.

Methods: We evaluated the operational aspects of making changes to these adaptive platform trials and identified both common and trial-specific challenges. The operational steps and challenges linked to both the addition of new research comparisons and stopping recruitment following pre-planned interim analysis were considered in our evaluation.

Results: Specific operational challenges in these adaptive platform protocols, additional to those in traditional two-arm trials, were identified. Key lessons are presented describing some of the solutions and considerations over conducting these trials. Careful consideration on the practicality of the protocol structure (modular versus single protocol), the longevity and continuity of trial oversight committees, and having clear clinical and scientific criteria for the addition of new research comparisons were identified as some of the most common challenges.

(Continued on next page)

Hague *et al. Trials* (2019) 20:294
https://doi.org/10.1186/s13063-019-3322-7

Trials

METHODOLOGY Open Access

Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons

Dominic Hague[1,2*], Stephen Townsend[1,2], Lindsey Masters[1,2], Mary Rauchenberger[1,2], Nadine Van Looy[1,2], Carlos Diaz-Montana[1,2], Melissa Gannon[1,3], Nicholas James[4], Tim Maughan[5], Mahesh K. B. Parmar[1,2], Louise Brown[1,2], Matthew R. Sydes[1,2] and for the STAMPEDE and FOCUS4 investigators

Abstract

Background: There is limited research and literature on the data management challenges encountered in multi-arm, multi-stage platform and umbrella protocols. These trial designs allow both (1) seamless addition of new research comparisons and (2) early stopping of accrual to individual comparisons that do not show sufficient activity. FOCUS4 (colorectal cancer) and STAMPEDE (prostate cancer), run from the Medical Research Council Clinical Trials Unit (CTU) at UCL, are two leading UK examples of clinical trials implementing adaptive platform protocol designs. To date, STAMPEDE has added five new research comparisons, closed two research comparisons following pre-planned interim analysis (lack of benefit), adapted the control arm following results from STAMPEDE and other relevant trials, and completed recruitment to six research comparisons. FOCUS4 has closed one research comparison following pre-planned interim analysis (lack of benefit) and added one new research comparison, with a number of further comparisons in the pipeline. We share our experiences from the operational aspects of running these adaptive trials, focusing on data management.

Methods: We held discussion groups with STAMPEDE and FOCUS4 CTU data management staff to identify data management challenges specific to adaptive platform protocols. We collated data on a number of case report form (CRF) changes, database amendments and database growth since each trial began.

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Experience from UK Clinical Trials Unit: late phase trials

Love et al. Trials (2022) 23:757
https://doi.org/10.1186/s13063-022-06680-4

Trials

METHODOLOGY Open Access

Practical guidance for running late-phase platform protocols for clinical trials: lessons from experienced UK clinical trials units

Sharon B. Love[1*], Fay Cafferty[2], Claire Snowdon[2], Karen Carty[3], Joshua Savage[4], Philip Pallmann[5], Lucy McParland[6], Louise Brown[1], Lindsey Masters[1], Francesca Schiavone[1], Dominic Hague[1], Stephen Townsend[1], Claire Amos[1], Annabelle South[1], Kate Sturgeon[1], Ruth Langley[1], Timothy Maughan[7], Nicholas James[2], Emma Hall[2], Sarah Kernaghan[2], Judith Bliss[2], Nick Turner[2], Andrew Tutt[8], Christina Yap[2,9], Charlotte Firth[9], Anthony Kong[10], Hisham Mehanna[11], Colin Watts[12], Robert Hills[13], Ian Thomas[14], Mhairi Copland[15], Sue Bell[16], David Sebag-Montefiore[17], Robert Jones[18], Mahesh K. B. Parmar[1†] and Matthew R. Sydes[1†]

Abstract

Background: Late-phase platform protocols (including basket, umbrella, multi-arm multi-stage (MAMS), and master protocols) are generally agreed to be more efficient than traditional two-arm clinical trial designs but are not extensively used. We have gathered the experience of running a number of successful platform protocols together to present some operational recommendations.

Methods: Representatives of six UK clinical trials units with experience in running late-phase platform protocols attended a 1-day meeting structured to discuss various practical aspects of running these trials. We report and give guidance on operational aspects which are either harder to implement compared to a traditional late-phase trial or are specific to platform protocols.

Results: We present a list of practical recommendations for trialists intending to design and conduct late-phase platform protocols. Our recommendations cover the entire life cycle of a platform trial: from protocol development, obtaining funding, and trial set-up, to a wide range of operational and regulatory aspects such as staffing, oversight, data handling, and data management, to the reporting of results, with a particular focus on communication with trial participants and stakeholders as well as public and patient involvement.

Discussion: Platform protocols enable many questions to be answered efficiently to the benefit of patients. Our practical lessons from running platform trials will support trial teams in learning how to run these trials more effectively and efficiently.

Keywords: Platform protocols, Trial conduct, Multi-arm multi-stage trials, Umbrella trials, Basket trials, Stratified medicine, Complex innovative designs, Methodology

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Working on adaptive platform trials

Morrell *et al. Trials* (2019) 20:297
https://doi.org/10.1186/s13063-019-3377-5

Trials

COMMENTARY Open Access

Mind the gap? The platform trial as a working environment

Liz Morrell[1*], Joshua Hordern[2], Louise Brown[3], Matthew R. Sydes[3], Claire L. Amos[3], Richard S. Kaplan[3], Mahesh K. B. Parmar[3] and Timothy S. Maughan[4,5]

Abstract

Background: Trials have become bigger and more complicated due to the complexity introduced by biomarker stratification, and the advent of multi-arm multi-stage trials, and umbrella and basket platform designs. The trials unit at University College London has been at the forefront of this work, with ground-breaking trials such as STAMPEDE and FOCUS4. The trial management and data management teams on these trials have summarised the operational challenges, to enable the broader clinical trials community to learn from their experiences. In a small-scale qualitative study, we examined the personal experience of individual researchers working on these trials.

Commentary: We found reports of high workloads, with potentially significant stress for individuals and with an impact on their career choices. We conclude that there was an initial underestimation of the work required and of the inherent, largely unanticipated, challenges. We discuss the importance of fully understanding these trials' resource requirements, both for those writing grant applications and critically, for those with responsibility for deciding on funding.
The working environment was characterised by three features: complexity, scale and heightened expectations. These features are highly attractive for professional development and engender high levels of loyalty and commitment. We observed a trade-off between these intrinsic rewards and the continuous demands of overlapping tasks, balancing a mix of routine and high-profile work, and the changing nature of pivotal roles. Such demands present challenges for colleague relationships, by enhancing the potential for competition and by disrupting the natural opportunities to pause, review and celebrate team achievements. In addition, molecular stratification in effect brings the patient into the trial office, as a specific individual, despite anonymisation, who is owed test results and a treatment decision. We discuss these observations with a view to interconnecting the need for compassion for patients with caring for the researchers engaged in the research ecosystem who are aiming to produce much hoped-for advances in medical science.

Conclusions: There is a need for increased awareness of the challenge these studies place on those throughout the team delivering the study. Such considerations must influence leaders and funders, both in their initial budget considerations and throughout delivery.

Keywords: Precision medicine, Stratified medicine, Biomarker, Platform trial, Trial management, Qualitative, Efficiency, Researcher, Adaptive design, Compassion

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Experience from STAMPEDE and FOCUS4

- Protocol development
- Database set up
- Ethics and regulatory approval
- Contracts
- Drug Supply

New questions, new designs

Paradigm of evidence-based medicine

- “One regimen to rule them all”
  - “Standard of care”, SOC, “control”: simultaneously maximising good outcomes and minimising bad outcomes (toxicity) as best we can
  - Recommended in guidelines, should be generally used in all/most patients
- Iteratively improve this “optimal regimen” through series of (generally two-arm) randomised controlled trials vs SOC
  - Tuberculosis
  - Cancer
  - HIV
- Innovation: compare multiple new interventions vs SOC to iteratively improve SOC faster

Choosing SOC

- Clinical guidelines
- Clinical practice

… Is there actually always a SOC?

An example from AntiMicrobial Resistance

- Rising antimicrobial resistance (AMR) leading to increasing numbers of multi-drug resistant (MDR) bacterial infections
  - And stronger and stronger antibiotics being used empirically ☹
- Lots of questions around treatment of MDR bacterial infections, which have high mortality and morbidity
  - Carbapenemase Producing *Enterobacteriaecae* (CPE)

PRACTical

Review > Lancet Infect Dis. 2021 Jun;21(6):e175-e181. doi: 10.1016/S1473-3099(20)30791-X.
Epub 2021 Apr 21.

Personalised randomised controlled trial designs–a new paradigm to define optimal treatments for carbapenem-resistant infections

A Sarah Walker [1], Ian R White [2], Rebecca M Turner [2], Li Yang Hsu [3], Tsin Wen Yeo [4], Nicholas J White [5], Mike Sharland [6], Guy E Thwaites [7]

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DOI: 10.1016/S1473-3099(20)30791-X

Why not use “platform” trials – why do we need even more innovative designs?

