

Platform Trials Symposium Program

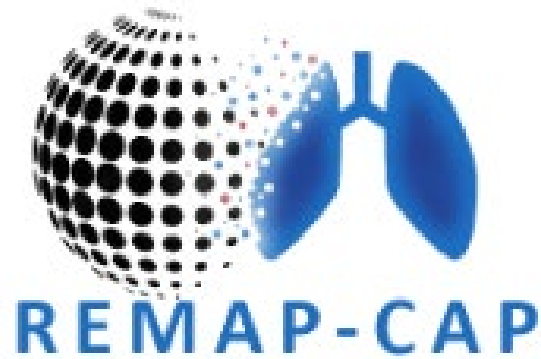
UK	CH	BNE	Session
07:00	08:00	16:00	<i>Keynote — Global scalability of platform trials</i> Steve Webb (AUS) 30 min presentation + 10 min Q&A
07:40	08:40	16:40	<i>Presentation — Federated platform trials and data-sharing frameworks</i> Paul Mouncey (UK) 15 min + 5 min Q&A
08:00	09:00	17:00	<i>Presentation — Workforce capability and capacity building</i> Patricia Gilholm (AUS) • Rebecca Mitting (UK) 15 min + 5 min Q&A
08:20	09:20	17:20	<i>Panel Discussion — Funding models for long-term infrastructure</i> Kristen Gibbons (AUS) • Padmanabhan Ramnarayan (UK) • Luregn Schlapbach (CH) 30 min discussion
08:50	09:50	17:50	<i>Presentation — Ethical considerations</i> Asha Bowen (AUS) 15 min + 5 min Q&A
09:10	10:10	18:10	<i>Presentation — Patient and Family Engagement</i> Julie Menzies (UK) 15 min + 5 min Q&A
09:30	10:30	18:30	Closing Remarks

Federated Platform Trials and Data - Sharing Frameworks

Paul Mouncey, Co - Director
ICNARC



Platform experience/disclosures



REMAP-CAP and PIVOTAL receive funding from the NIHR Health Technology Assessment programme. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Scope

- Platform trials
- Federated design
- Data oversight and sharing
- Planning for federation

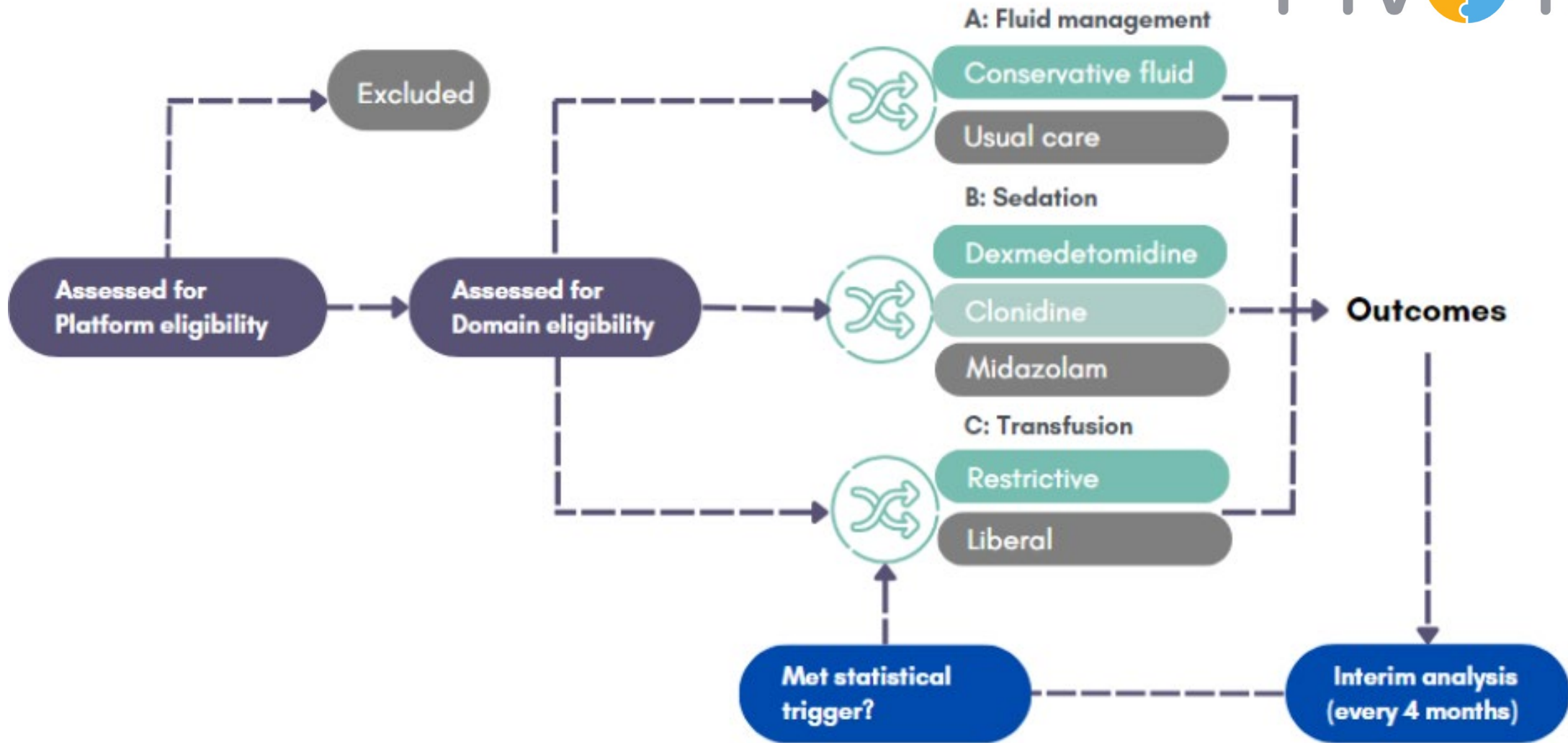
Platform trials

Platform trials

Table. General Characteristics of Traditional and Platform Trials^a

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

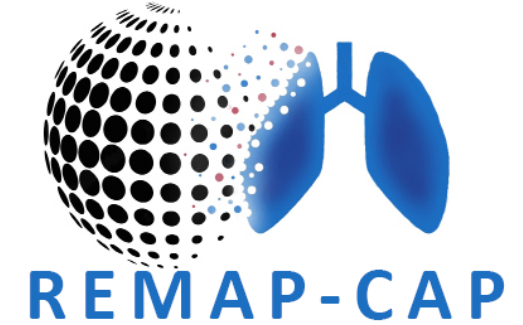
Platform trials



Platform trials



PANTHER



Federated design

Federated learning in observational research

Journal of the American Medical Informatics Association, 2024, **31(3)**, 651–665

<https://doi.org/10.1093/jamia/ocad235>

Advance access publication 21 December 2023

Research and Applications



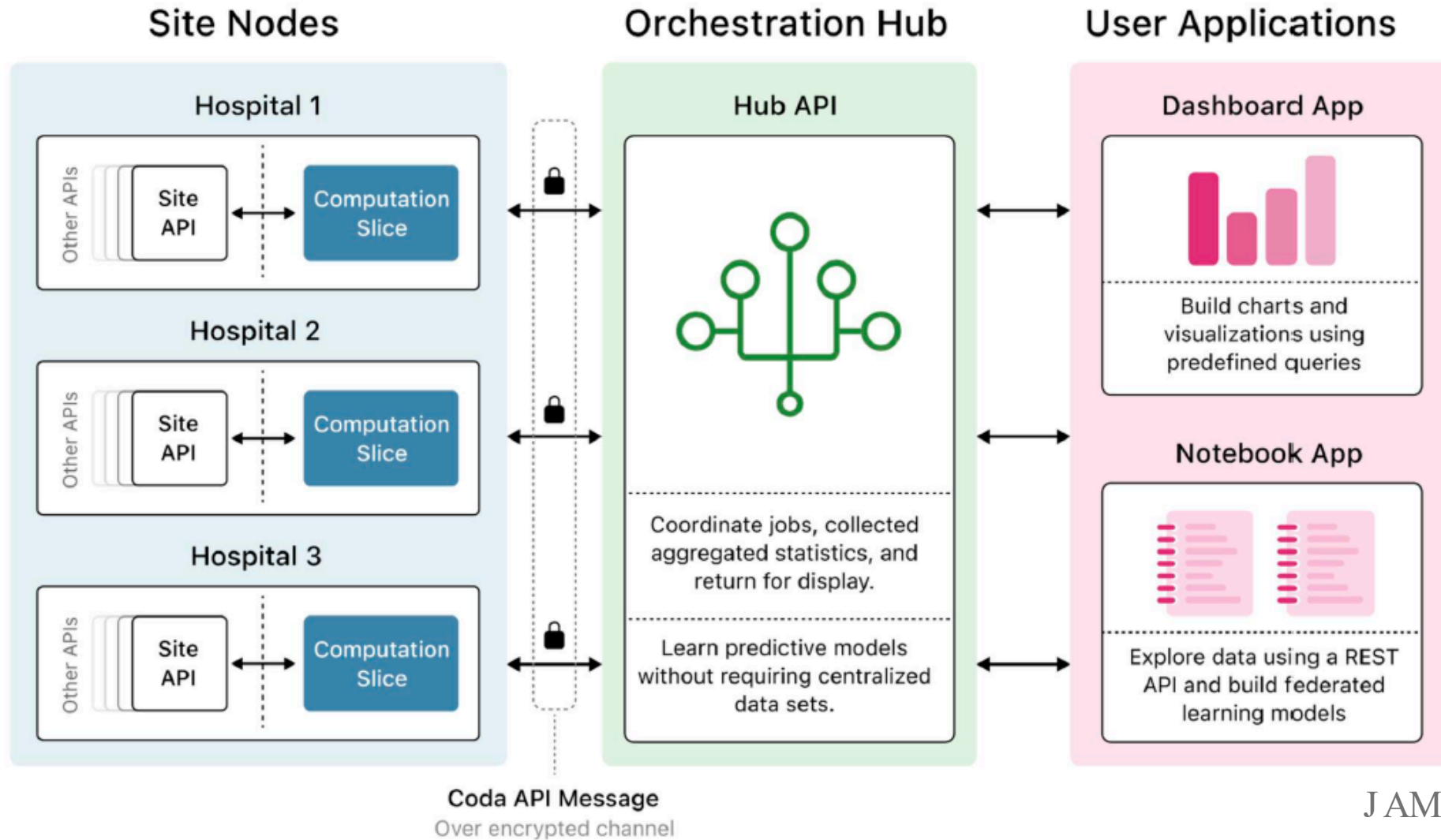
Research and Applications

CODA: an open-source platform for federated analysis and machine learning on distributed healthcare data

Louis Mullie , MD^{1,2,3}, Jonathan Afilalo , MD, MSc⁴, Patrick Archambault, MD, MSc^{5,6,7}, Rima Bouchakri, PhD⁸, Kip Brown, MPAff⁸, David L. Buckeridge , MD, PhD^{3,9}, Yiorgos Alexandros Cavayas, MD, MSc¹⁰, Alexis F. Turgeon, MD, MSc^{6,11}, Denis Martineau, BEng¹¹, François Lamontagne, MD, MSc¹², Martine Lebrasseur, RN⁸, Renald Lemieux, PhD¹², Jeffrey Li, BSc⁸, Michaël Sauthier, MD, PhD^{2,13}, Pascal St-Onge, MSc⁸, An Tang, MD, MSc^{2,14}, William Witteman, MSc⁷, Michaël Chassé, MD, PhD^{1,2,*}

ORIGINAL ARTICLE

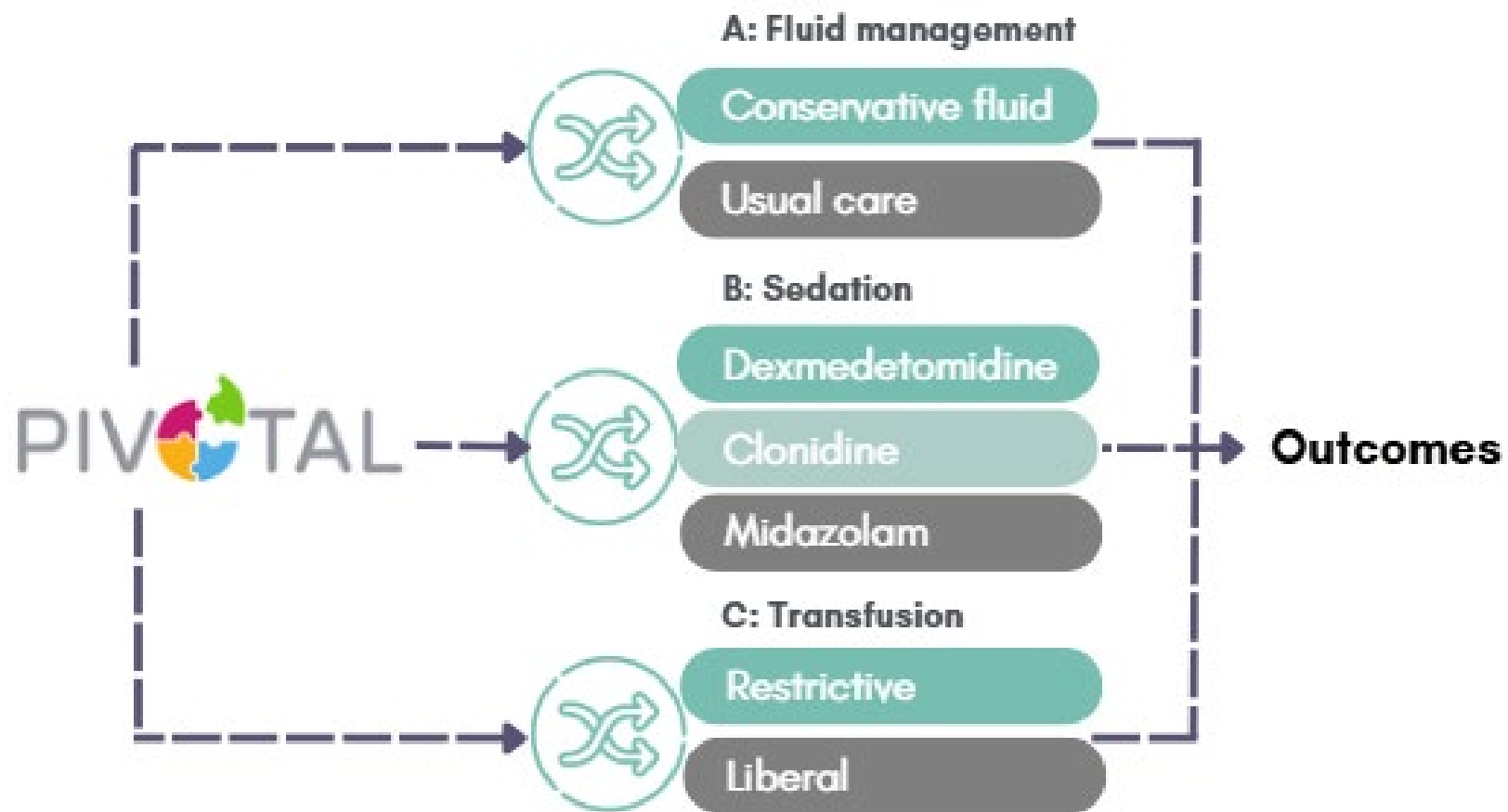
Federated learning in observational research

