Operationalising Adaptive Platform Trials

Arlen Wilcox

NHMRC Clinical Trials Centre, University of Sydney

2022 ACTA ASM

Australian Clinical Trials Alliance

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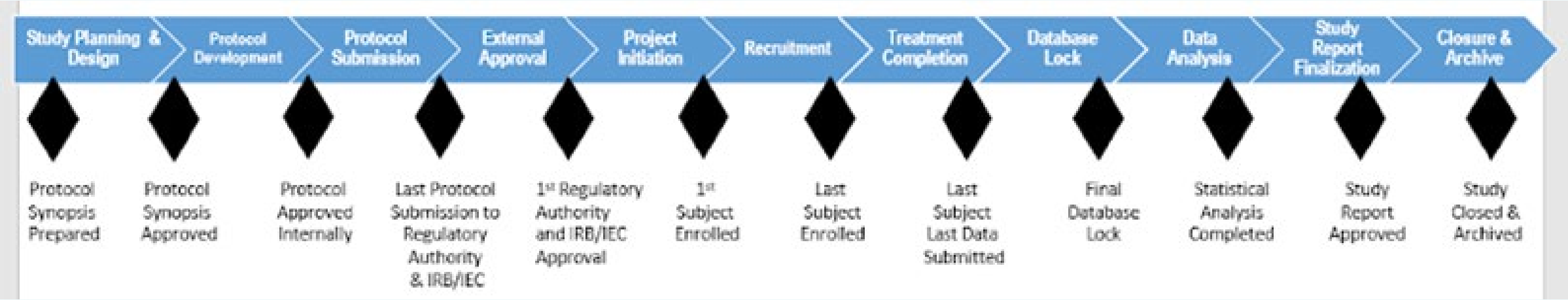
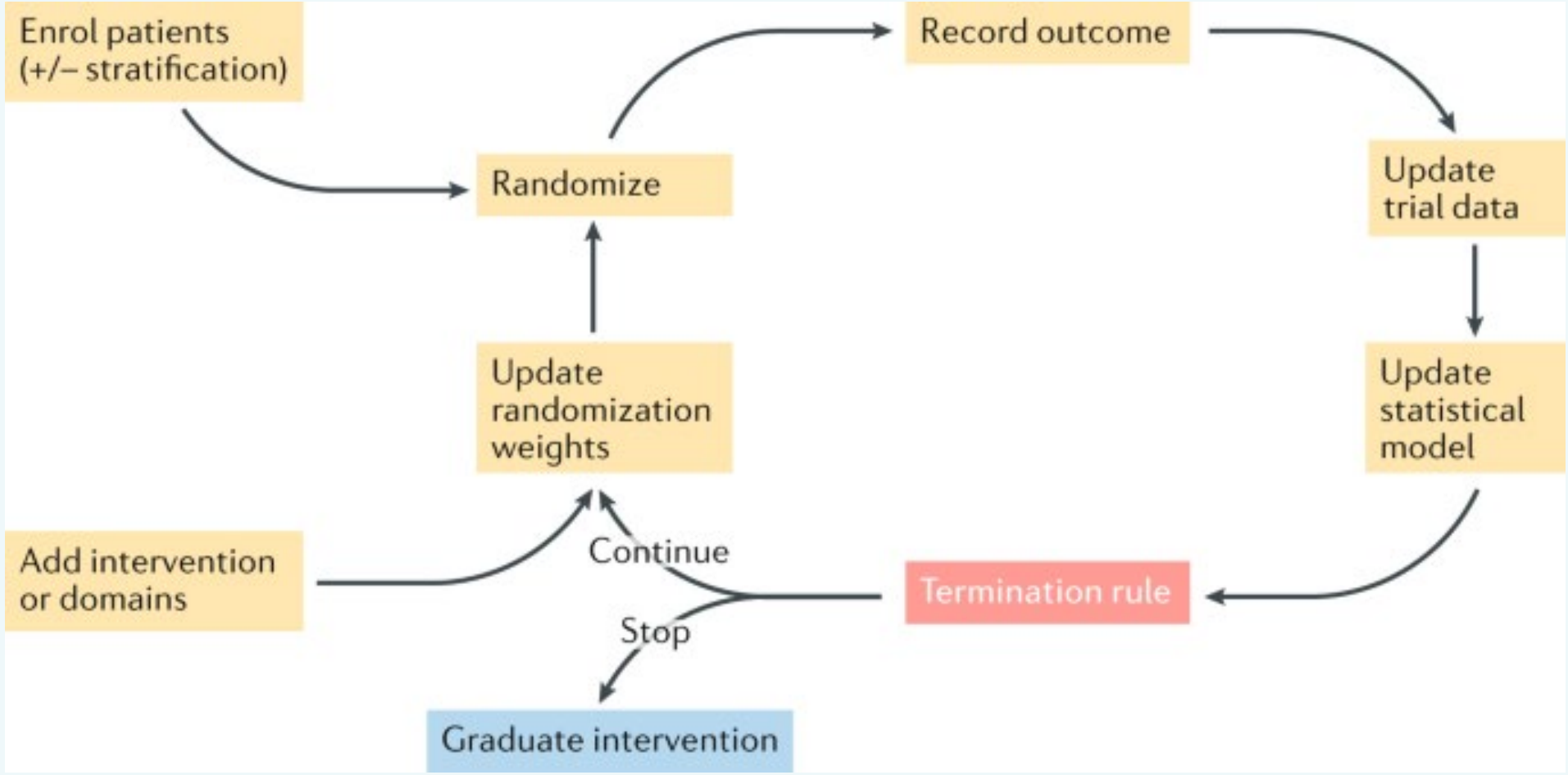
ACTA gratefully acknowledges operational funding from the Australian Government's Medical Research Future Fund