- Large numbers of antimicrobials/durations with very weak evidence base – but very strong opinions – what is “SOC”?
- Any one SOC will also likely not be possible for many patients
  - Antimicrobial resistance is generally “mosaic” cross-class: resistance genes are generally carried on variably present mobile genetic elements
  - Many antimicrobials have important contraindications
  - We will NEVER isolate a pathogen in many patients – did they ever have a bacterial infection (i.e. should the SOC really be nothing)?
  - Serious clinical condition of patients with non-cUTI MDR infections makes randomising against a potentially sub-standard SOC very hard

‘PRACTical’ designs vs Platform designs

- In a PRACTical design, there is simply no SOC
  - Each patient is randomised between a subset of regimens
  - These subsets of regimens differ from patient to patient
- In a traditional platform design, there is still one SOC which every patient has to have the potential to be randomised to
  - Test multiple intervention arms, which may stop or start whilst “platform” trial continues
  - SOC may change over time to one of these “test” arms
  - Patients may not have to be randomised to all “test” arms, but primary analysis is still pairwise comparison with SOC in patients randomised to SOC vs each “test”

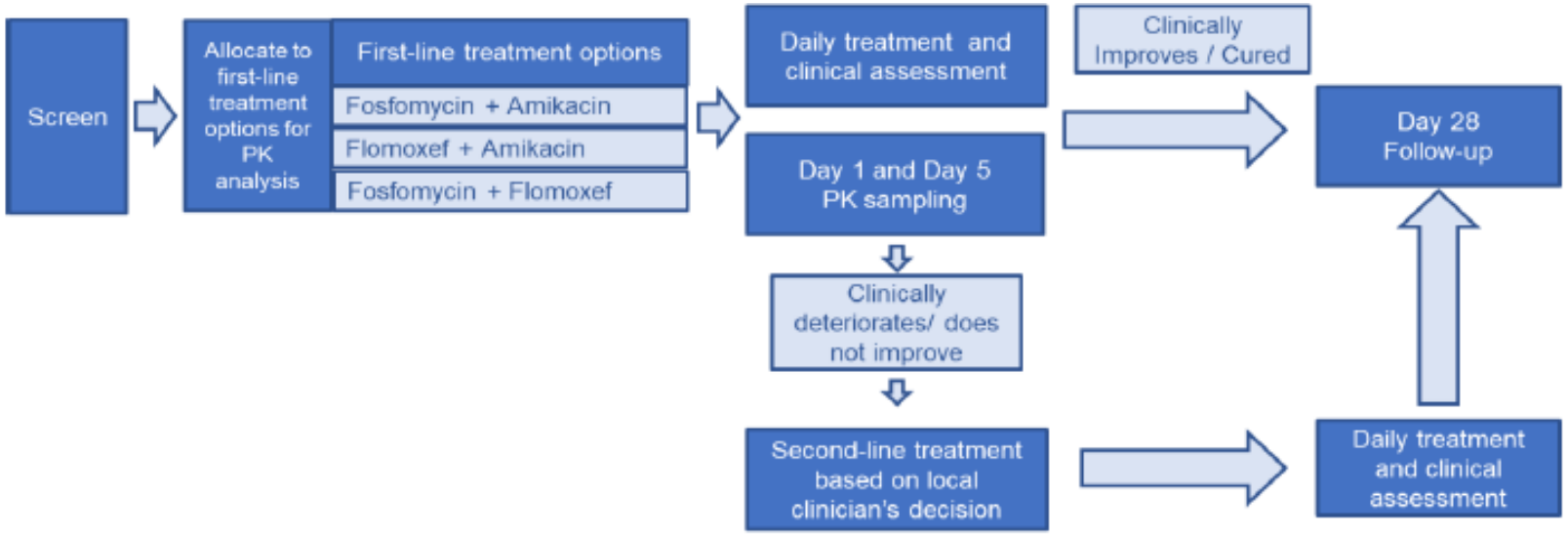
Research question

- Out of the X acceptable antibiotic regimens **for this baby** (based on timing of sepsis onset, prematurity, local epidemiology, availability), which is most likely to result in good clinical outcomes?
  - Identifies one of the best out of multiple options for a particular patient (and setting) BUT no SOC
  - Avoids the worst option(s), taking account of toxicity, resistance, availability, cost etc

Network meta-analysis analogy

- A network meta-analysis combines evidence from multiple trials in which different pairs (or sets) of treatments are compared to answer questions such as:
  - "What is the best treatment to recommend?"
  - "**What is the ranking of available treatments**?"
- A PRACTical trial combines evidence from multiple patients in which different pairs (or sets) of treatments are compared
  - Exploiting direct and indirect evidence across the network in a statistically principled way

NeoSep1 Part 1



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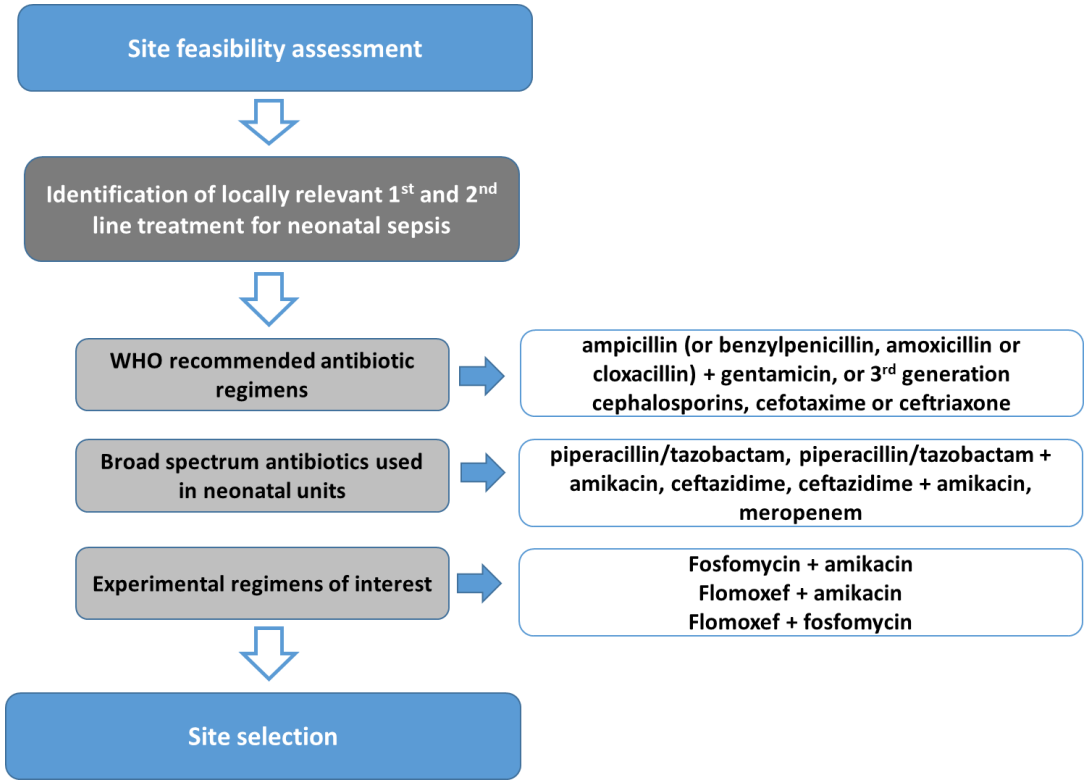
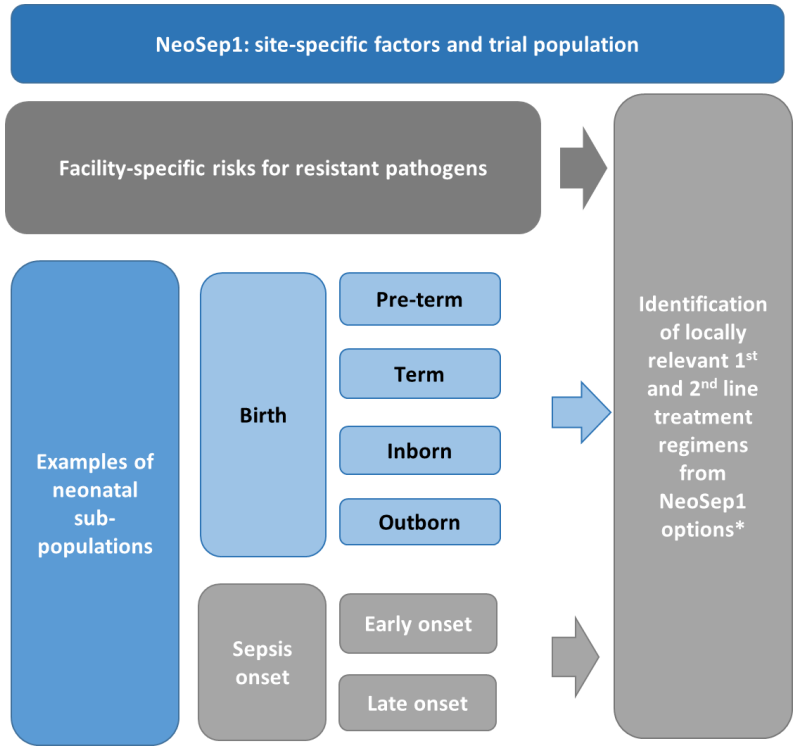
GARDP Global Antibiotic Research & Development Partnership