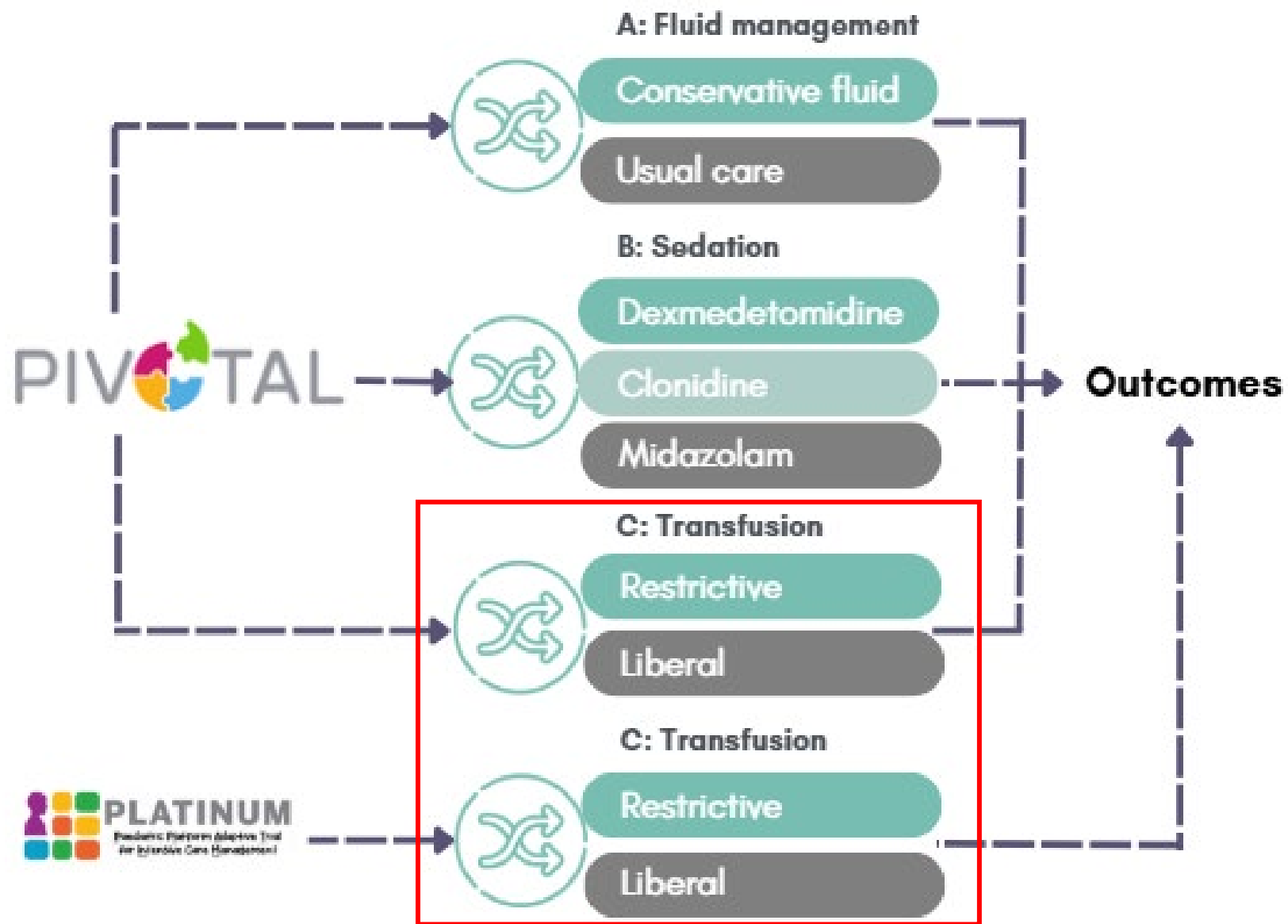


JAMIA 2024 31(3), 651–665

Using federated designs in trials





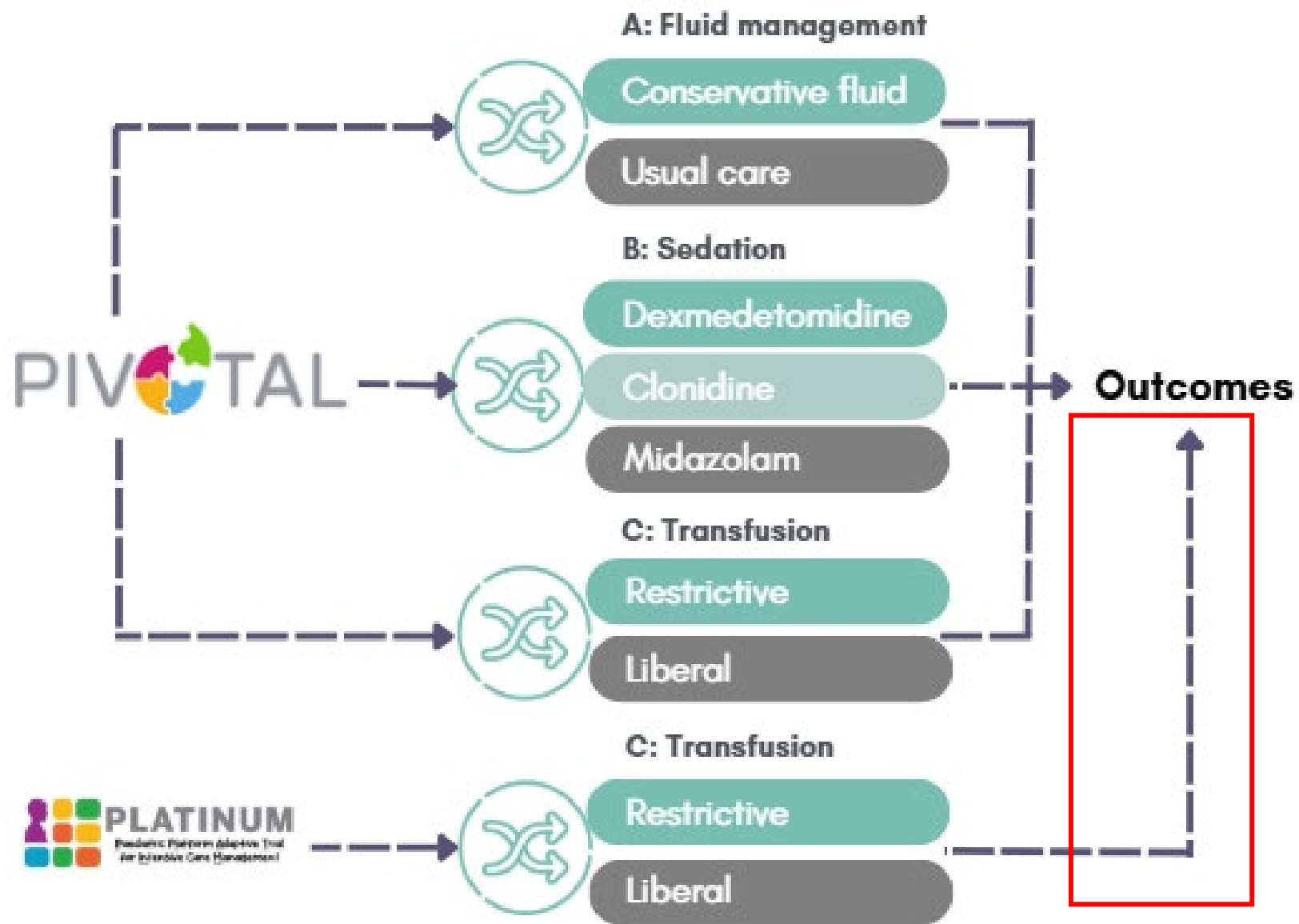


Advantages

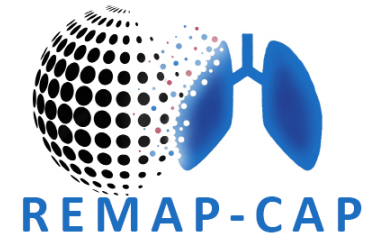
- Infrastructure already set-up internationally
- Flexibility of design allows adding new domains quickly
- Local ownership of individual trials
- Can support each other – be collaborative

Challenges

- Multiple Sponsors
- Independent trials assessing prioritised questions
- Individual governance structures
- Different healthcare systems
- Too much on a platform can dilute participation
- Different data infrastructure and ownership
- Using real-time data to inform adaptive analyses



Therapeutic anticoagulation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

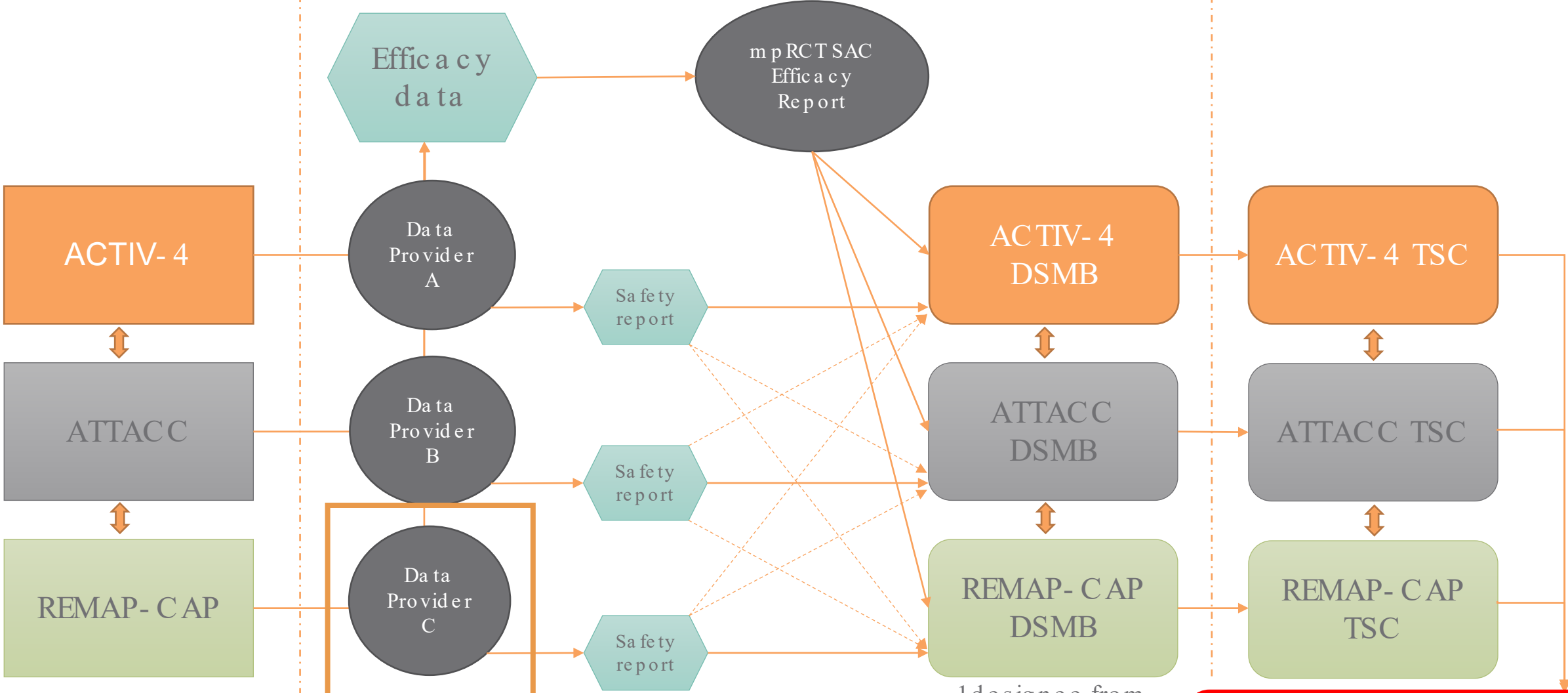
Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

Planning,
Designing phase

Patient enrollment, interim
analysis, safety monitoring

Study
conclusion



collaborative
cross-platform
interaction plan
shared

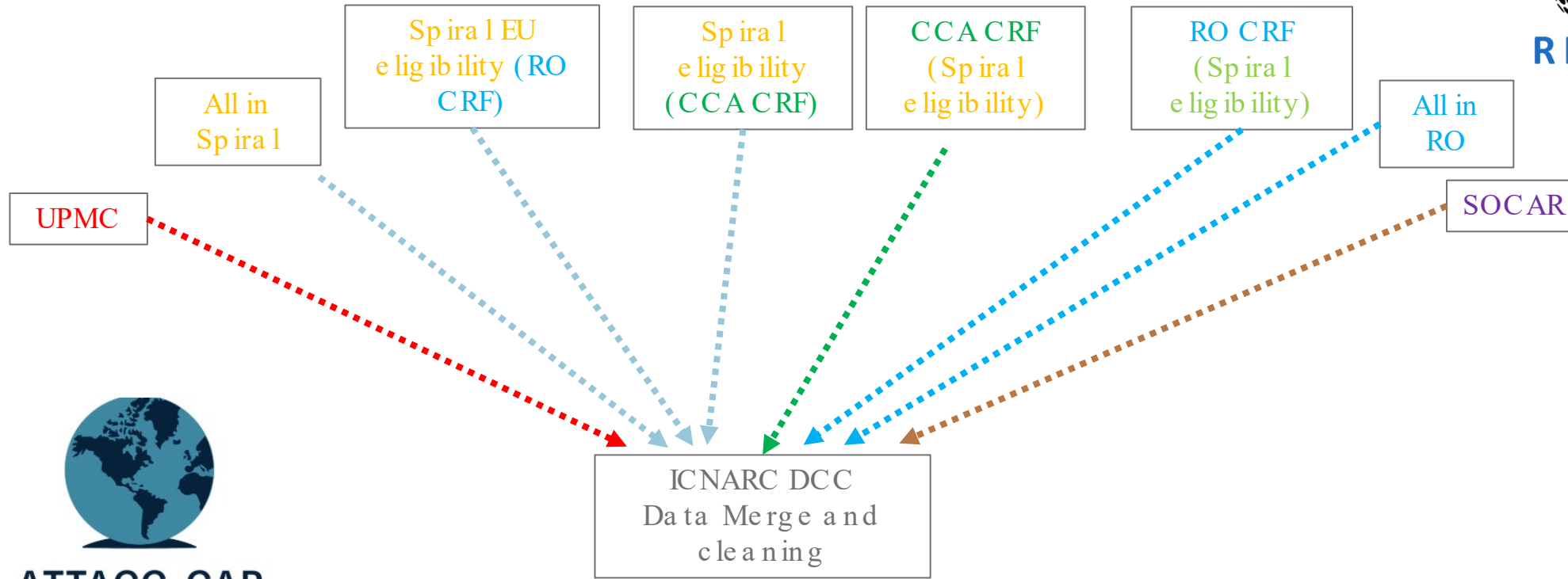
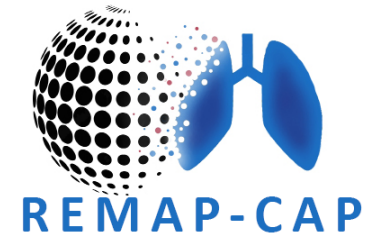
Efficacy and safety report shared
with DSMBs, and cross-platform
DSMB communication

1 designee from
each DSMB joins
the other DSMBs

Conclusion based on the
pre-planned stopping
rules

Courtesy of H Saito

REMAP-CAP data flow



ATTACC-CAP

ACTIV-4

Research

JAMA | **Original Investigation** | CARING FOR THE CRITICALLY ILL PATIENT

Intravenous Vitamin C for Patients Hospitalized With COVID-19 Two Harmonized Randomized Clinical Trials

The LOVIT-COVID Investigators, on behalf of the Canadian Critical Care Trials Group, and the REMAP-CAP Investigators

IMPORTANCE The efficacy of vitamin C for hospitalized patients with COVID-19 is uncertain.

OBJECTIVE To determine whether vitamin C improves outcomes for patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS Two prospectively harmonized randomized clinical trials enrolled critically ill patients receiving organ support in intensive care units (90 sites) and patients who were not critically ill (40 sites) between July 23, 2020, and July 15, 2022, on 4 continents.

← Editorial page 1739

+ Supplemental content

+ CME Quiz at
jamacmelookup.com



Lessening Organ
Dysfunction with
VITamin C

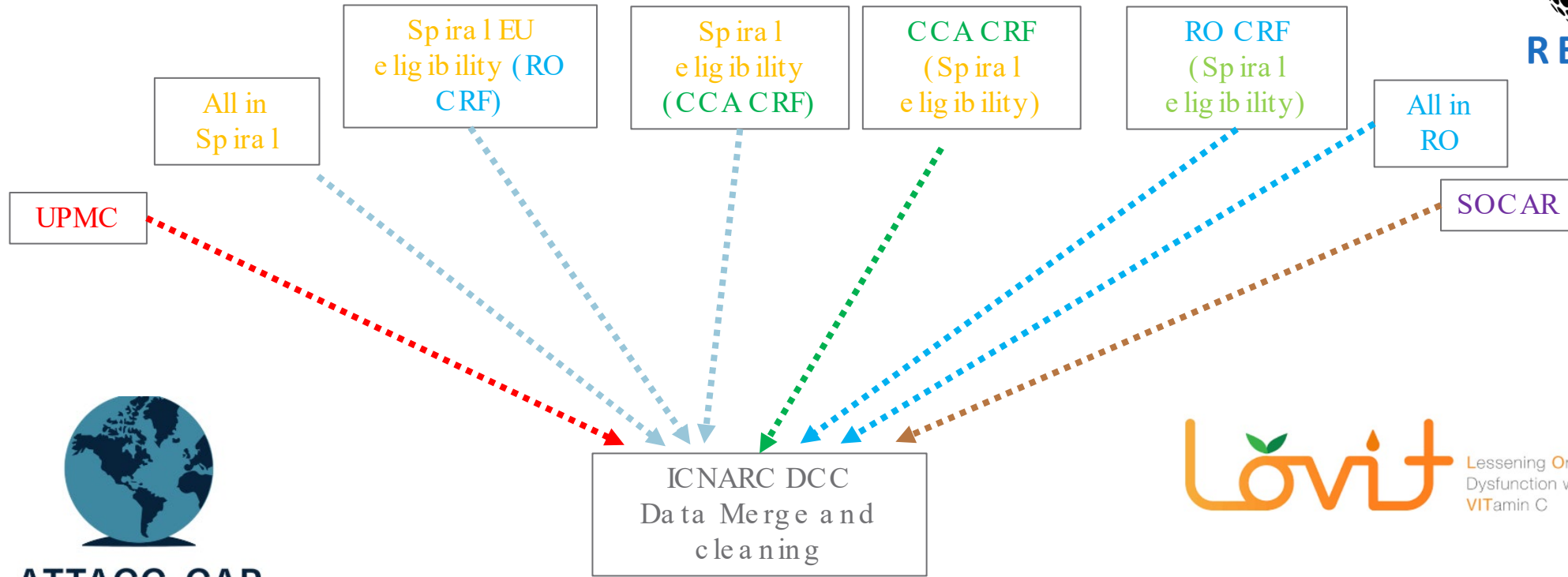
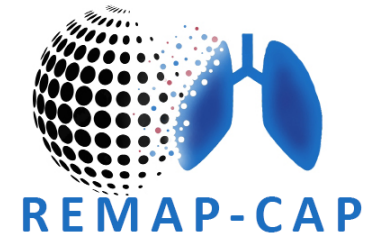
Vita m in C

- Vita m in C regim en ha rm onize d
- Sa m e prim a ry outcom e
- p la ce bo - co ntrolle d vs o pe n - la be l
- fre qu entist fra m ework vs Ba ye sia n
- RAR vs no RAR
- Sa m e co - lea ds
- De ci sion ma de prior to the sta rt of re cru itm en t

Vita m in C

- Sep a r a t e D S M B s
- S t o p p i n g t r i g g e r m e t a t R E M A P - C A P i n t e r i m a n a l y s i s o f s o l e l y R E M A P - C A P d a t a
- R e t r o s p e c t i v e d a t a h a r m o n i z a t i o n
- L o c k e d d a t a t r a n s f e r r e d f r o m L O V I T - C O V I D t o R E M A P - C A P D C C a n d a n a l y s e d i n R E M A P - C A P m o d e l