Traditional Delivery



Adaptive Platform Trials (APTs)



The Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov 2019*

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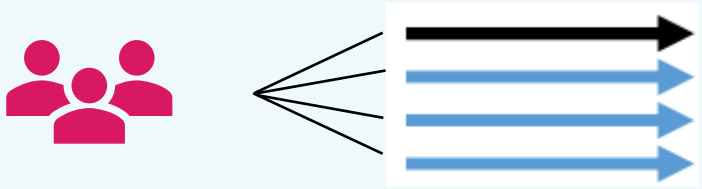
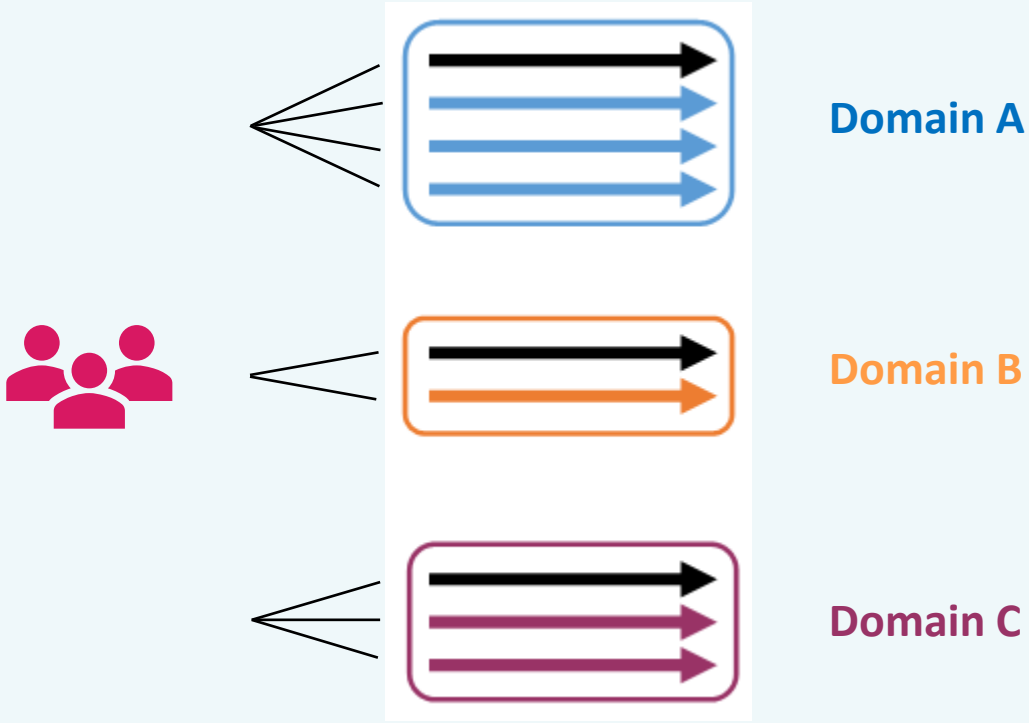
Multi-Arm, Multi-Domains & Multi-State