St George's University of London

Part of City St George's, University of London

NeoSep1 Part 2 set-up





* Local protocols and practice, not centrally determined

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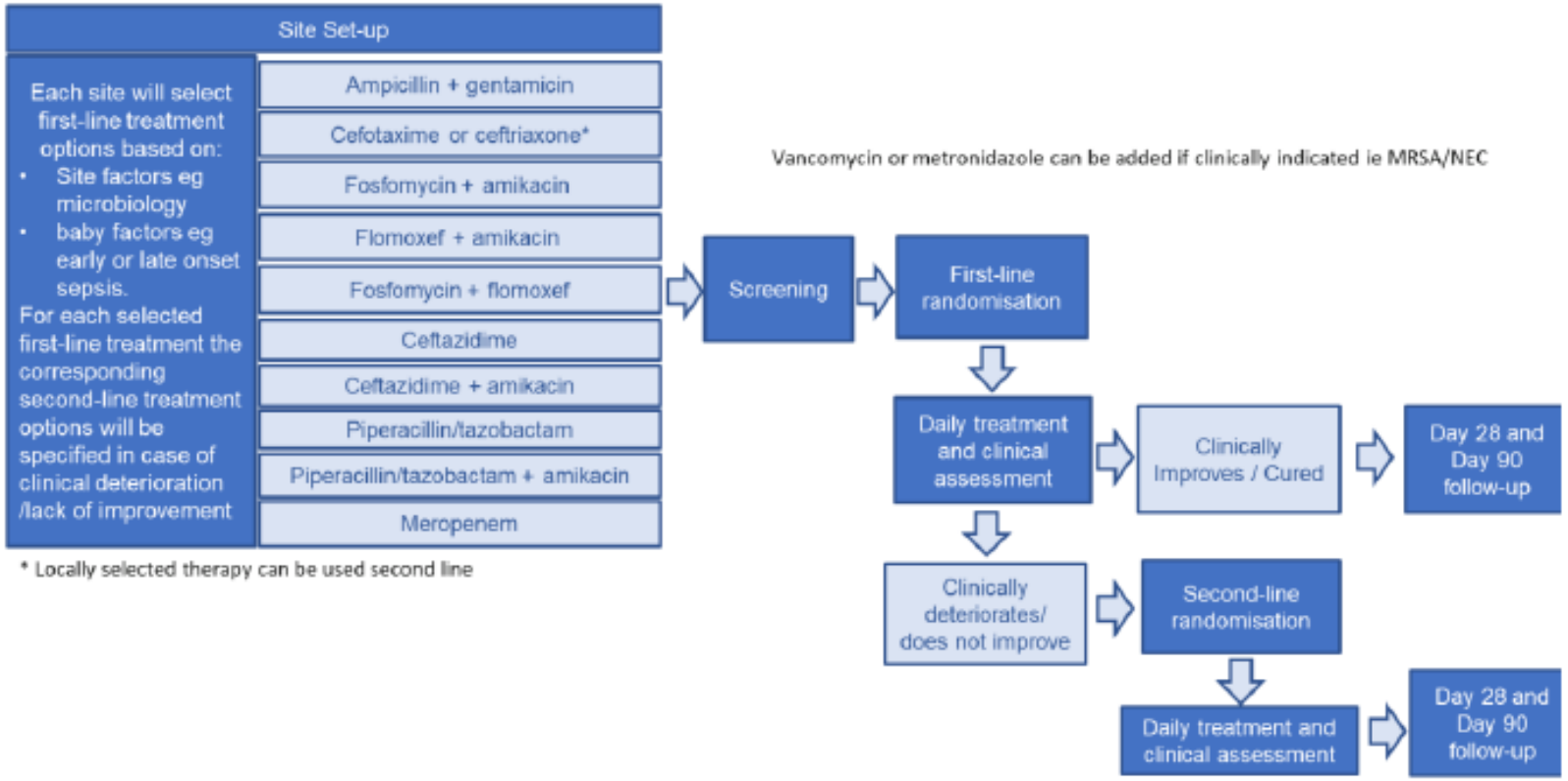
NeoSep1 Part 2



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GARDP Global Antibiotic Research & Development Partnership

St George's University of London

NeoSep1 randomisation list

Site set-up	
Each site selects first-line treatment options based on site and baby factors	Ampicillin + gentamicin
	Cefotaxime or ceftriaxone
	Fosfomycin + amikacin
	Flomoxef + amikacin
	Fosfomycin + flomoxef
	Ceftazidime
	Ceftazidime + amikacin
	Piperacillin/tazobactam
	Piperacillin/tazob + amikacin
	Meropenem

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NeoSepI

Site set-up	
Each site selects first-line treatment options based on site and baby factors	Ampicillin + gentamicin
	~~Cefotaxime or ceftriaxone~~
	Fosfomycin + amikacin
	Flomoxef + amikacin
	Fosfomycin + flomoxef
	~~Ceftazidime~~
	~~Ceftazidime + amikacin~~
	~~Piperacillin/tazobactam~~
	~~Piperacillin/tazob + amikacin~~
	~~Meropenem~~

- Early onset sepsis

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NeoSep1

Site set-up	
Each site selects first-line treatment options based on site and baby factors	~~Ampicillin + gentamicin~~
	~~Cefotaxime or ceftriaxone~~
	Fosfomycin + amikacin
	Flomoxef + amikacin
	Fosfomycin + flomoxef
	Ceftazidime
	Ceftazidime + amikacin
	Piperacillin/tazobactam
	Piperacillin/tazob + amikacin
	~~Meropenem~~

- Late onset sepsis

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NeoSep1

Site set-up

Each site selects first-line treatment options based on site and baby factors

- Ampicillin + gentamicin
- Cefotaxime or ceftriaxone
- Fosfomycin + amikacin
- Flomoxef + amikacin
- Fosfomycin + flomoxef
- Ceftazidime
- Ceftazidime + amikacin
- Piperacillin/tazobactam
- Piperacillin/tazob + amikacin
- Meropenem

Screening → Randomise: First line → Daily assessment

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NeoSepI

Site set-up

Each site selects first-line treatment options based on site and baby factors

- Ampicillin + gentamicin
- Cefotaxime or ceftriaxone
- Fosfomycin + amikacin
- Flomoxef + amikacin
- Fosfomycin + flomoxef
- Ceftazidime
- Ceftazidime + amikacin
- Piperacillin/tazobactam
- Piperacillin/tazob + amikacin
- Meropenem

Screening → Randomise: First line → Daily assessment → Cure/ Improved → Complete F/U

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NeoSepI

Site set-up

Each site selects first-line treatment options based on site and baby factors

- Ampicillin + gentamicin
- Cefotaxime or ceftriaxone
- Fosfomycin + amikacin
- Flomoxef + amikacin
- Fosfomycin + flomoxef
- Ceftazidime
- Ceftazidime + amikacin
- Piperacillin/tazobactam
- Piperacillin/tazob + amikacin
- Meropenem

Screening → Randomise: First line → Daily assessment → Cure/ Improved → Complete F/U

Daily assessment → Deteriorates /not improved

In NeoOBS study, 25% of initial regimens in Group 1-4 were escalated, mainly to carbapenems, and usually for clinical indications

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Sequential Multiple Assignment Randomised controlled Trials – SMART designs

A "SMART" Design for Building Individualized Treatment Sequences

H. Lei,[1] I. Nahum-Shani,[2] K. Lynch,[3] D. Oslin,[4] and S.A. Murphy[5]

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Annu. Rev. Clin. Psychol. 2012. 8:21–48

Keywords

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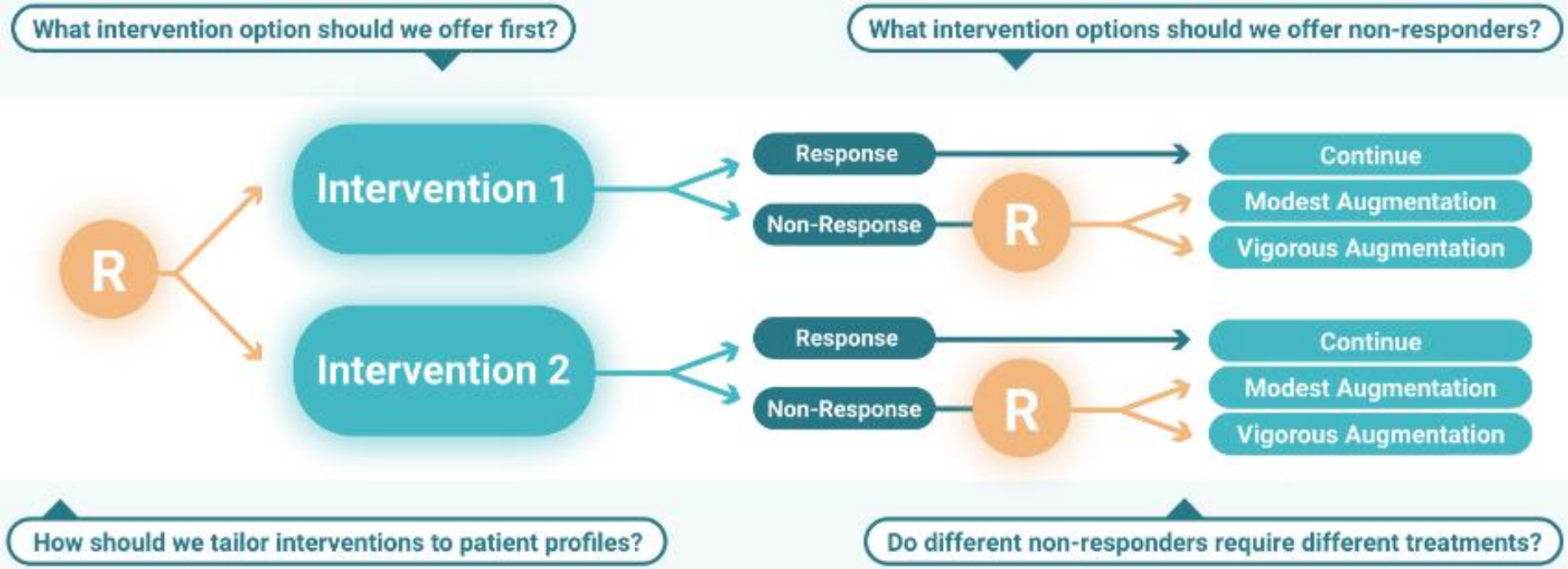
doi: 10.1146/annurev-clinpsy-032511-143152