REMAP-CAP data flow



ATTACC-CAP



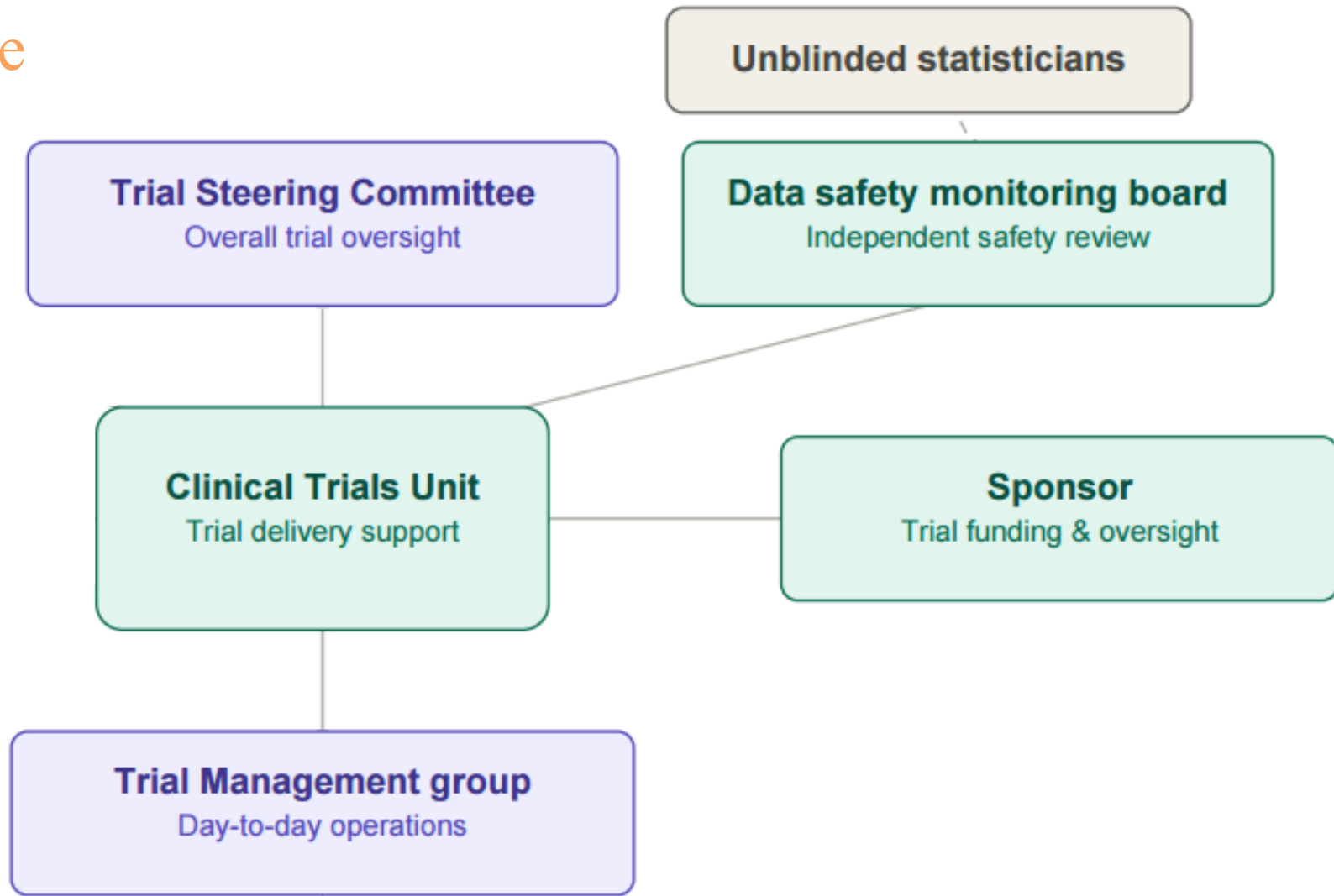
ACTIV-4

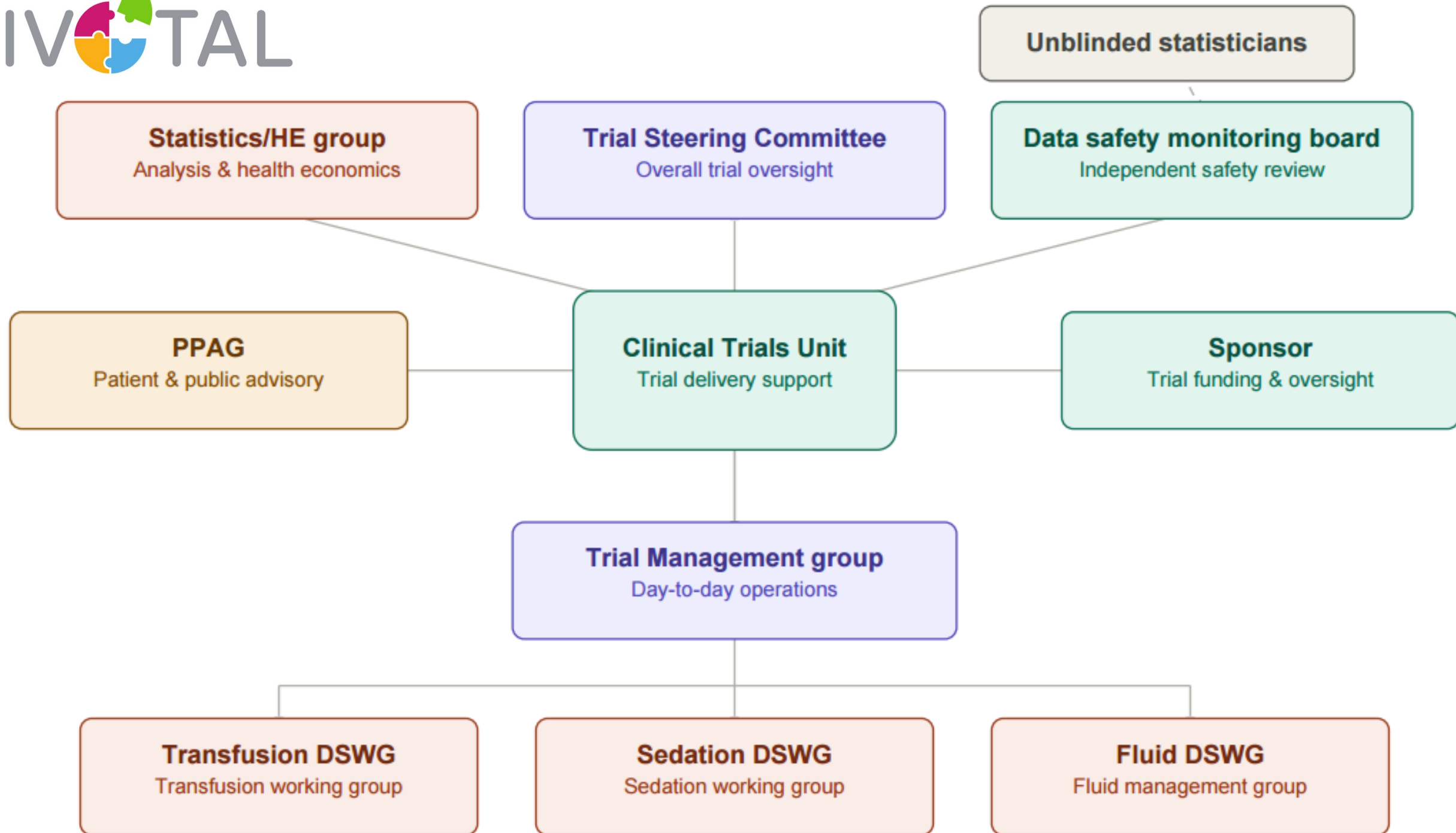
Data oversight and sharing

Ensuring the quality of your trial

- Platforms are complicated!

Governance structure





Need for a dequate central study oversight

- TMG/ TSC – overall platform trial metrics, domain exception reporting
- DSWG – domain recruitment/adherence
- DSMB – adaptive analysis, secondary outcomes, safety monitoring
- Clinical trials unit – study/site quality triggers, data cleaning, on site monitoring
- Sponsor – ownership of the data with data sharing agreements

Needs agreement to a minimum standard across different platforms – consistency of approach

Committee report structure

[illegible]

Planning for federation

Planning for federation

- Make friends with similar platforms
- Have upfront discussions on data specifications and reporting
- Align data specification and definitions across domains
- Collect core outcome sets where possible
- Map to relevant data standards (CDISC)
- Have clarity in leadership
 - Management/analysis/safety
- Look for opportunities for regional within domain leadership
- Agreements for data sharing/ownership in place

If you can't align upfront...

Obtaining data from multiple systems

- Understand the structure of each data set
- Put prospective processes in place to enable federation
- Clear data / export specification
- Clarity on responsibilities
- Maintain metadata
- Build relationship with the stakeholders / data providers

FAIR principles



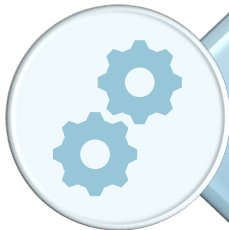
Findable

Metadata registered in searchable resource



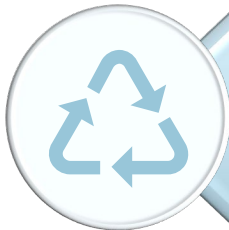
Accessible

Transparent access process



Interoperable

Uses standardised coding



Reusable

Data are well described

Core Minimal Dataset

Objective: Develop a core minimal dataset of key variables to collect in critical care trials evaluating treatments in adult general ICU patients (baseline, disease-specific)

- ✓ Harmonization of data collected in critical care trials.
- ✓ Limit wastage of resources.
- ✓ Better and (hopefully) more equitable conduct of trials.
- ✓ Enhanced prospective federation of trial data and IPD-MA.
- ✓ Complementing the utility and uptake of core outcome sets (COS)



Summary

- Platform trials have exploded across critical care
- Infrastructure can be used to add questions efficiently
- Collaborative approach can get to answer quicker than in any one platform
- COVID-19 shows that federating platforms can be done
- Ensure quality of delivery with consistent standards
- Plan in advance by aligning data specifications, even if no immediate plan to federate
- Ensure there is clarity about responsibilities in data sharing, governance and storage.

Any QUESTIONS?

Email: Paul.Mouncey@icnarc.org

X @paulmouncey

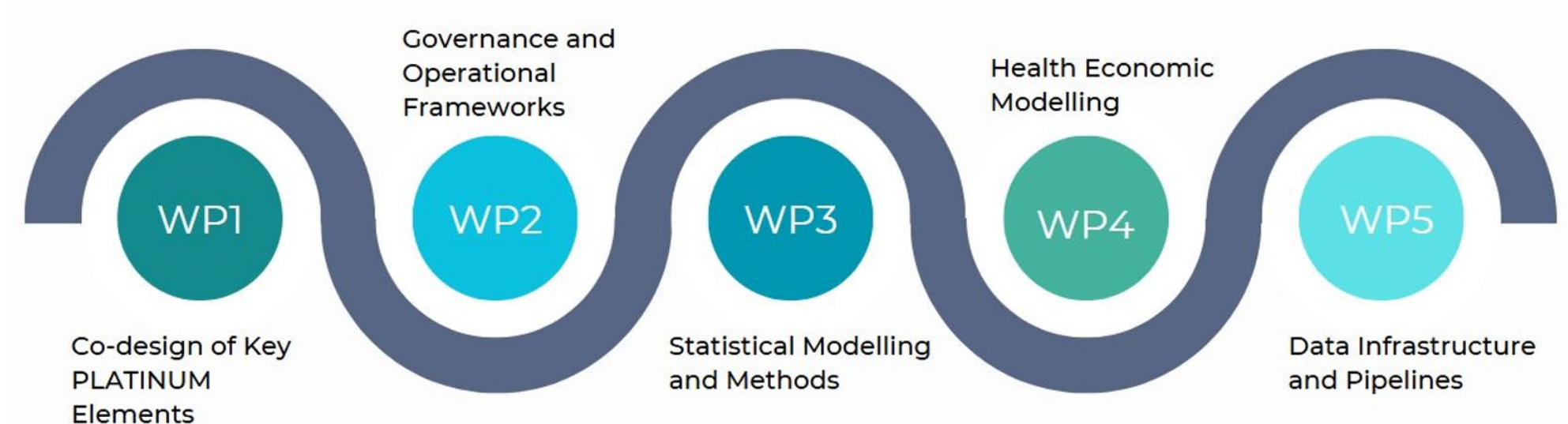
Workforce Capability and Capacity Building for Platform Trials

An ECR Perspective

Presented by:

Dr Rebecca Mitting
PICU Consultant/PhD Candidate
Imperial College London
St Mary's Hospital

Dr Trish Gilholm
Research Fellow/Biostatistician
Children's Intensive Care Research Program
The University of Queensland



Steering Committee Members (EMCRs) :

Kristen Gibbons, Warwick Butt, Fenella Gill, **Nathalia Costa**, Simon Erickson, Sai Raman, Debbie Long, Johnny Millar, Marino Festa, **Ben Gelbart**, **Anton Pak**, **Alyssa Serratore**, **Trish Gilholm**, **Ash Quadir**, **Christabel Hong**, Shane George, **Alex Hussey**, **Kate Masterson**, Renate Le Marsney, David Pennisi

Barriers and Facilitators to Implementation



Barriers

1. Infrastructure requirements (86%)
2. Statistical Complexity (82%)
3. Limited Expertise (73%)



Facilitators

1. Training and education (90%)
2. Access to experienced statisticians (90%)
3. Increase in funding (88%)



Gilholm et al 2024



Methodological Capability for Design of Platform Trials



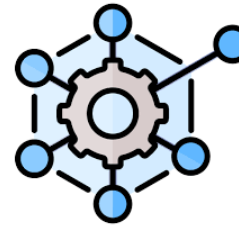
1. Lack of formal training pathways



2. Learning is informal and self-directed



3. Limited pool of expertise



4. High methodological complexity



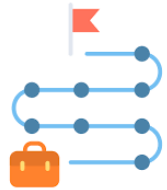
5. Resource- and time-intensive
design process



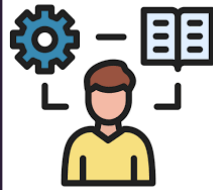
6. Capacity building is challenging
but essential



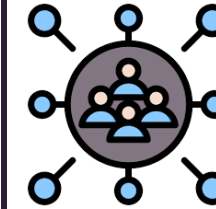
Building Methodological Workforce Capacity



1. Create structured learning pathways



2. Formalise “learning by doing”



3. Expand the pool of expertise



4. Lower the barrier to methodological complexity

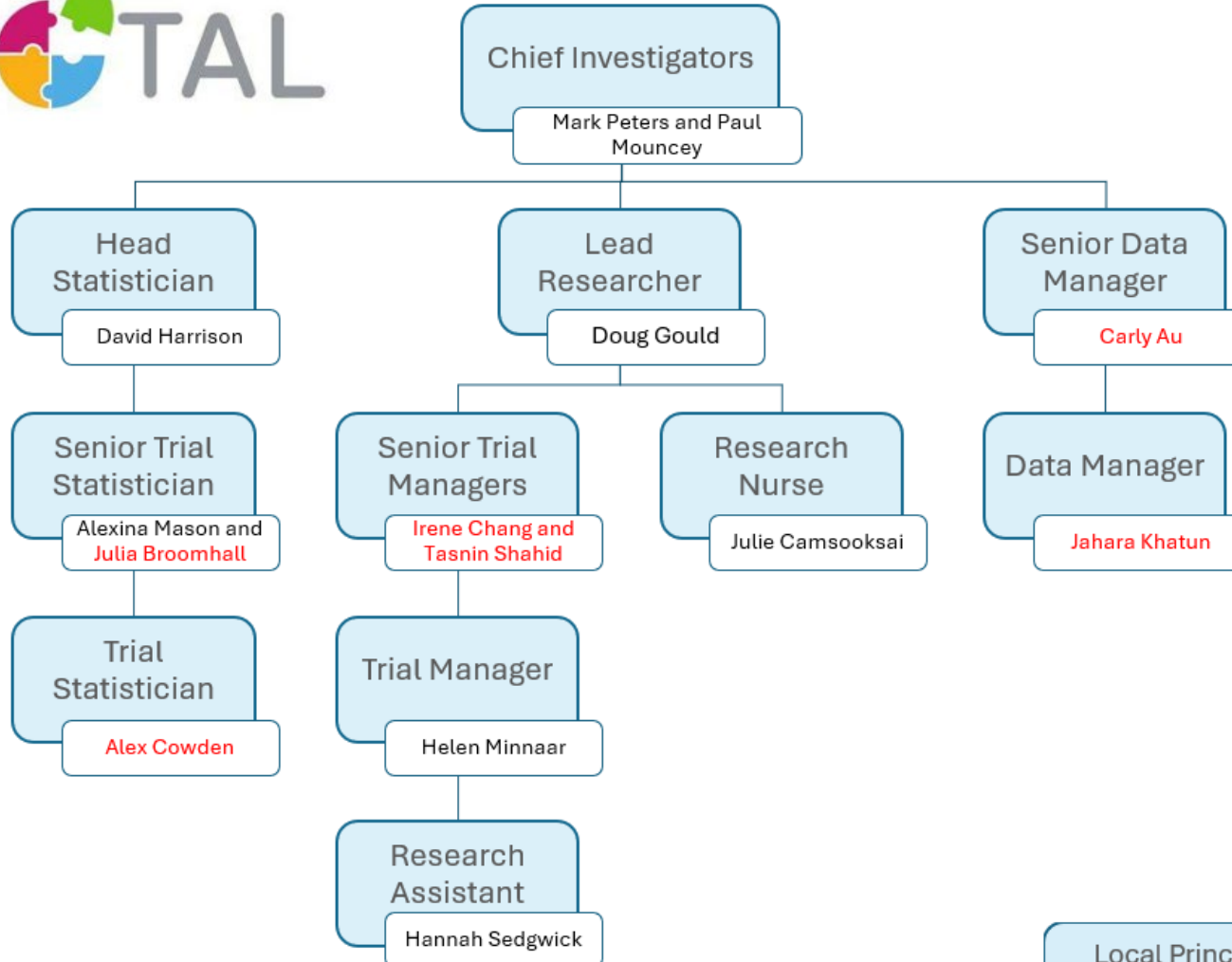


5. Protect time for design work



6. Build capacity through teams, not individuals

Experiences from the UK.....



Red = ECR

PIVOTAL Domain Leads

Fluid domain:

Angela Aramburo
Lyvonne Tume

Sedation domain:

Rebecca Mitting

Blood transfusion thresholds domain:

Avishay Sarfatti
Samiran Ray
Simon Stanworth

Local Principal
Investigators

Associate Principal
Investigators

NIHR-funded Incubators

Incubators support research capacity building in key areas across England.

Barriers and
facilitators to
research in PIC

- enhance opportunities for paediatric critical care (PCC) professionals in:
 - networking
 - mentoring
 - participation
 - research career development support
- highlight its impact on clinical care by widening:
 - access to research methods training
 - exposure to PCC research
- engage with and harness diverse patient and public voices to co-develop initiatives and raise awareness of Paediatric Critical Care research.

Apprenticeship programmes

Principal Investigator Pipeline Programme

A free programme to develop health and care professionals (excluding doctors and dentists) to become principal investigators on NIHR portfolio studies.



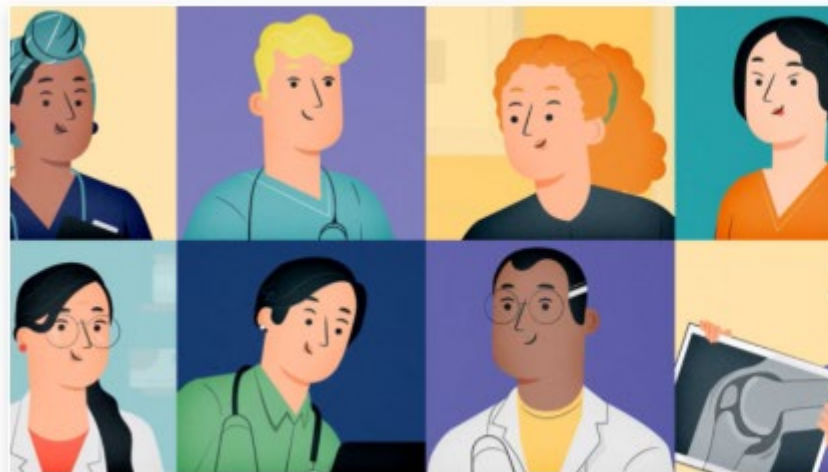
What to expect

During the programme, you will undertake 4 Elements:

- **Element 1:** Consists of 8 pre-recorded modules for you to view in your own time over 2 months. You will then be invited to take part in online facilitated discussions around the video content.
- **Element 2:** You will work alongside a local PI who will supervise you to practice what you learned in Element 1. You will need to identify a local PI to support you with Element 2.
- **Element 3:** You will take on the role of a PI for an NIHR portfolio study. Before you start this element, you will need to find a suitable study. Your local R&D office, Research Delivery Network (RDN) Study Support Service, or local PIs will be able to help you identify an appropriate study. Element 3 also includes an online discussion session with your peers and a facilitator.
- **Element 4:** Focuses on leadership and mentorship with an online workbook and a facilitated discussion.

Apprenticeship programmes

Associate Principal Investigator Scheme



In Summary

Platform trials bring an added layer of complexity, both for clinicians and for statisticians and trial managers

Training, mentorship and collaboration are key to successful trials, as well as for building the research workforce of the future.

Early and mid career researchers must be embedded within trial infrastructure throughout the life cycle of the project

Funders should look favourably on projects which include plans for training and mentorship of EMCRs and be prepared to provide resource for this.

Thank you for listening

We are happy to take questions both now and by email;

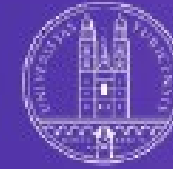
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p.gilhom@qu.edu.au



THE UNIVERSITY
OF QUEENSLAND
AUSTRALIA

IMPERIAL



Universität
Zürich^{UZH}

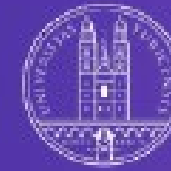
International Platform Trials Symposium

Funding Models for Long-Term Platform Trial Infrastructure

Prof Kristen Gibbons, The University of Queensland

Prof Padmanabhan Ramnarayan, Imperial College London

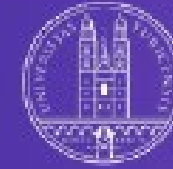
Prof Luregn Schlapbach, University of Zurich



“Perpetual” trial platform

Table. General Characteristics of Traditional and Platform Trials^a

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Challenges

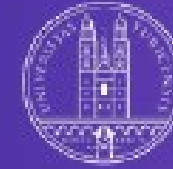
High setup “cost”

Long-term stakeholder
engagement

Platform trials

“One-off” funding
models

International
collaborations



Platform set up

Development of a Platform Trial in Paediatric Intensive Care

Start Date:

March 2023

End Date:

January 2024

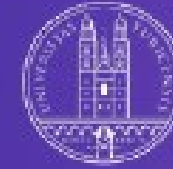
Parent/patient engagement

PICU clinician engagement

Statistical modelling

Health economics methodology

Data infrastructure (routinely collected)

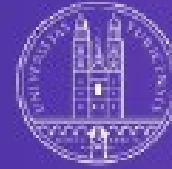


Long-term stakeholder engagement

Developing an adaptive paediatric intensive care unit platform trial with key stakeholders: a qualitative study

Tracy Karen Mitchell ¹, Julie C Menzies ², Padmanabhan Ramnarayan,³
Doug William Gould ⁴, Elizabeth Deja,⁵ Shelley Marsh,⁶ Jennifer Ainsworth,⁷
Jennifer Preston ⁷, Hannah Sedgwick,⁴ Carly Tibbins,⁸ Paul R Mouncey ⁴,
Mark J Peters,^{9,10} Kerry Woolfall⁵

Results A total of 86 participants (18 young people; 15 parents/carers; 53 PICU staff) took part in 1 of 10 focus groups between May and September 2023.



One-off funding

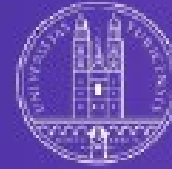
Pandemic preparedness – platform clinical trials in hospital and community settings

Proposed timescales that need to be covered

The baseline platform clinical trials should be designed with a 5-year timeline in mind, although there is potential for this to be extended.

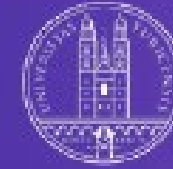
23/95 Platform studies to efficiently evaluate the clinical effectiveness of multiple interventions in areas of strategic importance commissioning brief

Applicants are encouraged to consider the sustainability of the platform beyond the initially funded work, where relevant.



Collaborations

- Timeline of funding calls not synchronous
- Focus of funding calls not consistent across funders
- Research priorities across boundaries not similar



Solutions

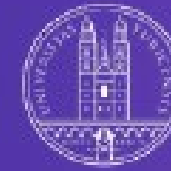
Funder advocacy

Joint research funding
calls

Platform trials

“Drip feed” funding

Federated funding
models



PICU CONNECT: fund platform trial(s)

Action 5: build a platform trial infrastructure in at least two regions by 2028

- Define a strategy for international platform trial infrastructure with the regional paediatric intensive care unit trial networks, and adult-focused and neonatal patient-focused trial hubs
- Define governance for international recruitment into platform trial hubs
- Start recruiting in at least one region

Building global collaborative research networks in paediatric critical care: a roadmap 

Luregn J Schlapbach*, Padmanabhan Ramnarayan*, Kristen S Gibbons, Brenda M Morrow, Natalie Napolitano, Lyvonne N Turme, Andrew C Argent, Akash Deep, Jan Hau Lee, Mark J Peters, Michael S D Agus, John Adabie Appiah, Jennifer Armstrong, Tigist Bacha, Warwick Butt, Daniela Carla de Souza, Jaime Fernández-Sarmiento, Heidi R Flori, Patricia Fontela, Ben Gelbart, Sebastián González-Dambruskas, Takamori Ikegami, Roberto Jabornik, Muralidharan Jayashree, Yasser M Kazzaz, Martin C J Kneyber, Debbie Long, Jenala Njirimadzi, Rujipat Samransamruajkit, Roelie M Wösten-van Asperen, Quan Wang, Katie O'Hearn, Kusum Menon*, on behalf of the Australian and New Zealand Intensive Care Society Paediatric Study Group, Brazilian Research Network in Pediatric Intensive Care, Canadian Critical Care Trials Group, European Society of Paediatric and Neonatal Intensive Care, Pediatric Collaborative Network of Latin America, Pediatric Acute & Critical Care Medicine Asian Network, Pediatric Acute Lung Injury and Sepsis Investigators, United Kingdom Paediatric Critical Care Society Study Group, Pediatric Intensive Care Latin-American Society, World Federation of Pediatric Intensive & Critical Care Societies



PICU CONNECT: funder advocacy

Action 6: build an active programme of funder advocacy by 2027

- Pitch paediatric critical care topics to international funding bodies (eg, the Wellcome Trust and Gates Foundation) and philanthropic organisations
- Work with national funders to advocate for novel funding approaches, including joint funding calls across international boundaries, as well as targeted support of exchanges such as PhD and scholarships across regions

Building global collaborative research networks in paediatric critical care: a roadmap  

Luregn J Schlapbach*, Padmanabhan Ramnarayan*, Kristen S Gibbons, Brenda M Morrow, Natalie Napolitano, Lyvonne N Turme, Andrew C Argent, Akash Deep, Jan Hau Lee, Mark J Peters, Michael S D Agus, John Adabie Appiah, Jennifer Armstrong, Tigist Bacha, Warwick Butt, Daniela Carla de Souza, Jaime Fernández-Sarmiento, Heidi R Flori, Patricia Fontela, Ben Gelbart, Sebastián González-Dambraskas, Takanari Ikegami, Roberto Jaborniskiy, Muralidharan Jayashree, Yasser M Kazzaz, Martin C J Kneyber, Debbie Long, Jenala Njirimadzi, Rujipat Samransamruangkit, Roelie M Wösten-van Asperen, Quan Wang, Katie O'Hearn, Kusum Menon*, on behalf of the Australian and New Zealand Intensive Care Society Paediatric Study Group, Brazilian Research Network in Pediatric Intensive Care, Canadian Critical Care Trials Group, European Society of Paediatric and Neonatal Intensive Care, Pediatric Collaborative Network of Latin America, Pediatric Acute & Critical Care Medicine Asian Network, Pediatric Acute Lung Injury and Sepsis Investigators, United Kingdom Paediatric Critical Care Society Study Group, Pediatric Intensive Care Latin-American Society, World Federation of Pediatric Intensive & Critical Care Societies



Cross-country platform funding

Cross-programme

Australia-UK platform studies in areas of unmet clinical need

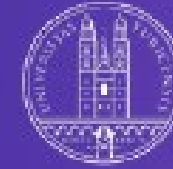
MRFF and NHMRC – 2025 Australia-UK Platform Studies in Areas of Unmet Clinical Need Grant Opportunity



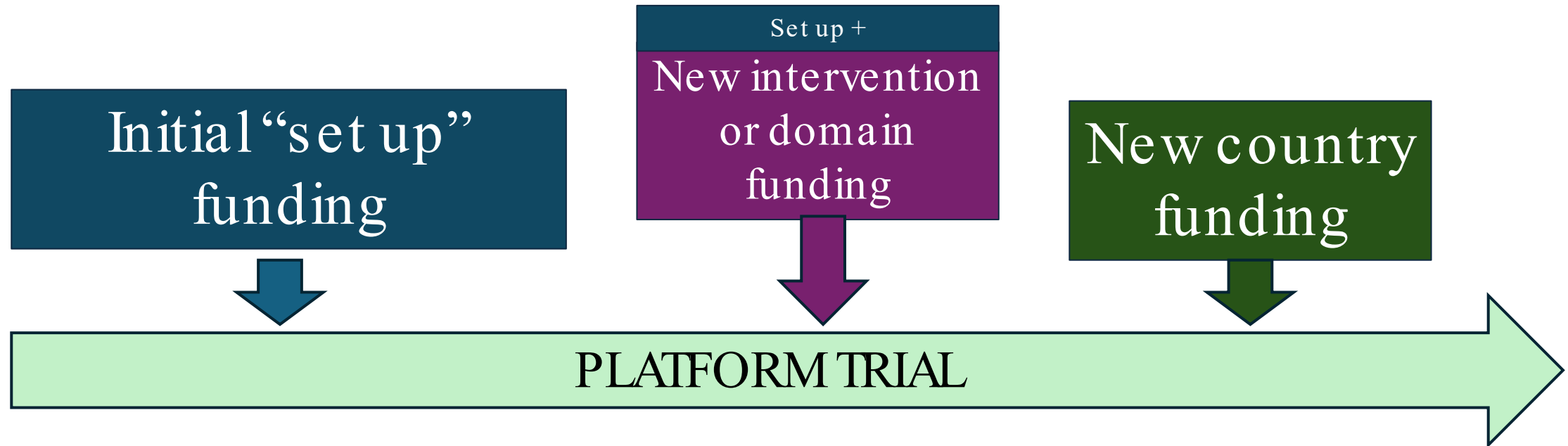
**Swiss National
Science Foundation**

**Swiss-UK investigator-led
randomised controlled clinical
trials in areas of unmet clinical
need**

**Call for clinical trials with the UK
launched**

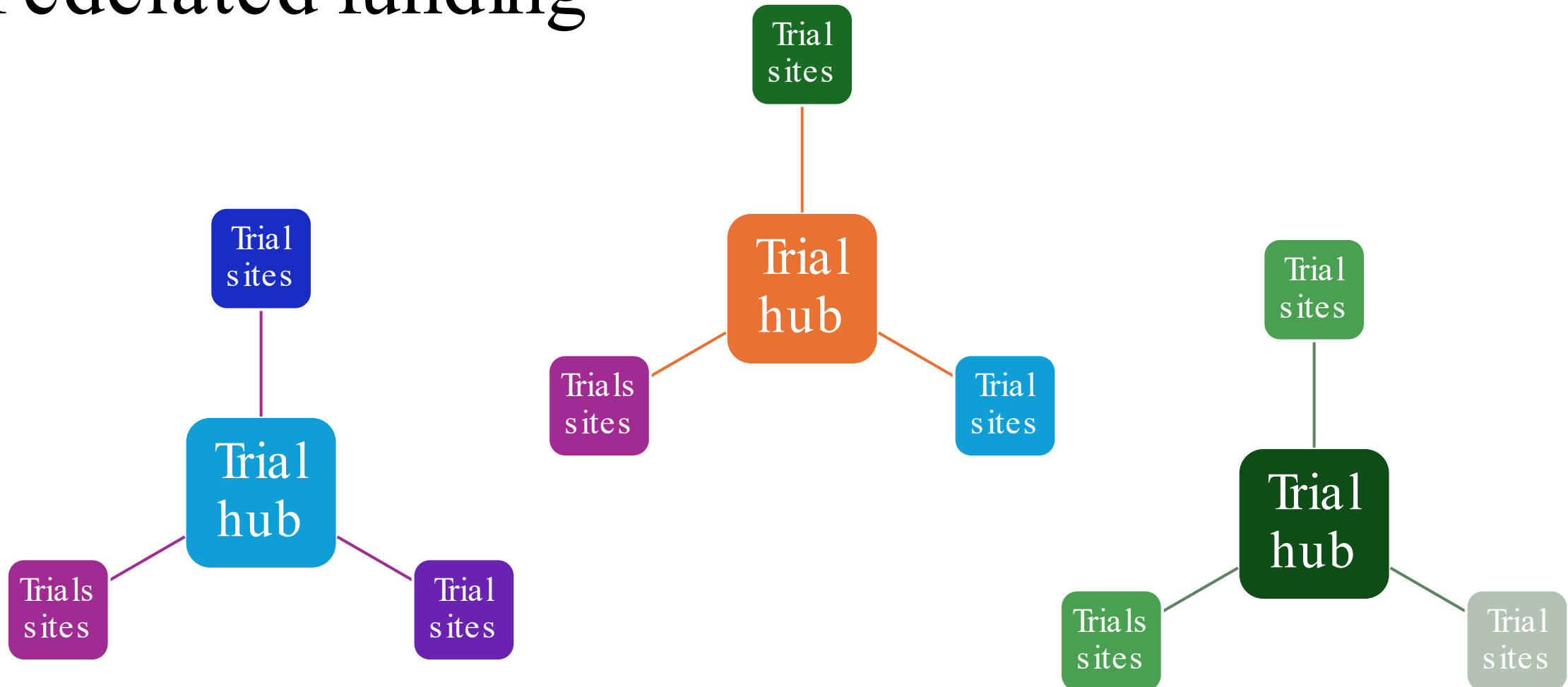


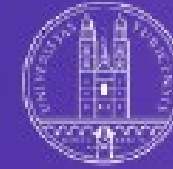
Funding “drip feed”





Federated funding

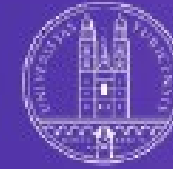




Federated funding for federated trials

- Large international funding
- Large (bi)national grants
- Coordination/hub
- Recruitment
- Nested/auxiliary work
- Capacity building



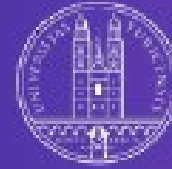


Federated funding for federated trials

- Large international funding
- Large (bi)national grants
- Coordination/hub
- Recruitment
- Nested/auxiliary work
- Capacity building



- Hub infrastructure/personnel
- Full platform - domains
- Analysis team
- Monitoring
- PPI
- International coordination
- National coordination
- Site recruitment
- Biobanking, shipment
- Sample analyses
- Workshops, webinars
- Travel/conference support
- ...