Sequential Multiple Assignment Randomised controlled Trials – SMART designs



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NeoSepI protocol implementation plan

Part 1

- Enrolment: 60 babies
- Empiric treatments:
  - fosfomycin and amikacin
  - flomoxef and amikacin
  - flomoxef and fosfomycin
- Outcome measures:
  - PK
  - Safety
- Expected duration: recruitment-driven

COMPLETED ☺

Part 2

- Enrolment: ~3,000 babies
- Relevant first and second line regimens in locally defined lists for specific groups of neonates
- Outcome measures:
  - Efficacy (28 and 90 day mortality)
  - Clinical status at day 28
  - Safety
- Expected duration: 36-42 months to reach sample size

EXPECTED TO OPEN IN DEC-2024 ☺

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NeoSep1

NeoSep1 Part 2
Final antibiotic randomisation list agreement:
Chris Hani Baragwanath Hospital, Johannesburg, South Africa

v1.0 22/09/2024

Six first-line randomisation lists have been designed by MRC CTU and SGUL for the NeoSep1 Part 2 trial. These combinations are outlined in Table 1 below.

Table 1: Possible first-line randomisation combinations

1	Penicillin* + Gentamicin Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef	4	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin Meropenem
2	Penicillin* + Gentamicin Cefotaxime or Ceftriaxone Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef	5	Cefotaxime or Ceftriaxone Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin
3	Penicillin* + Gentamicin Cefotaxime or Ceftriaxone Fosfomycin + Amikacin Flomoxef + amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin	6	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Meropenem

*Penicillin refers to a site-directed choice of one of ampicillin, benzylpenicillin, amoxicillin, cloxacillin or flucloxacillin

Specific additional antibiotics

These antibiotics can be added to address any gaps in coverage in specific scenarios as outlined below:

- Vancomycin for suspected MRSA and other Gram-positive infections
- Metronidazole for suspected anaerobic infections, including necrotising enterocolitis (NEC)
- Ampicillin for suspected *Listeria* infections, or for suspected enterococcal infections where this is a specific concern at a site, e.g., in outbreak situations
- Penicillin for congenital syphilis or for Group B Streptococcus

NeoSep1

First-line randomisation lists

The Chris Hani Baragwanath Hospital, Johannesburg site has defined and selected clinical subgroups that correspond to the neonates commonly treated on their neonatal unit and has agreed on the selected first-line antibiotic randomisation lists, chosen from Table 1. The Baragwanath site agrees that neonates falling into these clinical subgroups could be enrolled in the NeoSep1 Part 2 trial and can be randomised to receive any of the first-line antibiotic regimens within the corresponding selected randomisation list, as defined in Table 2.

Table 2: Chris Hani Baragwanath Hospital first line antibiotic randomisation list choices

Subgroup	Clinical subgroups	Agreed first line randomisation List	
A	Early-onset sepsis with or without meningitis	2	Ampicillin*± Gentamicin Cefotaxime† Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef
B	Nosocomial Sepsis	4	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin Meropenem
C	High index of suspicion of necrotising enterocolitis	4	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin Meropenem
D	Nosocomial meningitis	6	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Meropenem
E	Other neonates suitable for randomisation to List 2	2	Ampicillin*± Gentamicin Cefotaxime† Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef

*Site selection of penicillin: ampicillin chosen for subgroups A and E

†Site selection of 3rd generation cephalosporin: cefotaxime chosen for subgroups A and E

NeoSep1

Table 2 (cont…)

Subgroup	Clinical subgroups	Agreed first line randomisation List	
F	Other neonates suitable for randomisation to List 4	4	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Piperacillin/tazobactam + Amikacin Meropenem
G	Other neonates suitable for randomisation to List 6	6	Fosfomycin + Amikacin Flomoxef + Amikacin Fosfomycin + Flomoxef Ceftazidime + Amikacin Meropenem

NeoSep1

Second-line randomisation lists

The Chris Hani Baragwanath Hospital, Johannesburg site agrees that neonates enrolled in the NeoSep1 Part 2 trial who require second-line antibiotic treatment, e.g., if they are not improving or are deteriorating on first line therapy, can be randomised, where appropriate, to the second-line antibiotic regimens displayed in Table 3. Appropriate second-line antibiotic regimens are informed and determined by the first-line regimen the neonate has been randomised to and whether there is a low or high suspicion of meningitis.

Table 3: Chris Hani Baragwanath Hospital second line antibiotic randomisation list choices

Low suspicion of meningitis	
First-line Therapy Received	**Second-Line Randomisation list**
Ampicillin + Gentamicin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Piperacillin-Tazobactam + Amikacin • Meropenem
Cefotaxime	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Piperacillin-Tazobactam + Amikacin • Meropenem
Fosfomycin + Amikacin	• Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Piperacillin-Tazobactam + Amikacin • Meropenem
Flomoxef + Amikacin	• Fosfomycin + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Piperacillin-Tazobactam + Amikacin • Meropenem
Fosfomycin + Flomoxef	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Ceftazidime + Amikacin • Piperacillin-Tazobactam + Amikacin • Meropenem
Ceftazidime + Amikacin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Meropenem

NeoSep1

Table 3 (cont…)

Low suspicion of meningitis	
First-line Therapy Received	**Second-Line Randomisation list**
Piperacillin-Tazobactam + Amikacin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem
Meropenem	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef
High suspicion of meningitis	
Ampicillin + Gentamicin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem
Cefotaxime	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem
Fosfomycin + Amikacin	• Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem
Flomoxef + Amikacin	• Fosfomycin + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem
Fosfomycin + Flomoxef	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Ceftazidime + Amikacin • Meropenem
Ceftazidime + Amikacin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Meropenem
Piperacillin-Tazobactam + Amikacin	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef • Ceftazidime + Amikacin • Meropenem

NeoSep1 Part 2_Final Randomisation Lists_Chris Hani Baragwanath_South Africa_v1.0_20240922

NeoSep1

Table 3 (cont…)

High suspicion of meningitis	
First-line Therapy Received	**Second-Line Randomisation list**
Meropenem	• Fosfomycin + Amikacin • Flomoxef + Amikacin • Fosfomycin + Flomoxef

Locally selected therapy	None specified by site

I, the Principal Investigator for the NeoSep1 trial at Chris Hani Baragwanath Hospital, Johannesburg, South Africa, confirm that the above clinical subgroups and selected first- and second-line antibiotic randomisation lists have been agreed with the research and clinical teams involved with the NeoSep1 trial at this site. I understand these antibiotic randomisation lists (1st and 2nd line) cannot be changed without prior discussion and written agreement from the site team and the NeoSep1 management team. Any changes to the clinical sub-groups and/or antibiotic randomisation lists will need to be programmed in the database before they can be used for the purpose of the trial.

Signature: X _____ Name: Click or tap here to enter text.

Date: Click or tap to enter a date.

The NeoSep1 management team have reviewed and agree with the first- and second-line antibiotic randomisation lists chosen by the Chris Hani Baragwanath site for the NeoSep1 trial.

Signature: X _____ Name: Click or tap here to enter text.

Date: Click or tap to enter a date.