Funders perspectives

- Visibility for funder
- Meet funding purpose "make a difference"
- Often national or regional-local flavor
- Visibility and understanding of collaborative achievements
- Philanthropy local vs international scope
- Need for tangible deliverables in smaller grants-foundations too!
- Value creation by critical care
- Efficiency of funding use augmented by higher research/trial efficiency



REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

27,493

Patient randomisations

16,219

Total patients

240

Active sites



THE UNIVERSITY
OF QUEENSLAND
AUSTRALIA

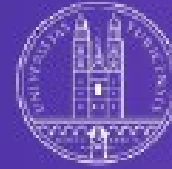
IMPERIAL



Universität
Zürich^{UZH}



REMAP-CAP trial 1
25 countries, 320 sites



Conclusions

- International platform trial collaboration to be matched by funding models
- Large funder calls for platform trials, international collaboration
- Federation globally
- Importance of smaller funding sources too!
- Challenges in regulatory aspects and administration of funding across diverse settings, LMICs

‘Children are not just small adults’:

Ethical considerations for Platform Trials

Professor Asha Bowen OAM

Paediatric Infectious Diseases Specialist, Perth Children’s Hospital

 @AshaBowen



Acknowledgement of country



Which statement do you agree most with?

1. Involving children in adaptive platform trials can be unethical.
2. Excluding children from adaptive platform trials can be unethical.

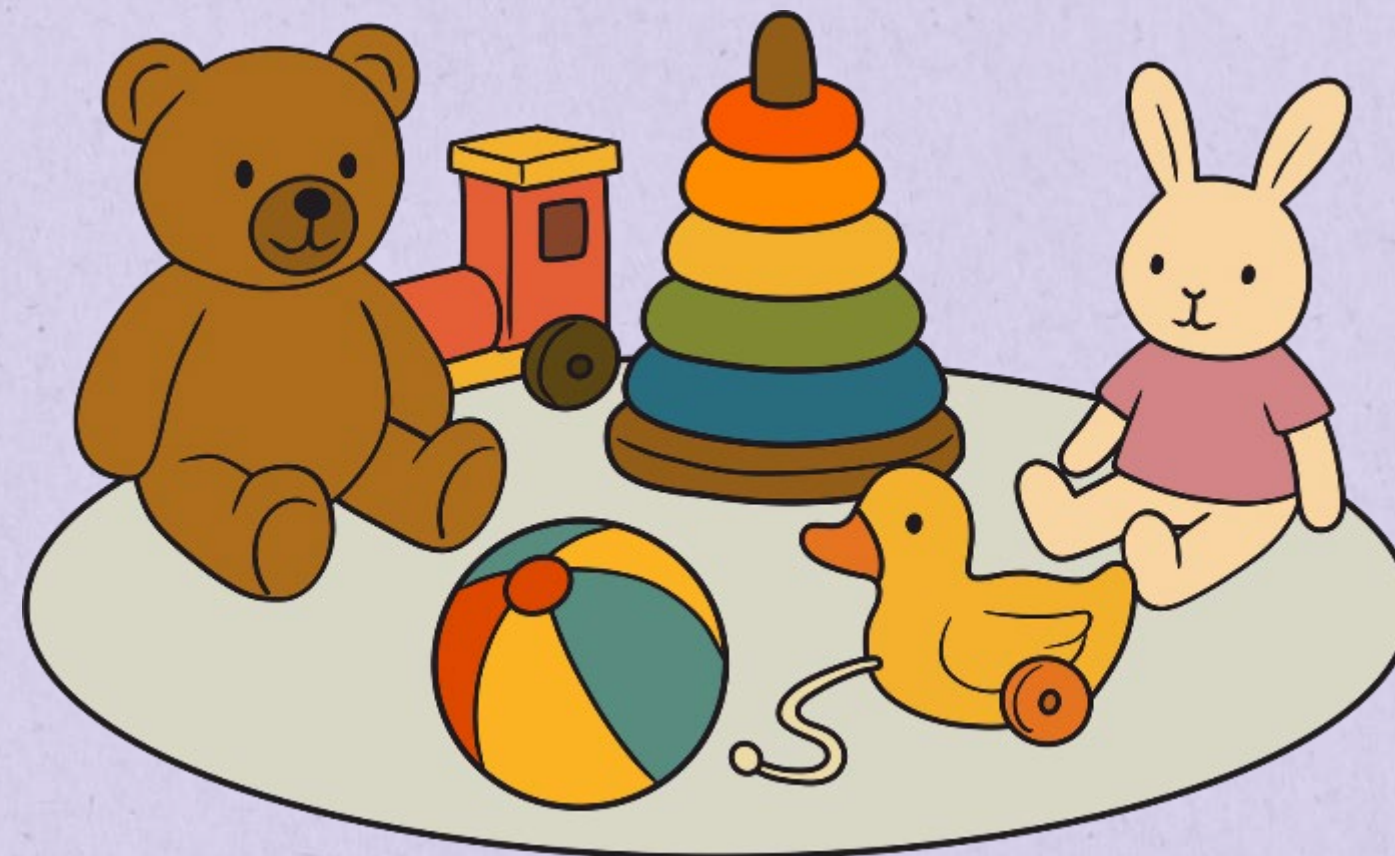


The ethical tension

Protecting children from research risk

versus

Protecting children from evidence gaps



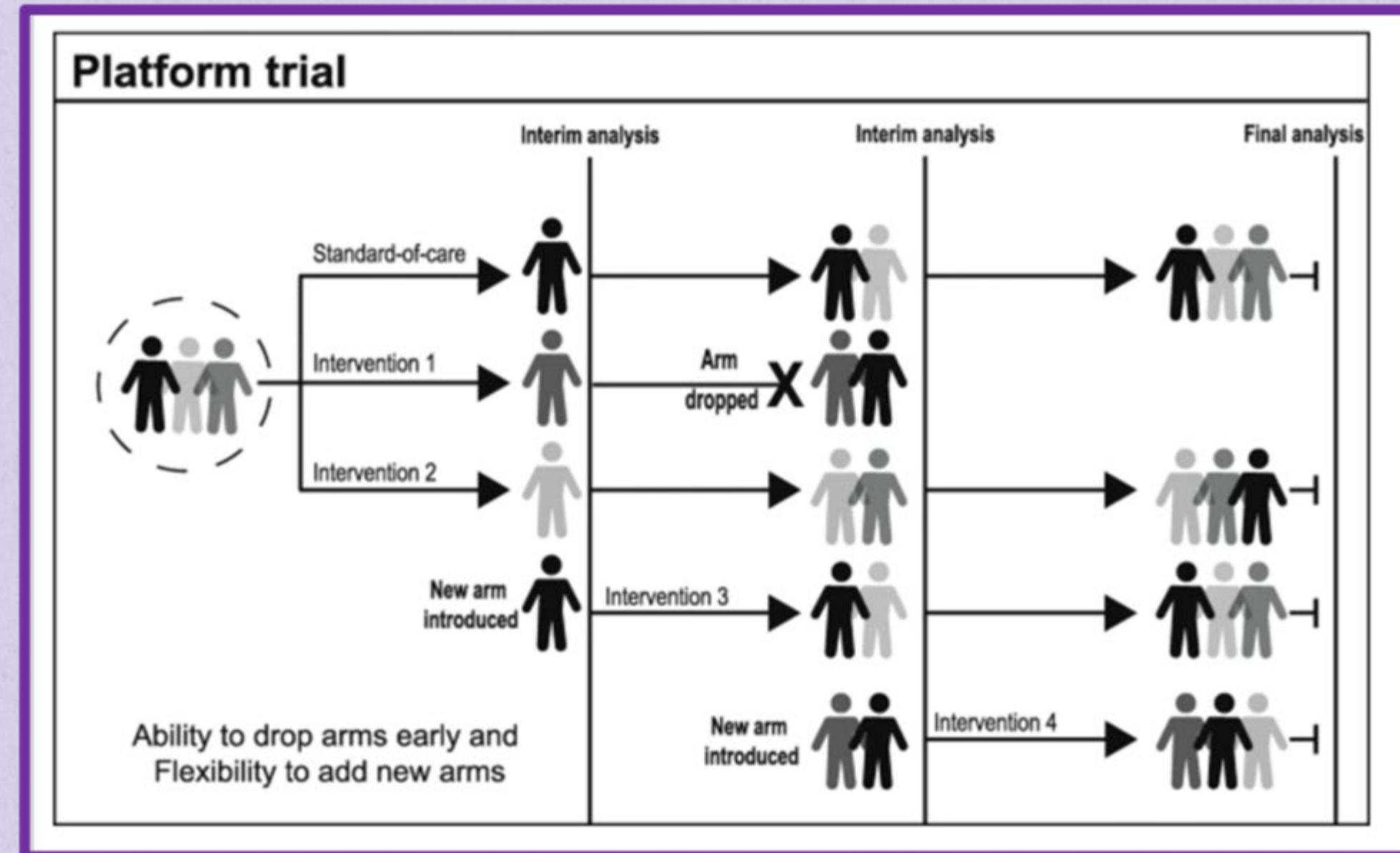
Children should not be included by default.
But they should not be excluded by default either.

Why platform trials raise specific issues

Adaptive platform trials:

- Evaluate several targeted therapies for a single disease.
- Use a decision algorithm (Bayesian model) to determine whether a therapy should be added or removed.

This continuous evaluation allows for more efficient testing of new therapies.



However, this makes consent, safety monitoring and communication more complex.

How to involve children

This Issue Views 1,470 | Citations 2 | Altmetric 7

Special Communication

August 19, 2024

Whole-of-Life Inclusion in Bayesian Adaptive Platform Clinical Trials

Anita J. Campbell, MBBS, PhD^{1,2,3}; Keerthi Anpalagan, BBiomedSc(Hons)^{2,3}; Emma J. Best, MMed^{4,5,6}; [et al](#)

» Author Affiliations

JAMA Pediatr. 2024;178(10):1066-1071. doi:10.1001/jamapediatrics.2024.2697

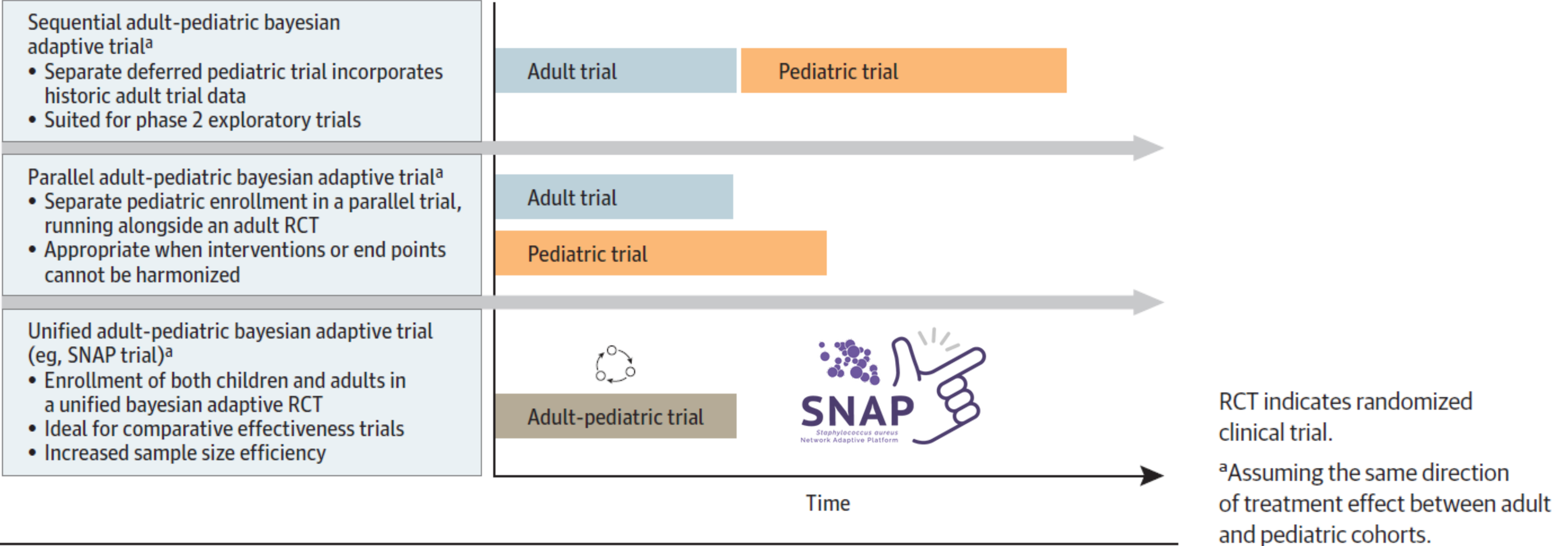
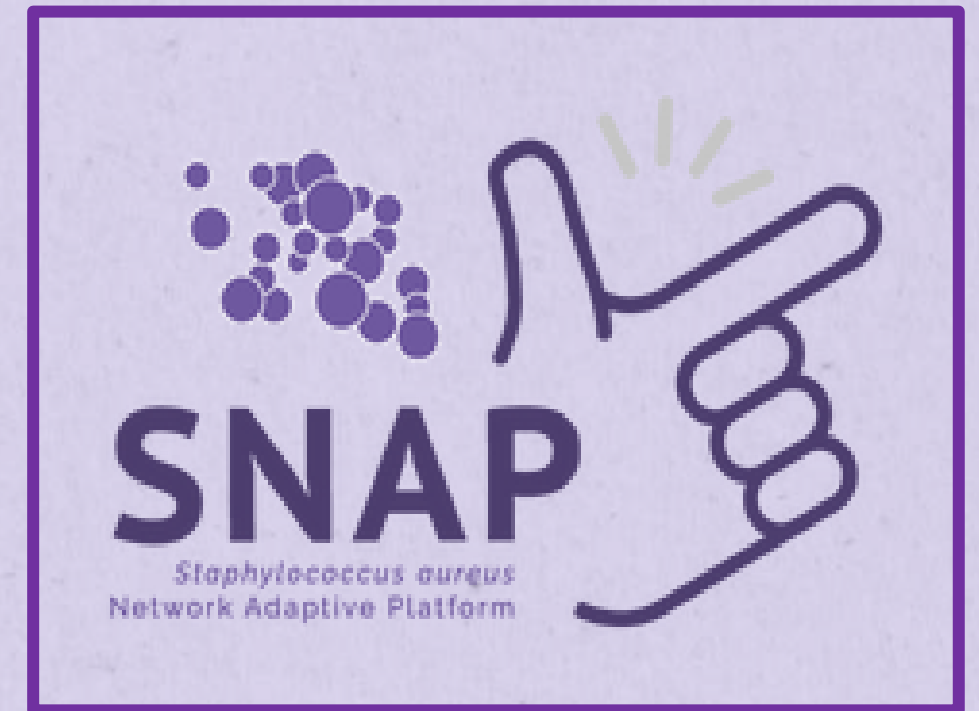


Figure. Examples of 3 Distinct Clinical Trial Design Strategies to Incorporate Children into Clinical Trials (Campbell *et al*. JAMA Peds. 2024)

SNAP-PY: When adult evidence is not enough



- SNAP-PY is the **paediatric and youth** arm of the broader *Staphylococcus aureus* Network Adaptive Platform trial.
- We enrol neonates, children and adolescents within a whole-of-life adaptive platform trial, to generate evidence for kids.
- Early ethical considerations included:
 - How to get funding?
 - How to balance the primary endpoint?
 - How to establish borrowing across ages?



(OG) Trial structure

Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain
PSSA	(Flu)cloxacillin vs Penicillin	No Clindamycin vs Clindamycin (days 1-5)	Continued IV vs Early oral switch At 7 days At 14 days
MSSA	(Flu)cloxacillin vs Cefazolin		
MRSA	Vancomycin vs Vancomycin plus cefazolin		

...or Registry

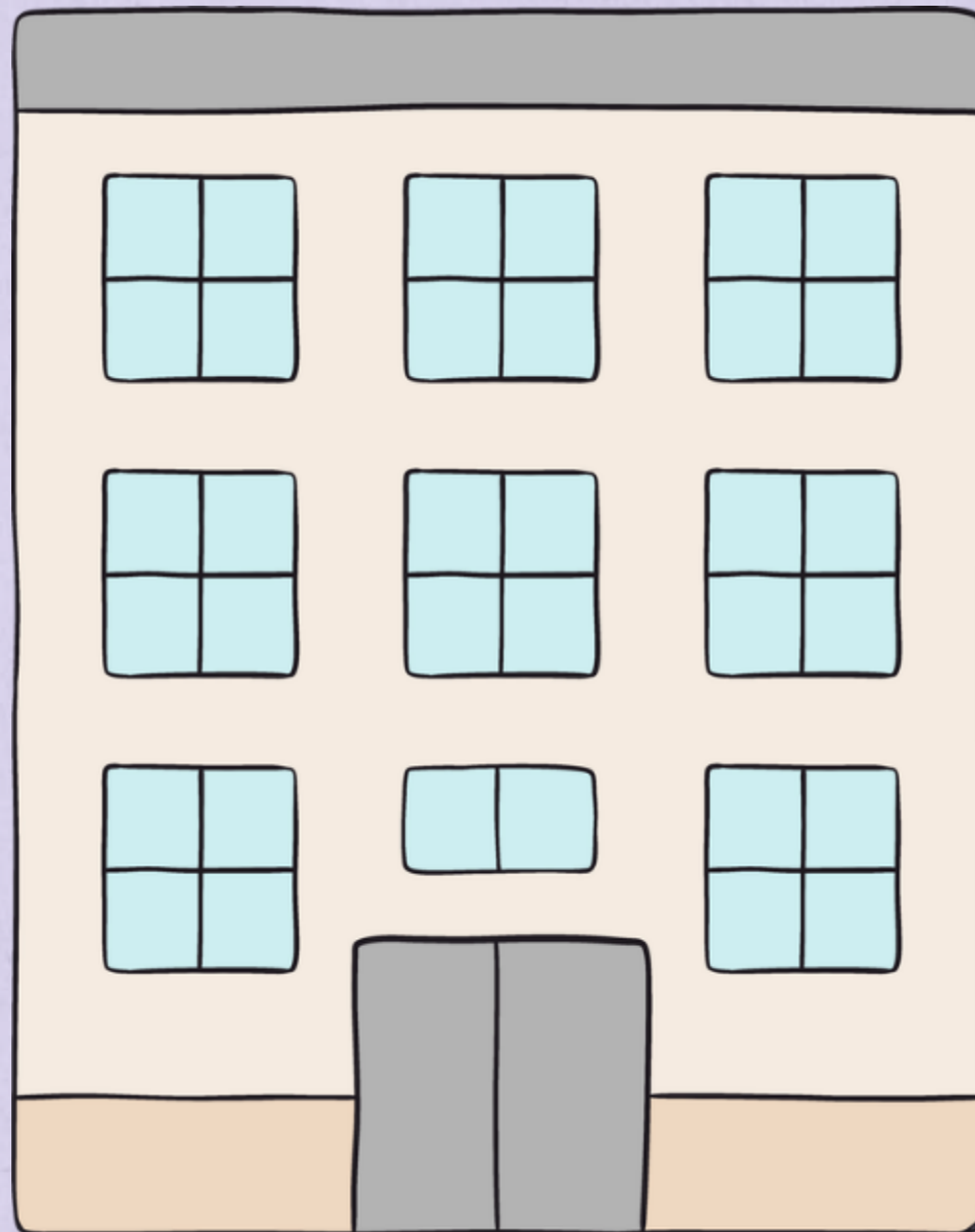
SNAP-PY: Funding

- Early Platform discussions planned to involve children
- Grantsmanship – adult physicians left kids out of original grant, but with commitment for their inclusion down the track in Australia
 - SNAP funded by NHMRC in 2019
 - SNAP-PY funded by NHMRC CTCS in 2021
 - SNAP commenced in Feb 2022, first paed site opened in August 2022
- Different models globally
 - UK integrate children and adults
 - Europe still have not enrolled children
 - Canada sequential involvement of children with separate grants

SNAP-PY: Design and Statistical models

- Mortality for SAB varies between children [(3-5%; highest in neonates) and adults (15-20%; highest in the extreme elderly)]
- Statistical Borrowing built into simulation models and parameterised based on observational data
- We developed a method for this, and tested it in a real-world clinical trial

Consent is not one moment!



Consent should be **age-appropriate, layered and ongoing.**

- Parent/guardian consent
- Child assent where appropriate
- Re-consent at adulthood
- Short, clear first layer
- Optional detail for families who want more
- Plain-language explanation that the trial may adapt over time

Families need agency, not information overload, especially in difficult periods such as a SAB diagnosis.

SNAP Primary Endpoint

- All-cause mortality at 90 days after platform entry.

SNAP-PY Specific Secondary Endpoints

- Mortality by day 90
- Total index hospitalisation longer than 30 days
- New foci between days 14 and 90
- Microbiological treatment failure between days 14 and 90

This difference recognises that adult mortality alone may not capture outcomes that are meaningful in paediatric SAB.

SNAP-PY: When adult evidence is not enough



The key ethical question became:

- *When adult results are available, should children continue to be randomised?*



What happened in SNAP?

- In the adult MSSA bacteraemia domain, cefazolin was shown to be non-inferior to flucloxacillin/cloxacillin.
- Adult data also showed higher acute kidney injury with flucloxacillin/cloxacillin compared with cefazolin.

This created a real paediatric dilemma.

Should the paediatric arm stop because the adult result was available, or continue because children may respond differently?

Continuing SNAP-PY meant:

Children would continue to be randomised after adult practice-changing results were available.

Stopping SNAP-PY meant:

Paediatric treatment decisions could be shaped by adult data that may not reflect paediatric safety, benefit or risk.

So the **ethical** question was not:
‘Is it ethical to include children?’

It was:

‘Is it ethical to stop before we know whether the adult result applies to children?’



Why SNAP-PY continued

- The adult answer did not fully answer the paediatric question.
- At the time the adult PSSA and MSSA silos were paused, there were more than 1700 randomised participants overall, but only around 100 were children.
- The DSMC had not seen the same acute kidney injury signal in children.
- Paediatricians also considered that children differ from adults in baseline comorbidities, renal risk, disease course and treatment tolerance.

The ethical concern was that stopping would leave children dependent on extrapolated adult evidence.

What made continuing ethical?

The decision was supported by:

- DSMC advice.
- Paediatric and pregnancy working group discussion.
- Consumer reference group support.
- Statistical working group input.
- Global trial steering committee endorsement.
- Ethics review.
- Paediatric-specific simulations.
- Strengthened creatinine testing for AKI assessment.



This is the difference between inclusion and ethical inclusion

Closing Early oral switch Domain

Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain
PSSA	(Flu)cloxacillin vs Penicillin	No Clindamycin vs Clindamycin (days 1-5)	Continued IV vs Early oral switch At 7 days At 14 days
MSSA	(Flu)cloxacillin vs Cefazolin		
MRSA	Vancomycin vs Vancomycin plus cefazolin		

Imaging: Radiation exposure

Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain	Diagnostic Domain (protocol v.2.0 only; adults only)
PSSA	(Flu)cloxacillin vs Penicillin	No Clindamycin vs Clindamycin (days 1-5)	Continued IV vs Early oral switch At 7 days At 14 days	No PET/CT vs PET/CT At 7 days
MSSA	(Flu)cloxacillin vs Cefazolin			
MRSA	Vancomycin vs Vancomycin plus cefazolin			

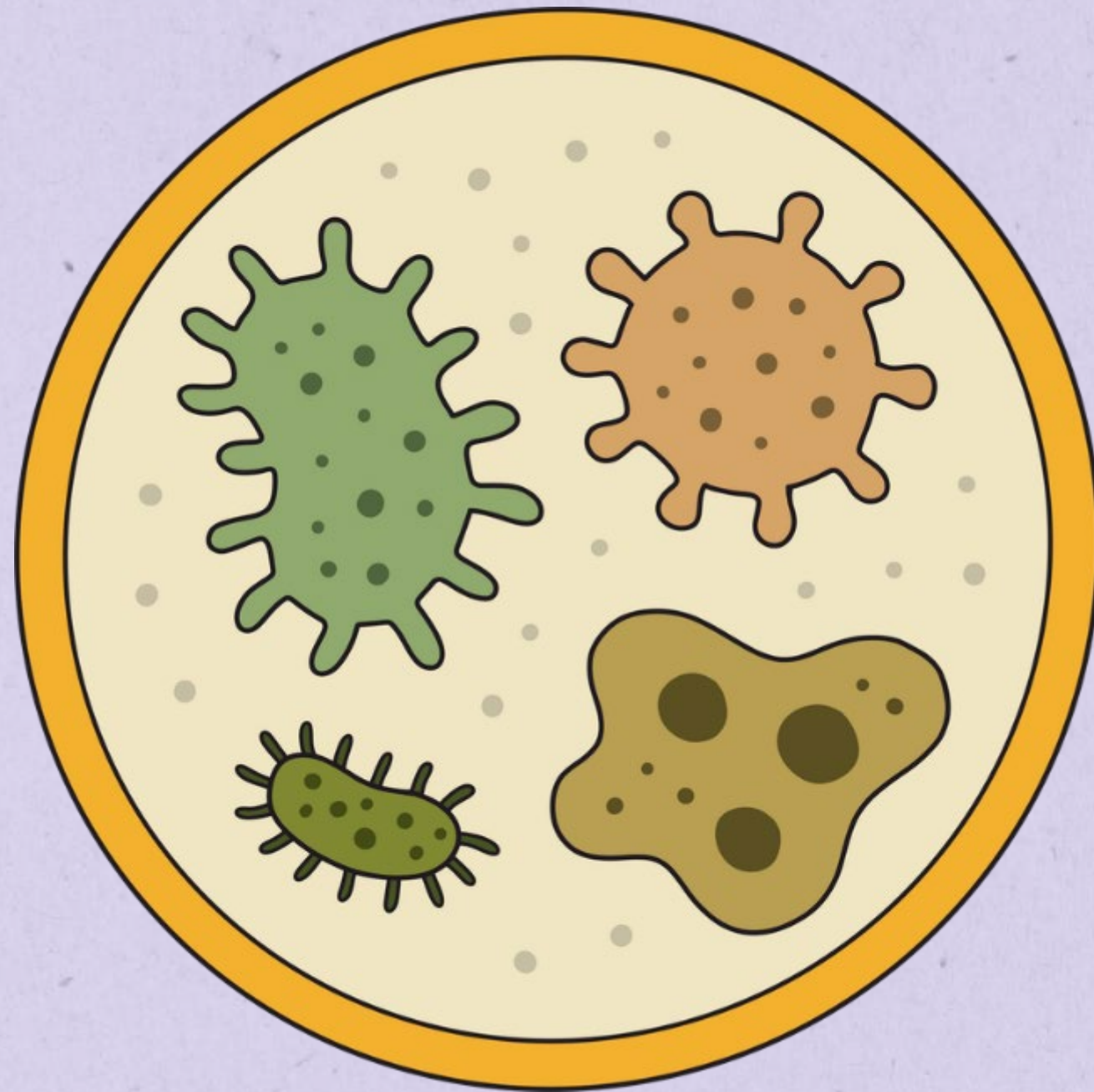
Equity and evidence

Excluding children can delay access to evidence-based care. This is especially important when:

- The condition affects children
- Clinicians will use the intervention anyway
- Adult-only evidence will be extrapolated into paediatric practice
- Paediatric safety signals may differ
- Children in underserved settings may be left behind
- Comparative effectiveness data needed



Lessons learned from SNAP-PY



- SNAP-PY shows that children should **not be included** in platform trials by *default*.
- But they should also **not be excluded** by *default*.
- When children are affected by the condition, and trial results are likely to shape paediatric care, exclusion can create its own ethical problem.

Excluding children may protect them from research risk, but it can also expose them to evidence-poor care.

Take home message

- The ethical question is not whether children should be **included** or **excluded**.
- The ethical question is whether the trial has been **designed well enough** to include them **safely, respectfully** and **meaningfully**.

SNAP-PY is an example of ethical paediatric persistence: continuing carefully, rather than relying only on adult evidence.

Editorial

 *Obstetric Medicine*

Walking the walk to include pregnant participants in non-obstetric clinical trials: Insights from the SNAP Trial

Obstetric Medicine

2023, Vol. 16(1) 3–4

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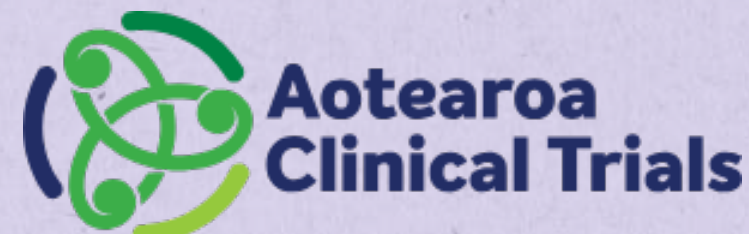
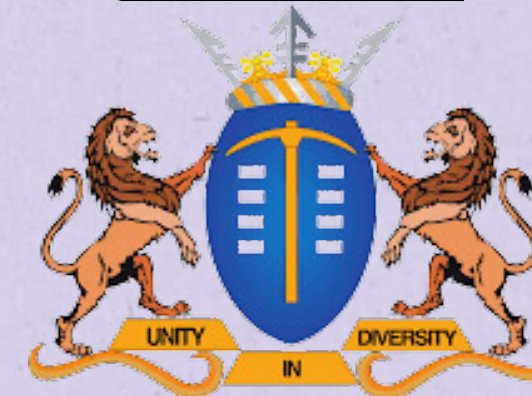
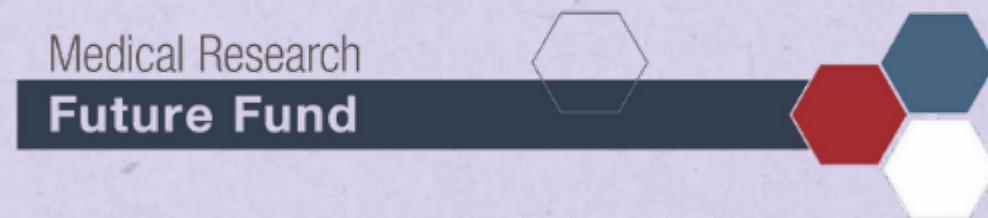
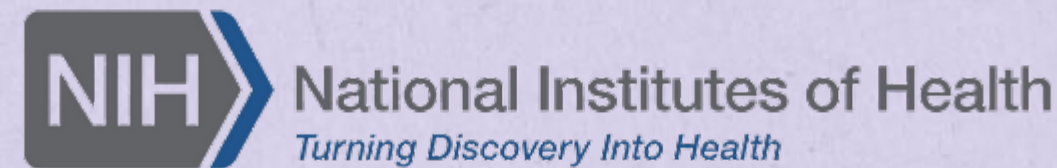
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 **SAGE**

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451092
Singapore NMRC CTGIITnov-
0002
UK NIHR 133719
US NIH 1R01AI173138-01A1
Netherlands ZonMw
10140022110014



A joint venture between The University of Melbourne and The Royal Melbourne Hospital

International Platform Trials Symposium: Patient and Family Engagement within Platform Trials

Dr Julie Menzies

RN, PhD

**Clinical Academic Nurse Researcher, Paediatric Critical Care
Lead Nurse (Research) Faculty Nursing Education and Research**

Bristol NHS Foundation Group

Visiting Fellow, University of the West of England, Bristol, UK

Hon Senior Research Fellow, Imperial College, London, UK



Plan

Terminology



Who



What



How



Why



Impact

Who have we engaged with?

What have they told us?

How have we engaged with people?

Why do we need to sustain this?

What impact is this having?

Patient and Public Involvement and Engagement (PPIE)

What it is..

research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them.



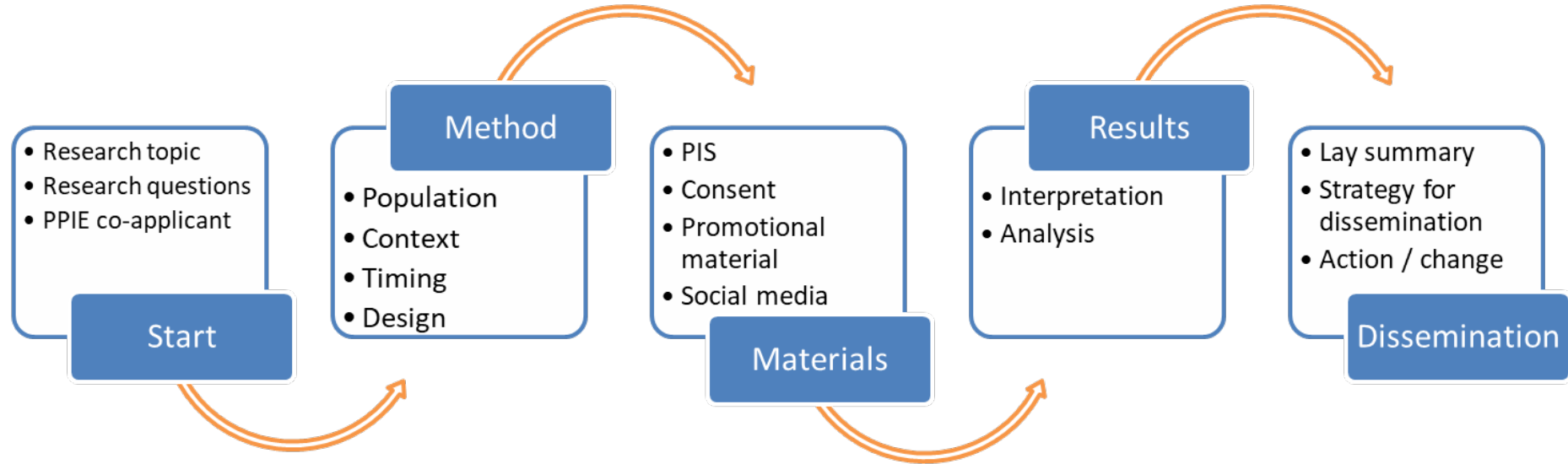
Involvement:

active, collaborative partnership between patients /the public and professionals throughout a project's lifecycle

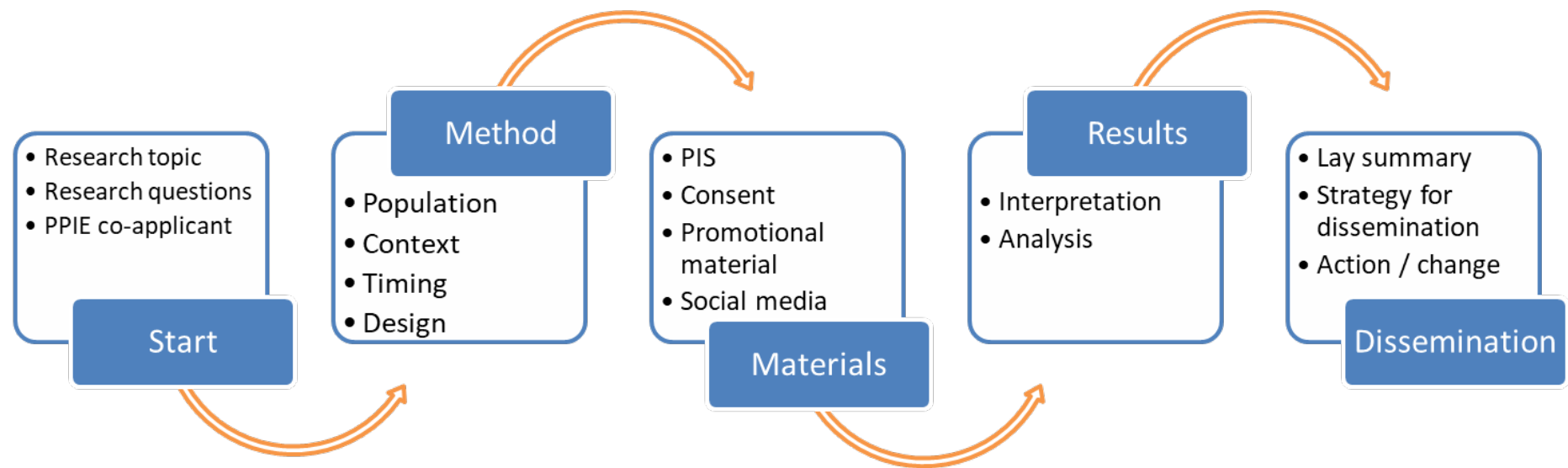
Engagement:

sharing information about research and research findings with patients and the public

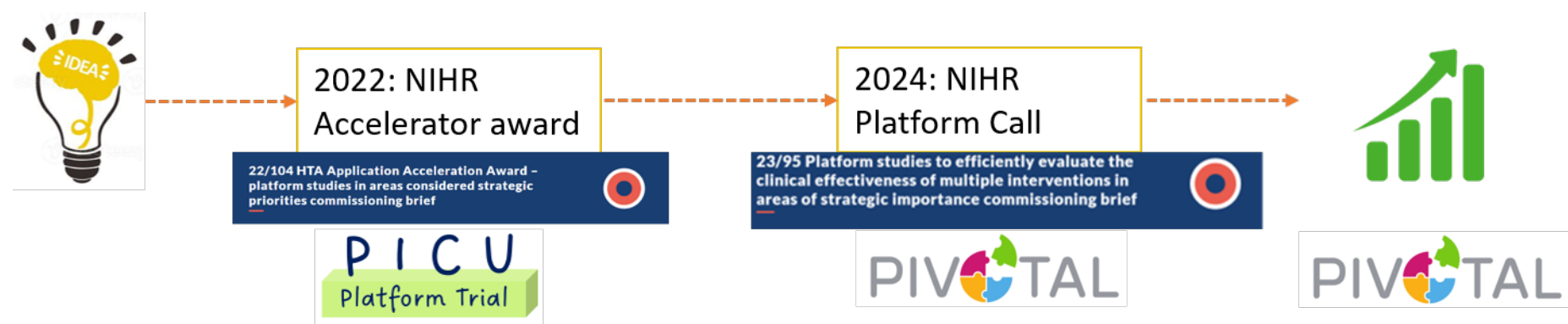
PPIE is a Golden thread 'woven' through..