NeoSep1 Part 2_Final Randomisation Lists_Chris Hani Baragwanath_South Africa_v1.0_20240922

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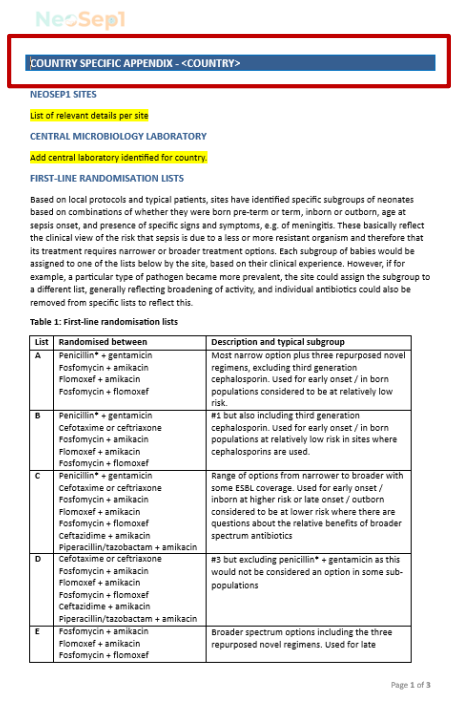
Lessons learned

- Protocol structure is key to successful implementation
  - Engagement with regulators and policy makers
  - Futureproofing protocol implementation
    - PK and dose confirmation study
    - Adding new treatment regimens to the trial
    - Country-specific appendix for antibiotic regimens list



NeoSep1

COUNTRY SPECIFIC APPENDIX - <COUNTRY>

NEOSEP1 SITES

List of relevant details per site

CENTRAL MICROBIOLOGY LABORATORY

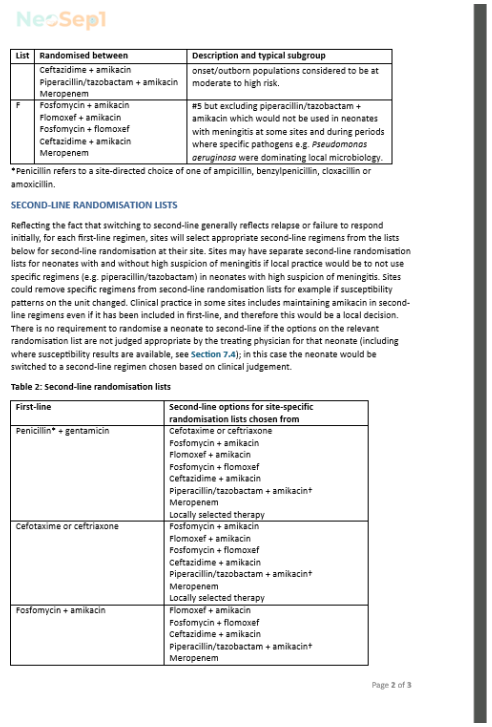
Add central laboratory identified for country.

FIRST-LINE RANDOMISATION LISTS

Based on local protocols and typical patients, sites have identified specific subgroups of neonates based on combinations of whether they were born pre-term or term, inborn or outborn, age at sepsis onset, and presence of specific signs and symptoms, e.g. of meningitis. These basically reflect the clinical view of the risk that sepsis is due to a less or more resistant organism and therefore that its treatment requires narrower or broader treatment options. Each subgroup of babies would be assigned to one of the lists below by the site, based on their clinical experience. However, if for example, a particular type of pathogen became more prevalent, the site could assign the subgroup to a different list, generally reflecting broadening of activity, and individual antibiotics could also be removed from specific lists to reflect this.

Table 1: First-line randomisation lists

List	Randomised between	Description and typical subgroup
A	Penicillin* + gentamicin Fosfomycin + amikacin Flomoxef + amacin Fosfomycin + flomoxef	Most narrow option plus three repurposed novel regimens, excluding third generation cephalosporin. Used for early onset / in born populations considered to be at relatively low risk.
B	Penicillin* + gentamicin Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef	#1 but also including third generation cephalosporin. Used for early onset / in born populations at relatively low risk in sites where cephalosporins are used.
C	Penicillin* + gentamicin Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin	Range of options from narrower to broader with some ESBL coverage. Used for early onset / inborn at higher risk or late onset / outborn considered to be at lower risk where there are questions about the relative benefits of broader spectrum antibiotics
D	Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin	#3 but excluding penicillin* + gentamicin as this would not be considered an option in some sub-populations
E	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef	Broader spectrum options including the three repurposed novel regimens. Used for late



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List	Randomised between	Description and typical subgroup
	Ceftazidime + amikacin Piperacillin/tazobactam + amikacin Meropenem	onset/outborn populations considered to be at moderate to high risk.
F	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Meropenem	#5 but excluding piperacillin/tazobactam + amikacin which would not be used in neonates with meningitis at some sites and during periods where specific pathogens e.g. *Pseudomonas aeruginosa* were dominating local microbiology.

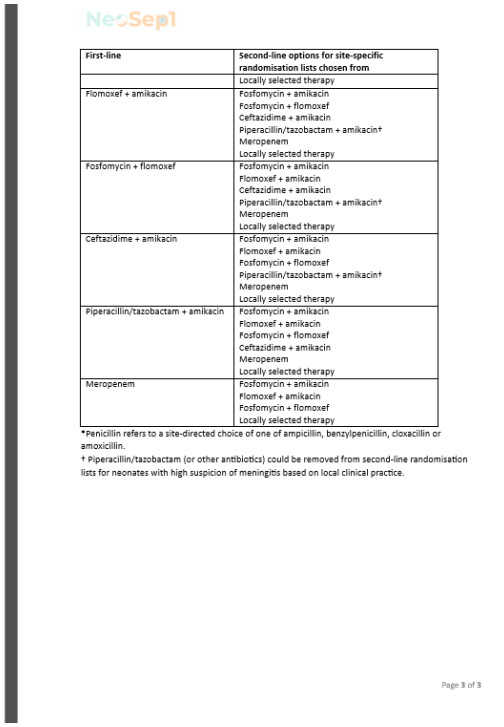
*Penicillin refers to a site-directed choice of one of ampicillin, benzylpenicillin, cloxacillin or amoxicillin.

SECOND-LINE RANDOMISATION LISTS

Reflecting the fact that switching to second-line generally reflects relapse or failure to respond initially, for each first-line regimen, sites will select appropriate second-line regimens from the lists below for second-line randomisation at their site. Sites may have separate second-line randomisation lists for neonates with and without high suspicion of meningitis if local practice would be to not use specific regimens (e.g. piperacillin/tazobactam) in neonates with high suspicion of meningitis. Sites could remove specific regimens from second-line randomisation lists for example if susceptibility patterns on the unit changed. Clinical practice in some sites includes maintaining amikacin in second-line regimens even if it has been included in first-line, and therefore this would be a local decision. There is no requirement to randomise a neonate to second-line if the options on the relevant randomisation list are not judged appropriate by the treating physician for that neonate (including where susceptibility results are available, see Section 7.4); in this case the neonate would be switched to a second-line regimen chosen based on clinical judgement.

Table 2: Second-line randomisation lists

First-line	Second-line options for site-specific randomisation lists chosen from
Penicillin* + gentamicin	Cefotaxime or ceftriaxone Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Cefotaxime or ceftriaxone	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Fosfomycin + amikacin	Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem



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First-line	Second-line options for site-specific randomisation lists chosen from
	Locally selected therapy
Flomoxef + amikacin	Fosfomycin + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Fosfomycin + flomoxef	Fosfomycin + amikacin Flomoxef + amikacin Ceftazidime + amikacin Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Ceftazidime + amikacin	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Piperacillin/tazobactam + amikacin† Meropenem Locally selected therapy
Piperacillin/tazobactam + amikacin	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Ceftazidime + amikacin Meropenem Locally selected therapy
Meropenem	Fosfomycin + amikacin Flomoxef + amikacin Fosfomycin + flomoxef Locally selected therapy

*Penicillin refers to a site-directed choice of one of ampicillin, benzylpenicillin, cloxacillin or amoxicillin.

† Piperacillin/tazobactam (or other antibiotics) could be removed from second-line randomisation lists for neonates with high suspicion of meningitis based on local clinical practice.

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Lessons learned

- Complex design requires an extensive educational package for sites
    - Podcast
    - Demonstration of possible randomisation scenarios
    - 1:1 site feasibility calls to understand local practice

Lessons learned

- Working with global and international sites and partners can bring challenges in contract negotiation and communication
    - Starting small before going big
    - Unpredictability of industry partners

Lessons learned

- Different operational requirements can lead to protracted development of trial procedures
  - Multiple collaborators can lead to duplication of processes
  - Importance of clear division of responsibilities
  - Public health trials ≠ regulatory trials

- Complex design and randomisation
  - Co-development of Part 1 and Part 2
  - Ongoing discussion and learning with sites

Lessons learned

- Need of aligned strategic outlook
  - Long-term commitment to public health goals
  - Collaboration and networking platform
  - Pragmatic, public health trial
  - Building trust

- Much more time and %FTE for data management, clinical operations and clinicians to get things right!

- Innovative trials may answer more questions more efficiently BUT they require substantive increases in funding for statistics, operations and clinical expertise, particularly at the funding and set-up stage, but also throughout the trial

Lessons learned

Database set-up

Treatment selection regimens

Randomisation system

Risk-proportionate management

Future-proofing conduct

Complex project management

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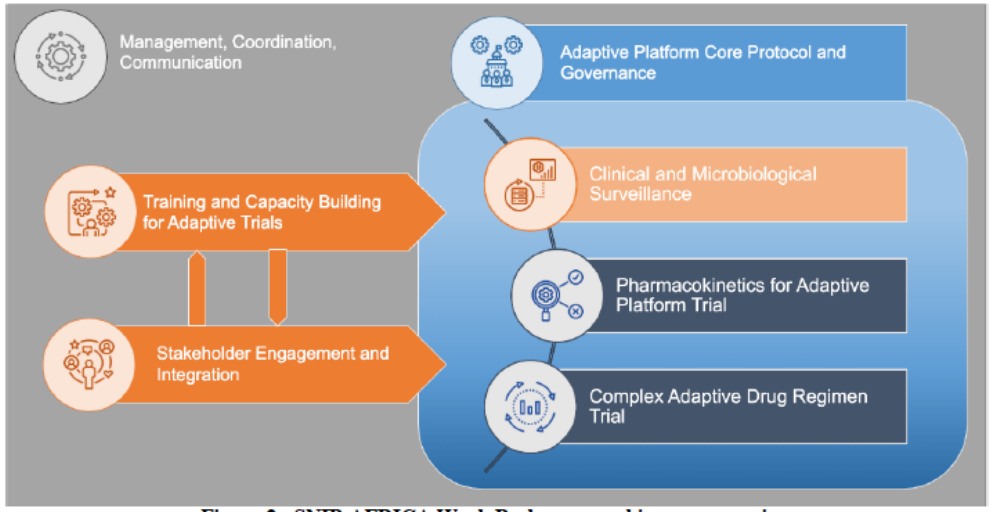
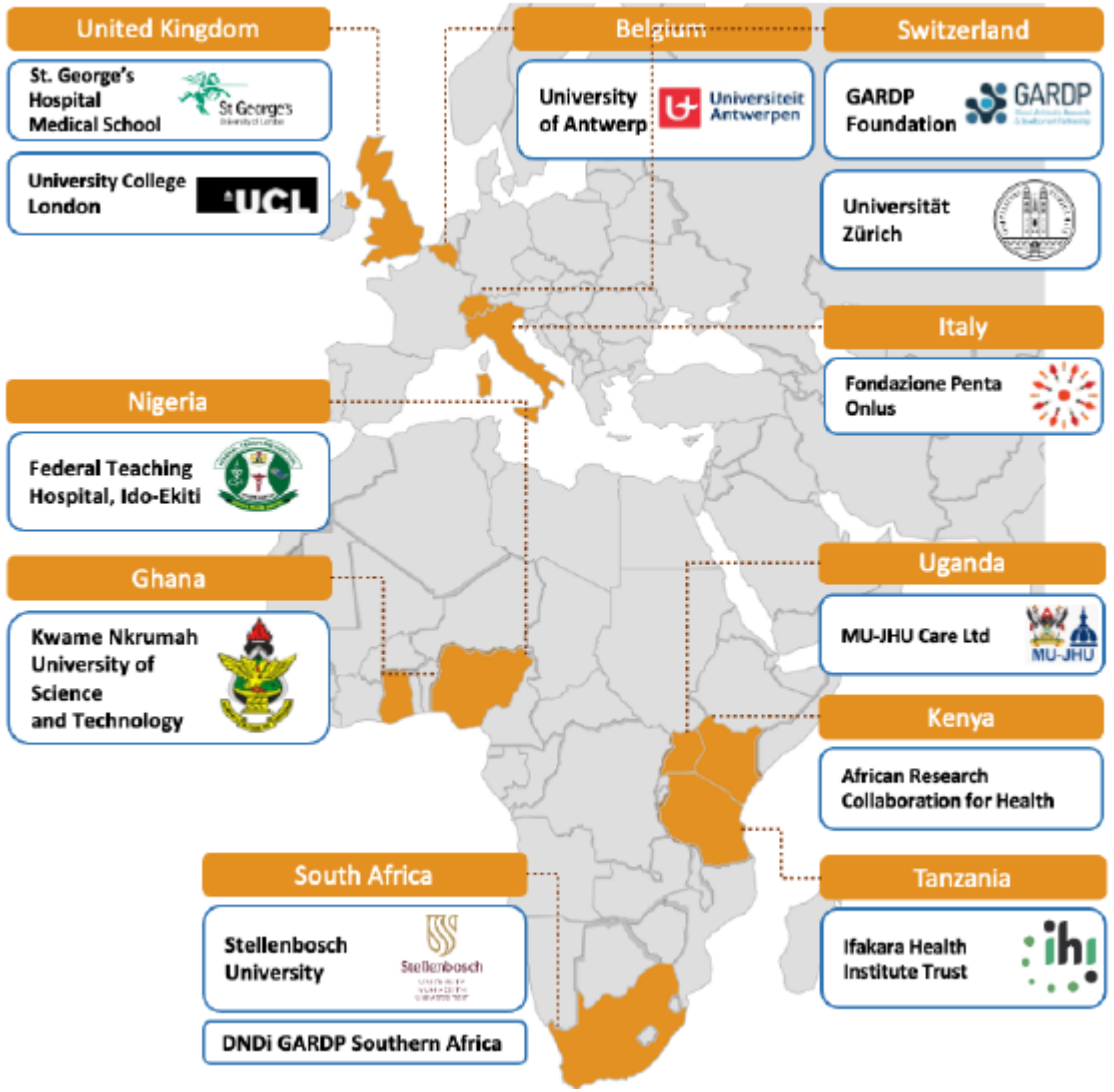
A different kind of platform

SNIP-AFRICA





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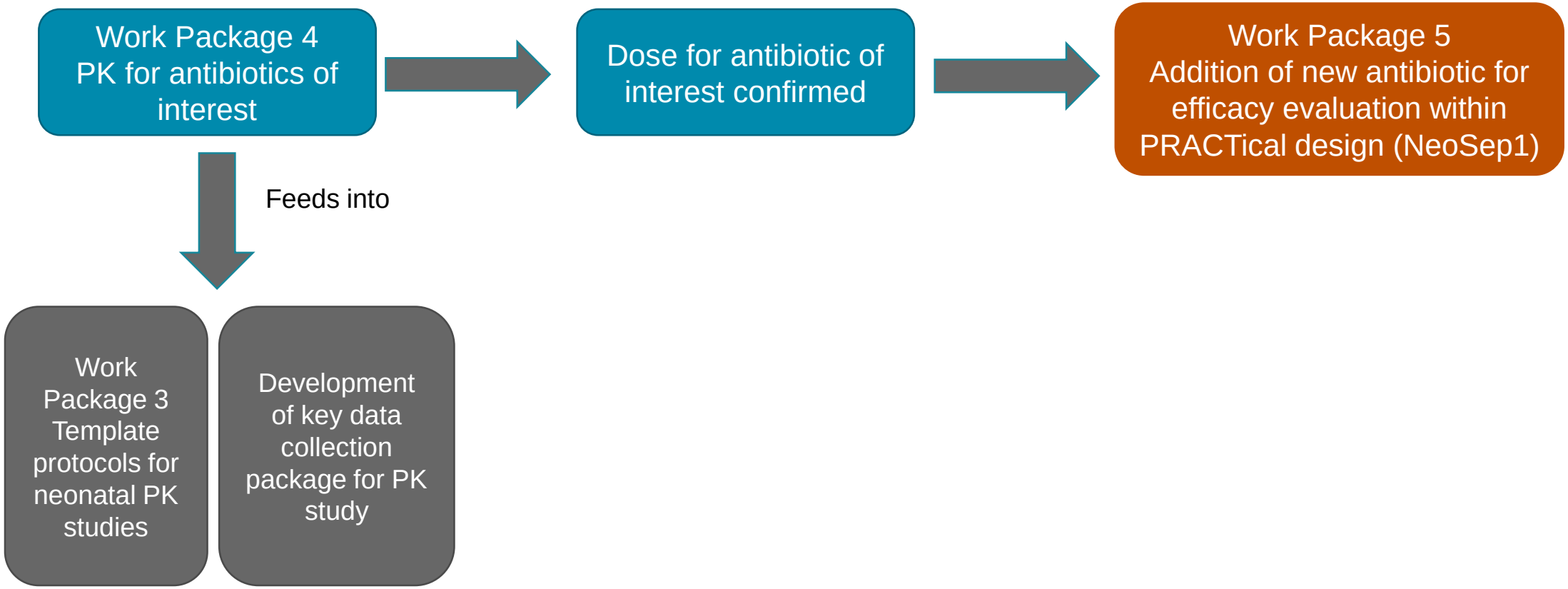
SNIP-AFRICA

Global Health EDCTP3

SNIP-AFRICA (Project No. 101103201) is supported by the Global Health EDCTP3 and its members (the European Union and the EDCTP Association).

SNIP-AFRICA how will it work in practice?