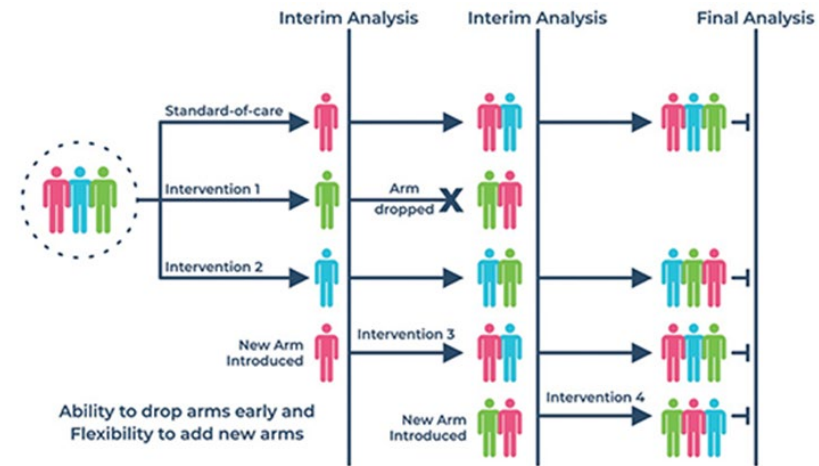
PPIE is a Golden thread ‘woven’ through...



PPIE to support PIVOTAL..



Where do you start??



Set-up

Dissemination

Study selection

Support

Governance

Maintenance

Oversight

Information

Number of studies

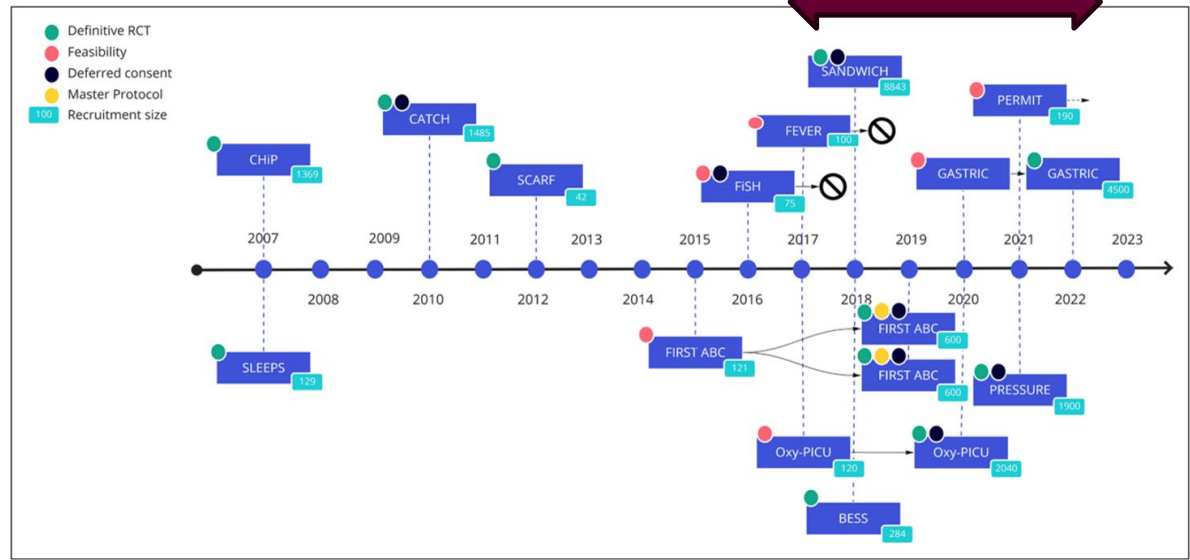
Consent





Initial PPIE 2022

Who



Approached Chief Investigators of PCC Trials in past five years to invite:

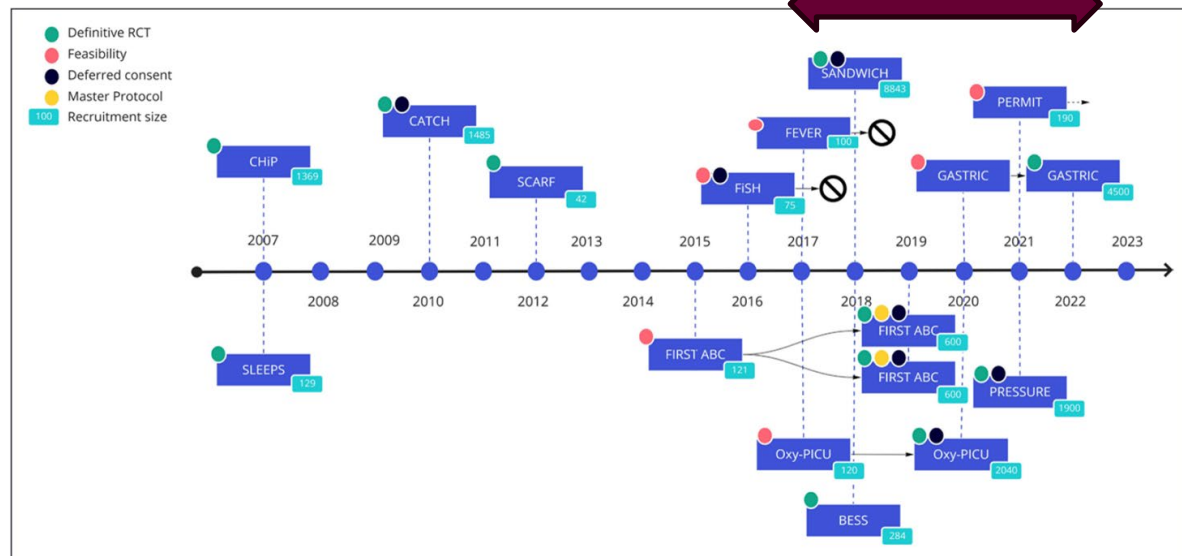
- PPIE co-applicants
- PPIE members
- PPIE representatives on Steering Groups

Key consideration:
Experience of PICU
AND
Experience of PPIE



Initial PPIE 2022

Who



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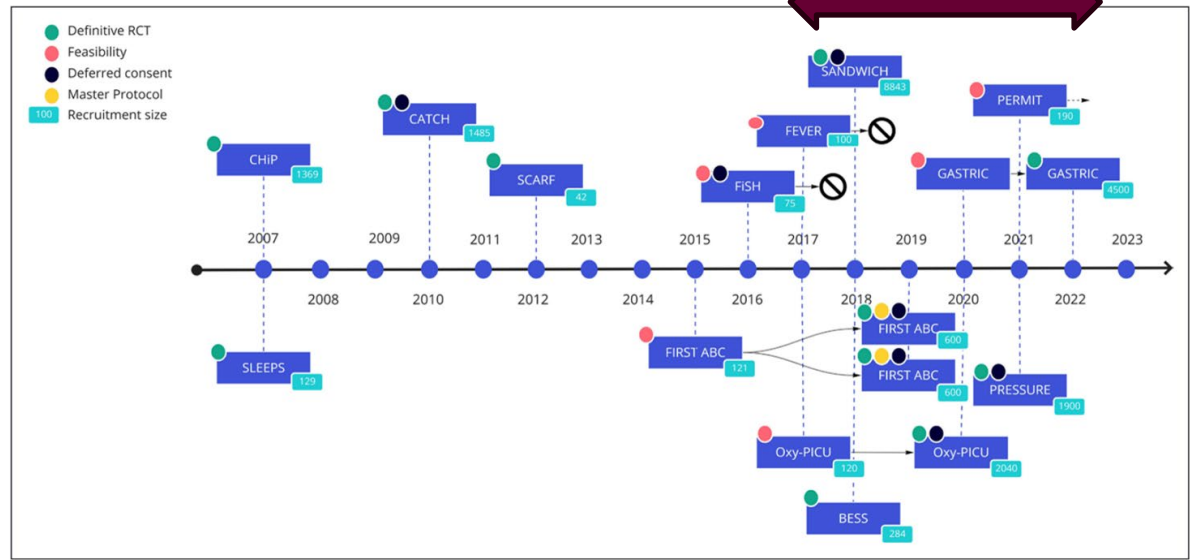
Key consideration:
Experience of PICU
AND
Experience of PPIE

- 10 Parents/carers
- Child admitted 4 UK PICUs
- Child aged 0-15yrs time of PICU admission
- Involved with 7 UK PICU trials
- Geographically spread
- Ethnically diverse
- Gender: 8 females, 2 males



Initial PPIE 2022

Who How



Approached Chief Investigators of PCC Trials in past five years to invite:

- PPIE co-applicants
- PPIE members
- PPIE representatives on Steering Groups

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Experience of PICU
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- Geographically spread
- Ethnically diverse
- Gender: 8 females, 2 males



How

Virtual Focus group May 2022

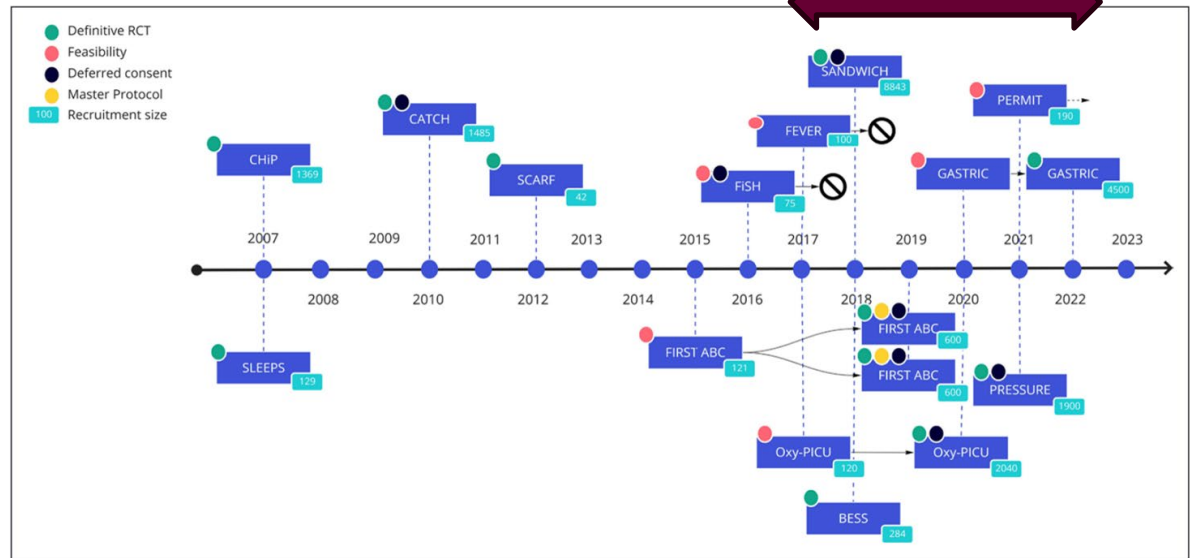
10 participants

- Acceptability of platform trials
- Potential challenges
- Potential benefits
- Practical considerations.



Initial PPIE 2022

Who How



Approached Chief Investigators of PCC Trials in past five years to invite:

- PPIE co-applicants
- PPIE members
- PPIE representatives on Steering Groups

Key consideration:
Experience of PICU
AND
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- Geographically spread
- Ethnically diverse



How

Virtual Focus group May 2022
10 participants

- Acceptability of platform trials
- Potential challenges
- Potential benefits



22/104 HTA Application Acceleration Award – platform studies in areas considered strategic priorities commissioning brief

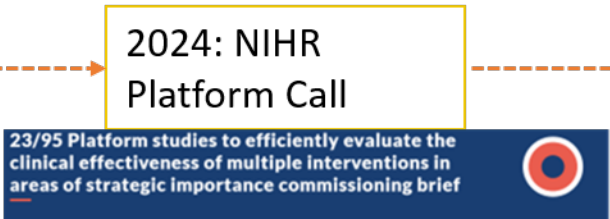




PPIE within the Accelerator Grant

2023-2024

Who



1.PAG: 10 members

Feedback:

Missing the voices of Young People



PPIE within the Accelerator Grant

2023-2024

Who



Young Person's Advisory Group (YPAG) (Bristol, UK).

Experience of:

- personal/ sibling /family member PICU/ICU admission OR
- trial participation OR
- in-hospital admission

110 members.
16 expressed interest
6 invited to participate.

6 YP
Age 13-21 yrs
Ethnically diverse
Gender: 4 females, 2
males



PPIE within the Accelerator Grant

2023-2024

Who How



Young Person's Advisory Group (YPAG)
(Bristol, UK).

Experience of:

- personal/ sibling /family member PICU/ICU admission OR
- trial participation OR
- in-hospital admission

110 members.
16 expressed interest
6 invited to participate.

6 YP
Age 13-21 yrs
Ethnically diverse
Gender: 4 females, 2 males



How

Virtual focus group meetings
1:1 phone / teams
Emails

} *Flexibility*



PIVOTAL 2024 application

Who How

PPIE Leads: Dr Julie Menzies & Prof Kerry Woolfall,
University of Liverpool



1. **PAG**: 10 members
2 members PPIE co-applicants

2. **YPAG** 6 members

£6.5 million

Platform studies to efficiently evaluate the clinical effectiveness of multiple interventions in areas of strategic importance commissioning brief



PPIE PIVOTAL 2025

Who



1.PAG: 10 members

2 members PPIE co-applicants



'Gap' Parents of children with congenital heart disease

1b. Cardiac PAG: 4 members

Recruited through Cardiac Consultants

- 1 male, 3 females
- Children different CHD / elective/ emergency pathways
- Varied ethnicity and geography (Mids/SE)



PPIE PIVOTAL 2025

Who



1. **PAG:** 10 members

2 members PPIE co-applicants



'Gap' Parents of children with congenital heart disease

2. **YPAG** 1 remaining member

Re-recruitment

1b. **Cardiac PAG:** 4 members

Recruited through Cardiac Consultants

- 1 male, 3 females
- Children different CHD / elective/ emergency pathways
- Varied ethnicity and geography (Mids/SE)

5 'new' members

- 4 males, 2 females
- Age 14-17years
- Varied ethnicity / geography within SW
- Varied health & care experience



PPIE PIVOTAL 2026

Who



1. PAG: 15 members (combined two groups)

- 6/10 original members
- 3/4 cardiac PAG
- 6 'new' members recruited from national PPIE group

2. Young Person's Advisory Group (YPAG)

6 members



Who

Good practice principles



Build relationships



Diversity: consider
and address 'gaps'



Training



Re-orientate each
time



Regular contact/
updates



Check in pre/post



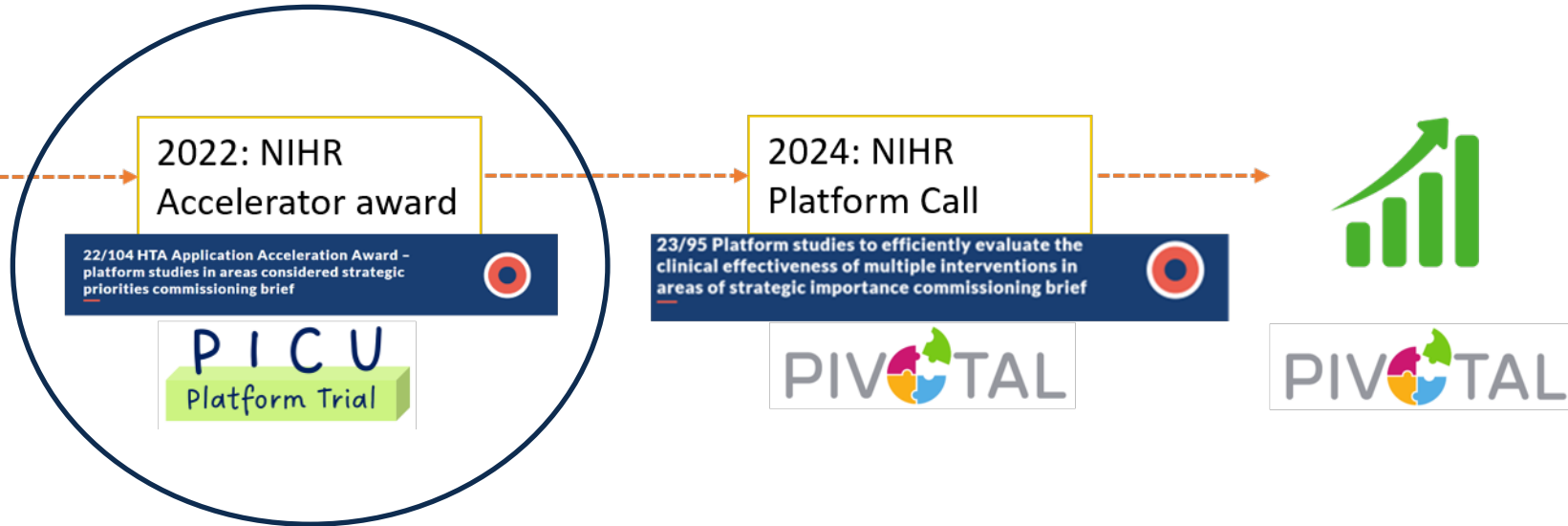
Payment (attendance
and prep)





What did people say?