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Different questions, same design

Snakebite

- 2700 species of snake worldwide
  - Small proportion (600) venomous and 250 of medical importance
  - Huge variability in size, shape and behaviour (highly adapted to environment)

- Snakebite → Highest Disability-adjusted life years (DALYs) among all neglected tropical diseases
- Antivenom as treatment for snakebites for over 100 years BUT
  - Issues with efficacy
  - Issues with quality
  - Issues with safety

Snakebite

https://www.who.int/publications/i/item/9789241515641

- Limited number of RCT since 1964
  - Approx 2,000 participants recruited in RCT
  - Mostly in Asia and Latin-America
- No global SOC

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ANYSNAKES trial

- Evaluate safety and efficacy of existing and new antivenoms in Sub-Saharan Africa
- Develop new evidence base for policy makers
  - Of the different antivenoms being evaluated, which is the best treatment to recommend?
  - What is the ranking of these antivenoms

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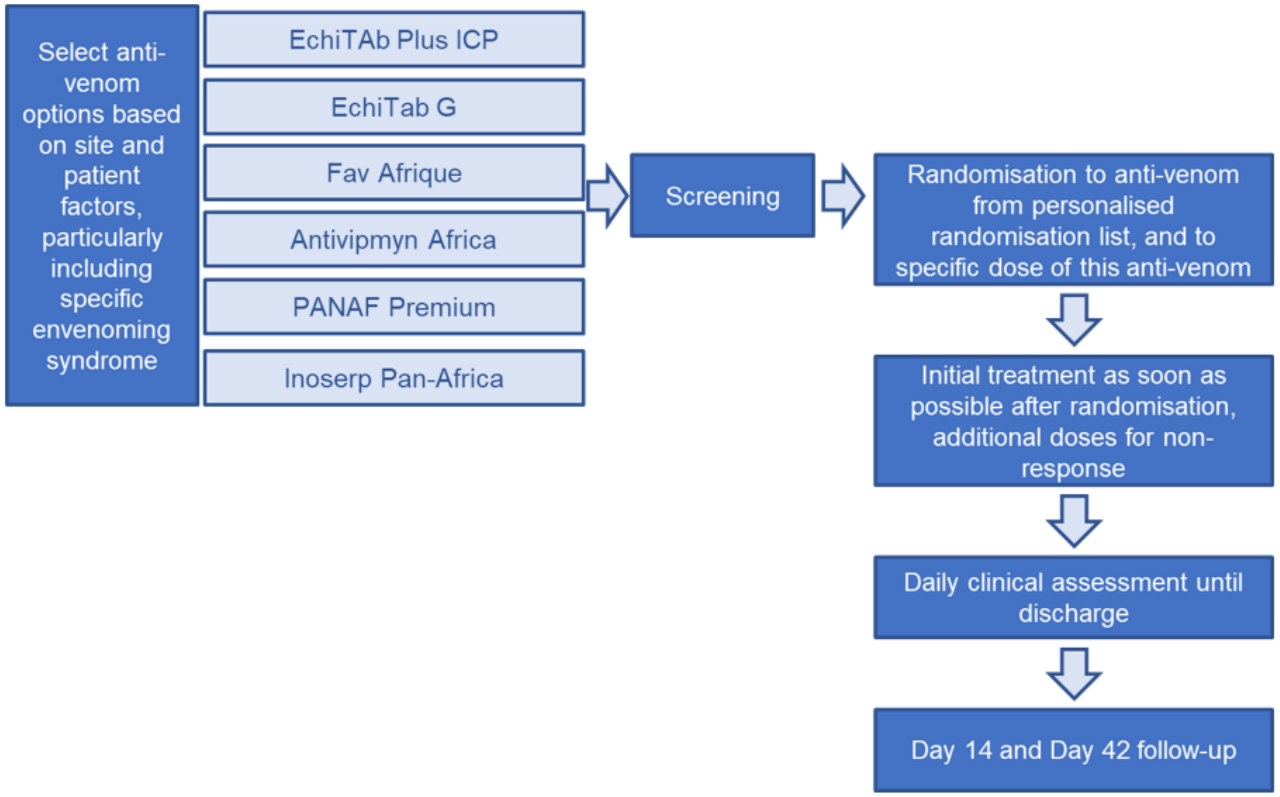
wellcome

LSTM

ANYSNAKES trial

- Clinical syndromes
  - Coagulopathy syndromes and Shock (2000 participants)
  - Neurotoxicity (100 participants)
- Implementation of PRACTical design + dose optimisation
  - Each site will select a set of antivenoms
  - Each participant will be randomised to a site-specific randomisation list based on clinical syndrome at presentation
- Discussion with regulators ongoing
  - AVAREF

ANYSNAKES trial



Anti-venom	Coagulopathy				Shock			
	Site 1	Site 2	Site 3	Site 4	Site 1	Site 2	Site 3	Site 4
A	X	X		X	X	X		X *
B	X	X	X		X	X	X *	
C	X		X	X				
D		X	X	X				

* no antivenom randomisation

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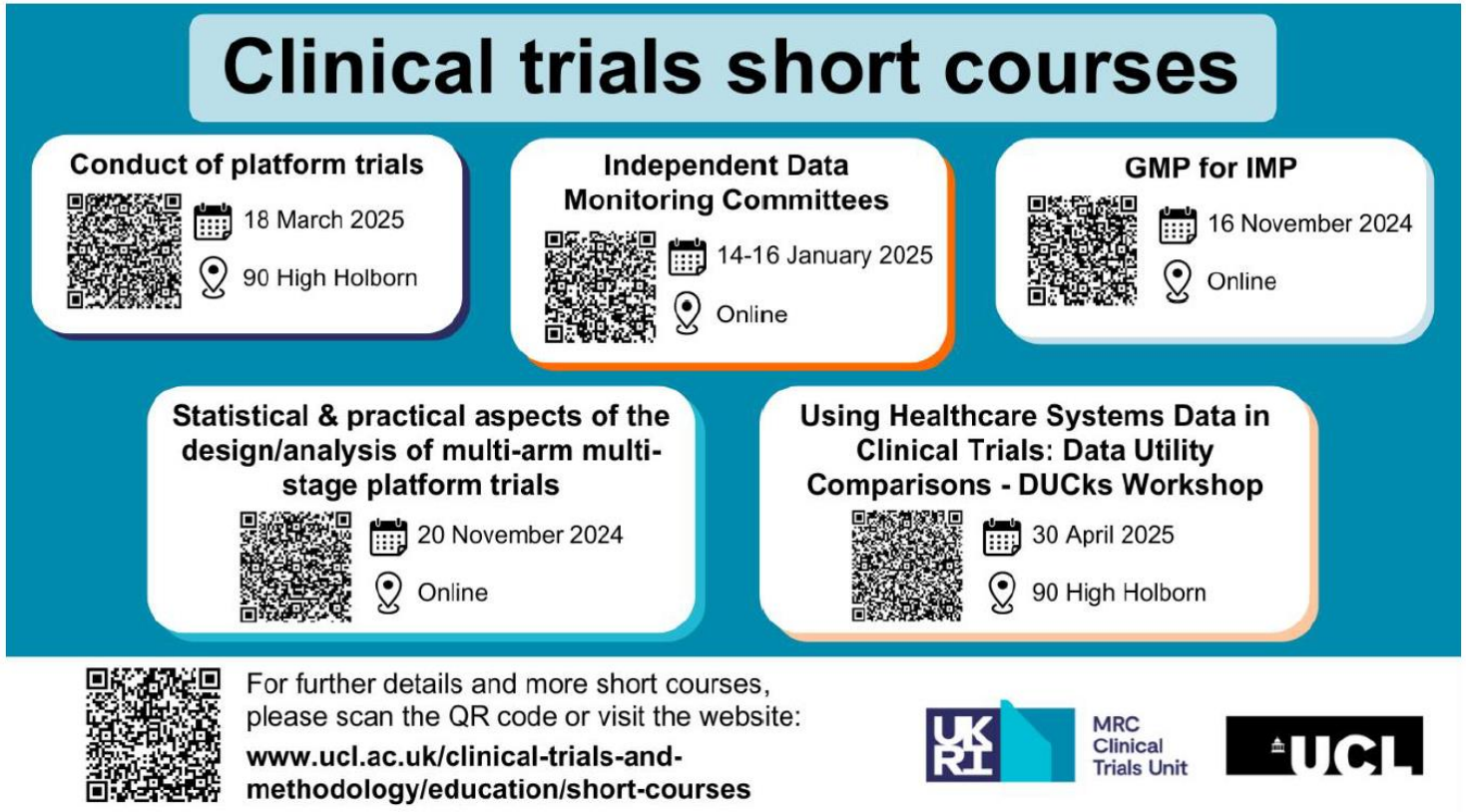
More to learn and more to do!

Courses and post-graduate education



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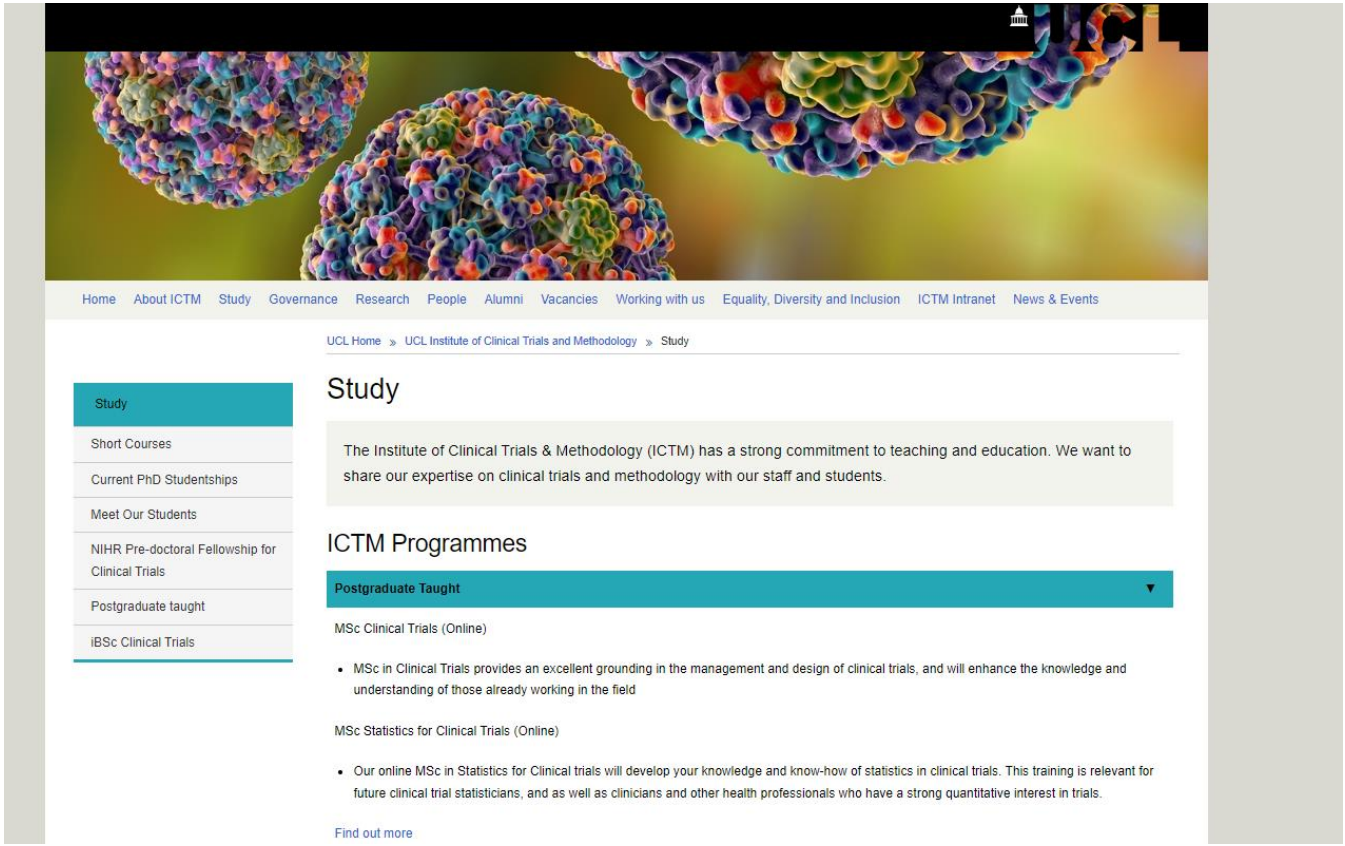
https://www.ucl.ac.uk/clinical-trials-and-methodology/study/short-courses/conduct-platform-trials

Courses and post-graduate education



https://www.ucl.ac.uk/clinical-trials-and-methodology/study/postgraduate-taught

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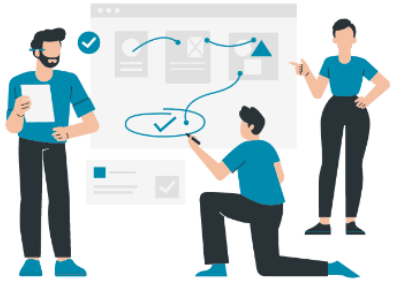

Sharing our expertise in Multi-Arm Multi-Stage (MAMS) trials and platform protocols

We run the "MAMS Clinic". This is an advisory service on how to optimise the design, implementation, and analysis of your multi-arm multi-stage (MAMS) randomised platform trial. We provide advice on how to maximise the efficient of testing several treatments for you and the community.

This initiative is led by our MAMS experts, including Prof **Mahesh Parmar** and Dr **Babak Choodari-Oskooei**. Our team can further advice on practical implementation.

The sessions are usually online and have a duration of one hour approximately.

In the short time we have been running the MAMS Clinics, we have provided advice to researchers from several institutions, including Ulm University (Germany), University of Rotterdam (the Netherlands), University of Nottingham (UK), University of Cambridge (UK), Bern University Hospital (Switzerland), Bradford Institute for Health Research (UK).

> *"The MAMS Clinic is an outstanding opportunity to discuss complex design problems with real experts, their support helped us a lot!"*
>
> Professor Dr Benjamin Mayer - Ulm University, Germany

> *"During our first discussion, Prof Parmar and Dr Choodari immediately understood what we had in mind and were able to tease out problems and potential solutions. They helped us shape and develop a strong trial design that fitted our representations. In addition, their expertise was*

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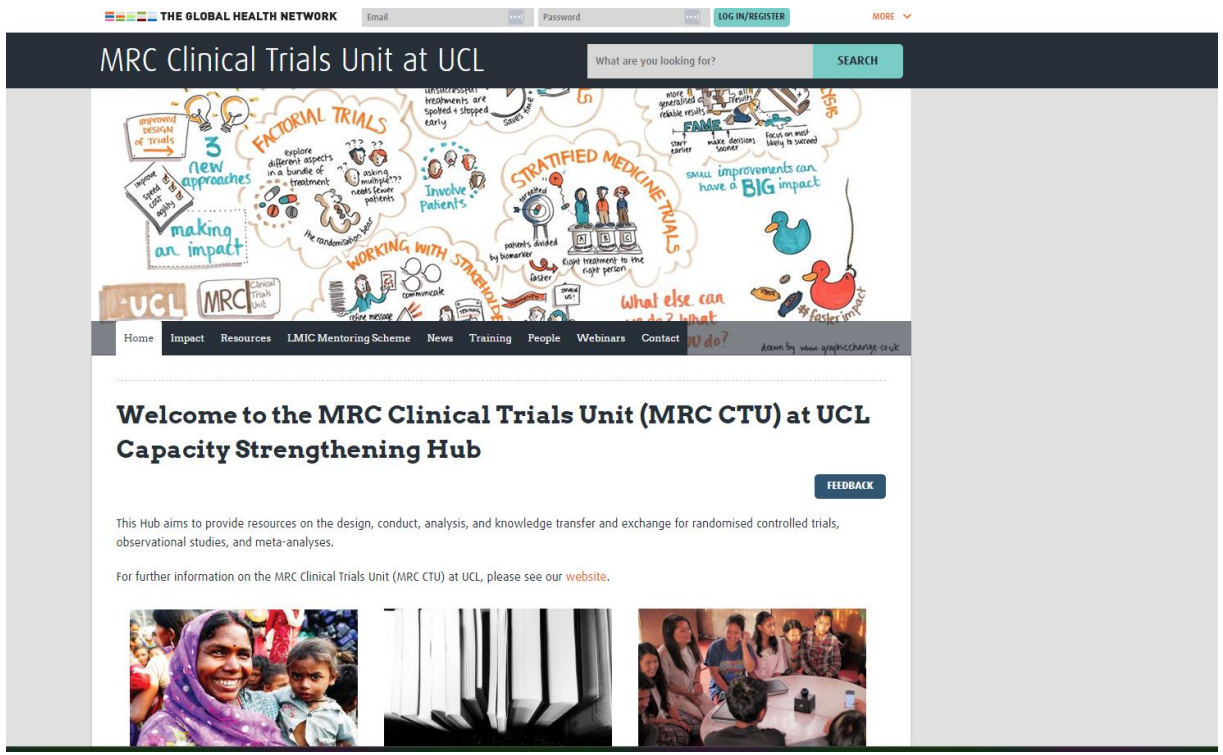
MRC CTU at UCL Capacity Strengthening Hub



EXPLORE ALL RESOURCES				
FUNDING AND GRANTS	LITERATURE SEARCHING	SETTING UP TRIALS OR STUDIES	TRIAL OR STUDY DESIGN	RECRUITMENT AND RETENTION
OBSERVATIONAL STUDIES	METHODOLOGY	META ANALYSIS	CLINICAL TRIALS	RISK ASSESSMENT
ETHICS	REGULATORY MATTERS	SAFETY MANAGEMENT	MANAGING AND SUPPORTING SITES	MONITORING
PATIENT AND PUBLIC INVOLVEMENT (PPI)	STATISTICS	QUALITY ASSESSMENT IN META ANALYSIS	DATA PREPARATION AND MANAGEMENT	DATA SHARING
HEALTH ECONOMICS	COMMUNICATION AND KNOWLEDGE TRANSFER	MENTORING	TRIAL AND STUDY MANAGEMENT	JOB ROLES IN TRIALS AND CLINICAL RESEARCH

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https://mrcctu.tghn.org/

MRC CTU at UCL: LMIC mentoring scheme

- Aim - to link those working on clinical trials and studies in different organisations/countries for online mentoring
- Mentoring can be role-specific or for other goals such as career development, promotion, work-life balance, or building self-confidence
- Mentoring to be North-South, South-South or South-North
- Self-led training, quiz and useful documents available on Hub
- 58 mentors/mentees matched so far
- We need more mentors – don't need to be very senior depending on subject

Webinar
'Making the best of Mentoring'
30 January 2024

Watch recording here

Looking for mentors from MRC CTU

Info and sign up here

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Adaptive platform trials: challenges, solutions and opportunities in trial conduct

Francesca Schiavone (PhD)
MRC Clinical Trials Unit at UCL
Institute for Clinical Trials and Methodology

03-Oct-2024| Adaptive Platform Trials Scientific Meeting| Toronto, ON, Canada

Smarter Studies
Global Impact
Better Health