What



PPIE

Qualitative work

Work package 1:

CYP: 18 (2 focus groups- 1 face to face, 1 virtual)
Parents/carers: 15 (2 focus group, virtual)

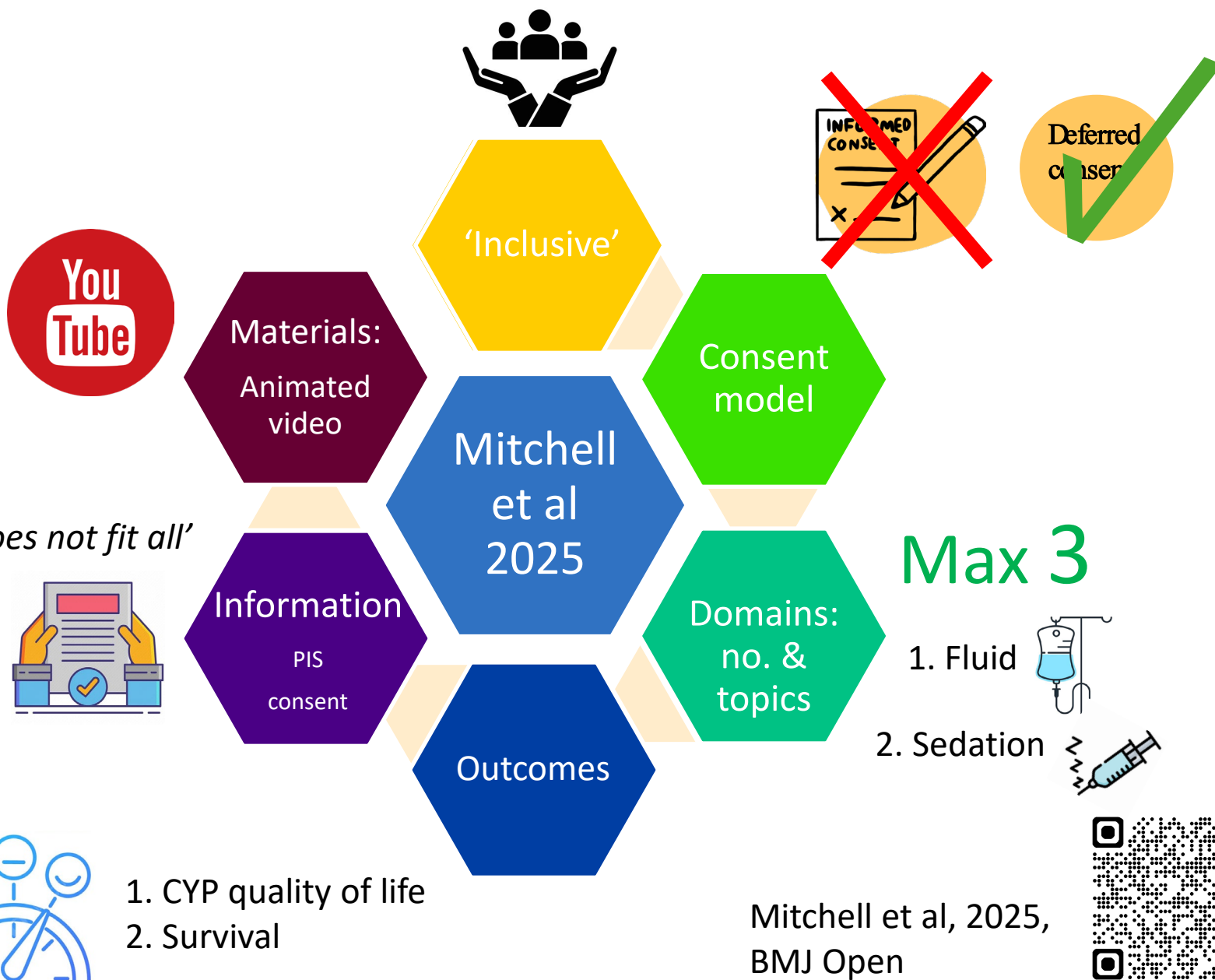
Work package 2:

Health Care Professionals: 53
4 FG- face to face (n=40)
2 FG- virtual (n=13)



Qualitative work 2023/24

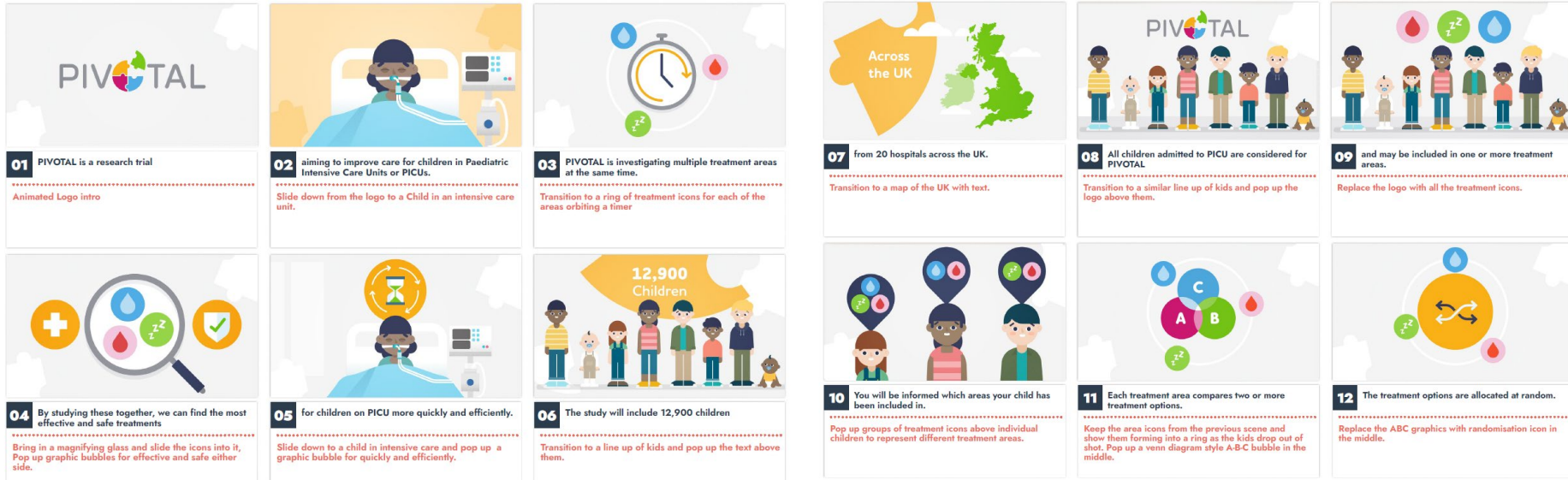
What





What

Animated video 2026





What

PAG feedback May 2026

“The language is too technical and hard for people where English is not their first language”

- Script amendments
- Illustration amendments
- PAG to re-review

“The message needs to be clearer that these are low risk treatments. I don’t think this is clear enough at the moment”

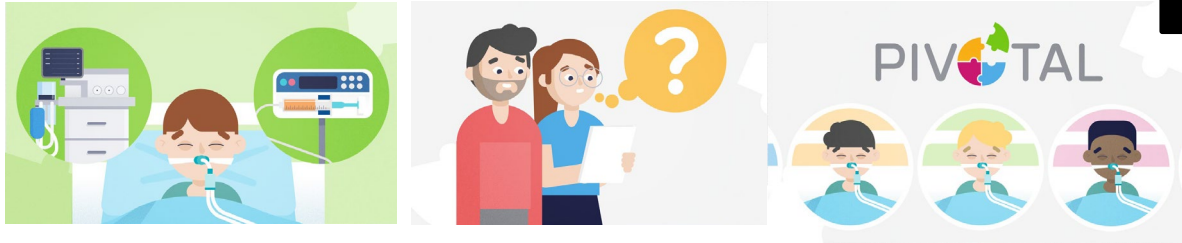


YPAG feedback June 2026

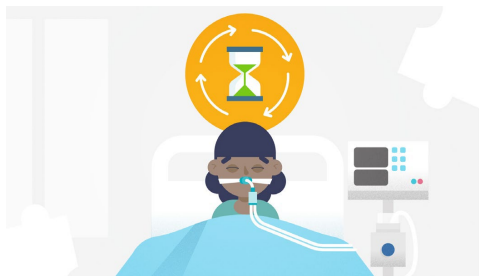
What

"Haemoglobin threshold is hard for a non-medical person"

- Script amendments
- Illustration amendments
- PAG to re-review



"All the children and parents look visibly distressed and shaken.. I know this might be the case in real life, but could you show both patients and parents with neutral expressions as this might worry viewers"



"With a timer on their head, it looks like the patient's running out of time, like they're going to die."



Impact

Impact



Listen



Act



Feedback



Principles

1. Timely
2. Clarity on where PPIE sought
3. Manage expectations
4. Not all feedback can be incorporated
5. Update on how acted on (or not)

Feedback 2022: NIHR Accelerator grant submitted

Feedback



Feedback 2024 – Platform Grant submitted

Background

Carrying out research to improve the care of children who are critically ill or injured is important. The way trials are usually designed it can take a long time to answer important research question and identify the best treatments.

Our aim: to set up a platform trial within Paediatric Intensive Care (PICU). This allows multiple research questions and treatments to be tested at the same time and the trial is adapted as it goes along. In other areas where a platform has been set up this has meant more questions can be answered, more efficiently and in less time.

Method

Aim: to hear the views of parents and design and set up of a platform trial.

Method: online focus groups

Who with? Parents of children having a child admitted to PICU patient and public involvement with a UK PICU study

PAG: 10 parents of children at time of admission) and All also had PPI roles

What did they say?

- Offering research to families in PICU is **extremely important**, but admission to PICU is an **upsetting time**. It can be hard to think about research at this time for some families
- Streamlining communication** about research is helpful so people can make an informed decision
- It sounds like it could be quite confusing**. Need clear information on the different domains, the different trials and how they can say yes or no.
- Future work needed:** how many trials can a child be in, what the domains are and review the information parents are given.
- In addition to PAG, need to hear the views of **young people and the health care professionals** who work in PICU
- Overall the group were **very supportive** of developing a platform trial for PICU

A huge thank you to the PAG for their time and support! from the Platform

PICU PLATFORM TRIAL- SUMMARY OF PATIENT AND PUBLIC INVOLVEMENT (PPI)

Method

Aim: To carry out patient and public involvement

'Thank you so much for updating us on the progress of the platform trial. I'll make sure the YPAG members who took part in your session are updated.. They will love to hear this update.'

YPAG facilitator

When did we carry out the PPI? PPI: Feb- April 2023

2023

We are interested in hearing your feedback about working with the trial team as PPI representatives. Please feedback via this very short on line survey. Thank you

WHEN

• YPAG: online meeting with follow up emails

• young people and parents views?

b) Recruitment: How should we recruit?

c) How can we hear their views?

d) Information: how can we improve information and consent forms?

e) Materials: How can we best carry out study?

Parents: offer online focus groups and flexibility in dates/ times

d) Information: YP and Parents commented on

- information sheets
- consent forms
- social media adverts

e) Material for the focus groups:

- Background information:** to help explain platform trials and the domains
- Preparation-** ideally send information in advance so give people time to read and understand it
- Preparation-** in the focus group to clarify understanding and answer any questions
- Questions:** simple as possible and avoid having too many.
- Create a **'mock'** information sheet that children/ parents to explain the platform study
- Use **images and plain English** where possible. This helps everyone, especially people where English is not their first language

Next Step

What did we do?

Who: the study recruited well from the 3 groups

- 18 YP from two YPAGs
- 15 parents from across UK
- 53 HCPs

Recruitment: Two focus groups: 1 face to face and 1 online

Parents: two on-line focus groups. Recruited through social media, the Paediatric Critical Care society, charities and databases of parents involved in previous PICU studies*

ICP: six focus groups. Recruitment- Paediatric Critical Care Society and social media

Method: Flexible approaches offered to all groups

d) Information:

- Information sheets & consent forms:** reduced wording, length and format and suggested images to add.
- Helped develop a **poster/ advert** for social media.

e) Material for the focus groups:

- Background information:** revised to explain platform trials and domains
- Questions:** number and length reduced
- 'Mock' information sheet** created to explain what a future platform trial could look like for use in the focus group.

*Parents had consented to be contacted by the trial team (ICNARC) about relevant future studies

PICU Platform Trial

A huge thank you to all the YPAG and PAG members who supported this work. We are currently writing up the results of all the work and applying for another funding grant to continue to take the work forward. We will share a summary of the results of the work as soon as we can!





Impact



23/95 Platform studies to efficiently evaluate the clinical effectiveness of multiple interventions in areas of strategic importance commissioning brief



Impact

- **Grant funded:** *“The committee considered this to be a strong application with good PPI”*
- **PAG & YPAG experience:** Positive feedback on the work and their involvement.



Open sites: 9

Recruitment to date: 138 participants

“I’m really happy to hear that the funding has been granted. I’m very happy to stay involved and help other families whose child is admitted to PICU”
(K, PAG member)

*“I’ve never had this before where a study we’ve advised on has got to this stage. It’s so exciting it’s actually open and people **right now** are going into the study.”*
(YPAG member, 27th May 2026)



Impact reporting

Impact

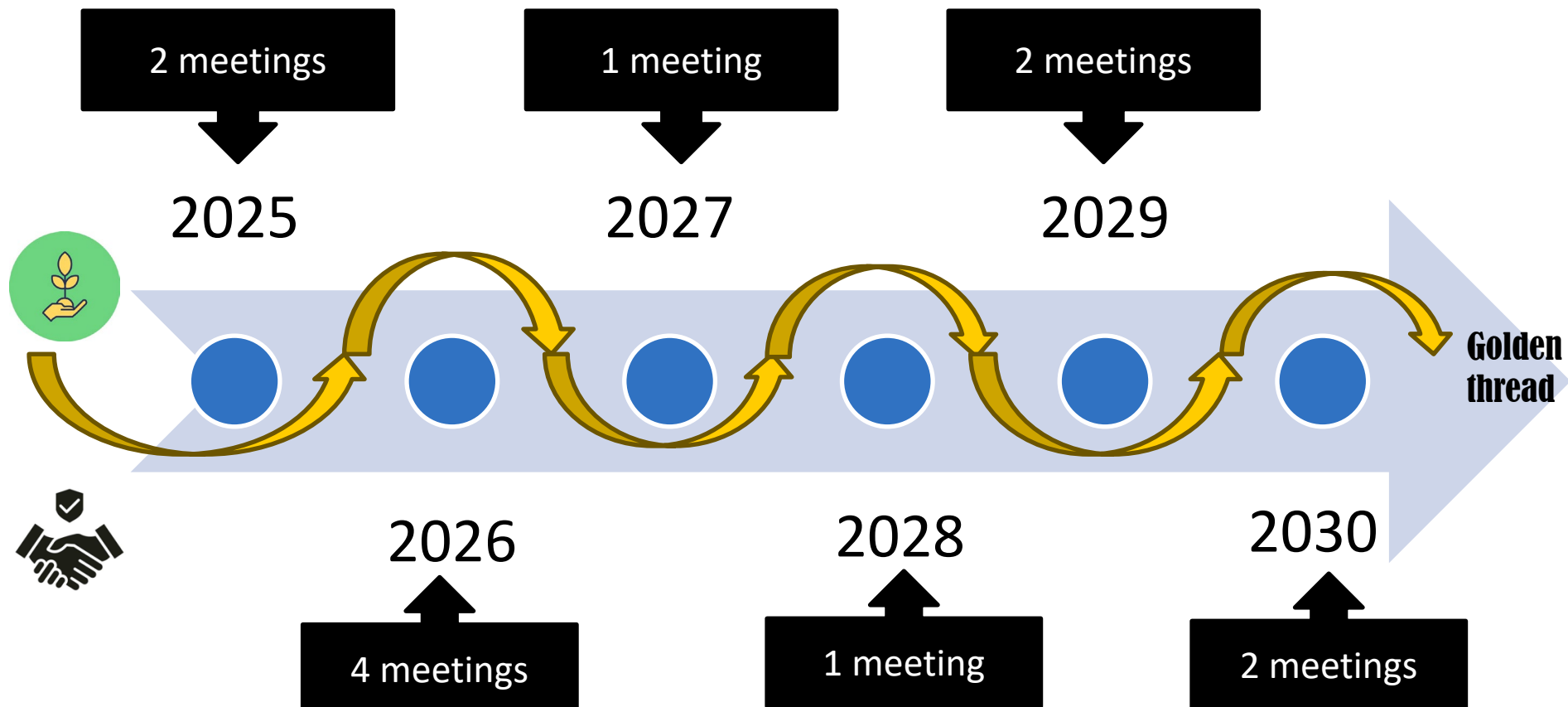
1. NIHR learning for involvement page
2. NIHR Standards for Involvement (2019)
3. Public Involvement in Research Impact Toolkit (**PIRIT**) (Newman et al 2023)
 - How to plan and integrate public involvement
 - Track public contributions
 - Report impact against the UK standards for Involvement





The PPIE 5-year plan

Why



YPAG- 6 members
PAG- 10 members
12 meetings / 63 months

Thank you for listening

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