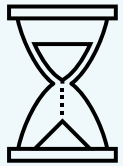


Multi-Arm, Multi-Domains & Multi-State

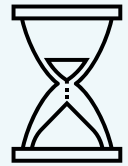


Multi-Arm, Multi-Domains & Multi-State

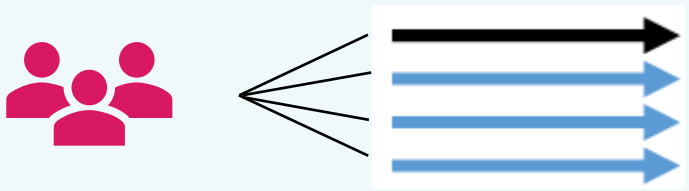
e.g. Pre Progression



e.g. Post Progression



e.g. Palliative



Operational Challenges

1. Modular Protocol & Participant Information Development
2. Dynamic Database Development & Management
3. Navigating Ethics, HREC Review, Registration, & Site Set Up
4. Utilisation & Adaptation of Sponsor / Coordinating Centre Processes & Procedures

1. Modular Protocol & Participant Information Development

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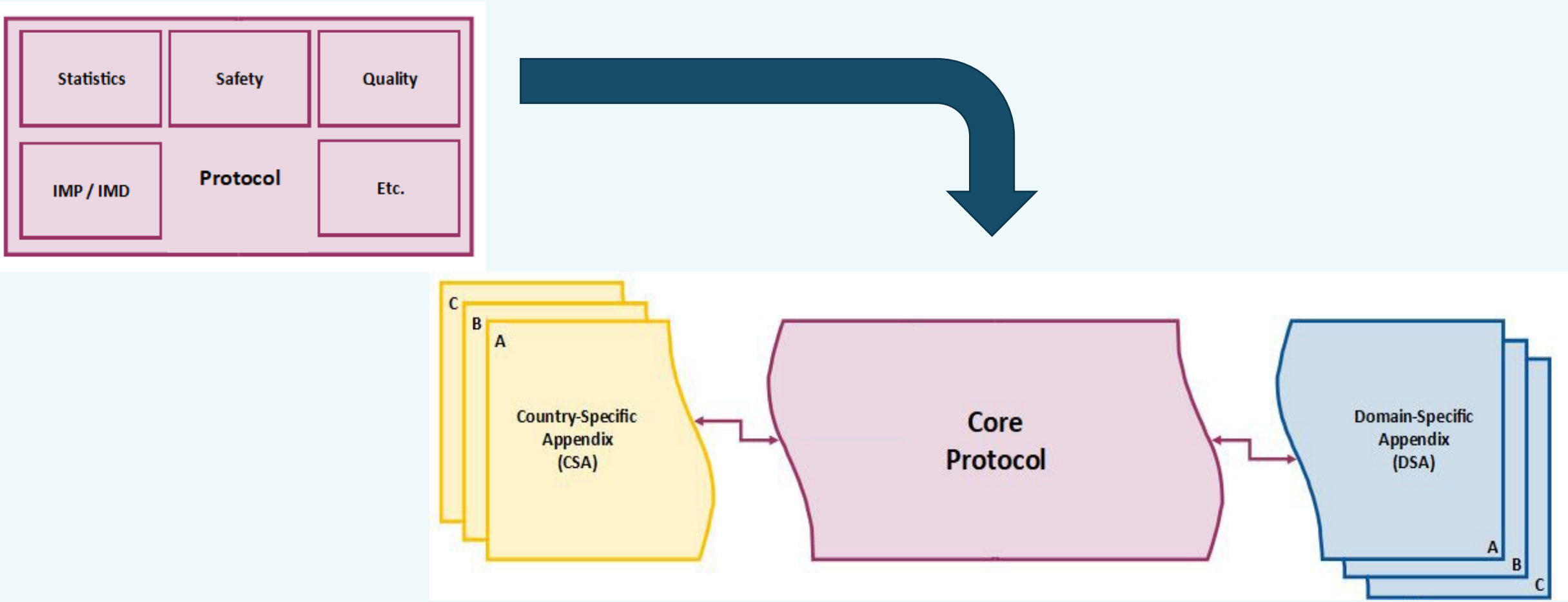
Protocol


Statistics
Safety
Quality
IMP / IMD
Protocol
Etc.
C
B
A
Country-Specific Appendix (CSA)
Core Protocol
Domain-Specific Appendix (DSA)
A
B
C

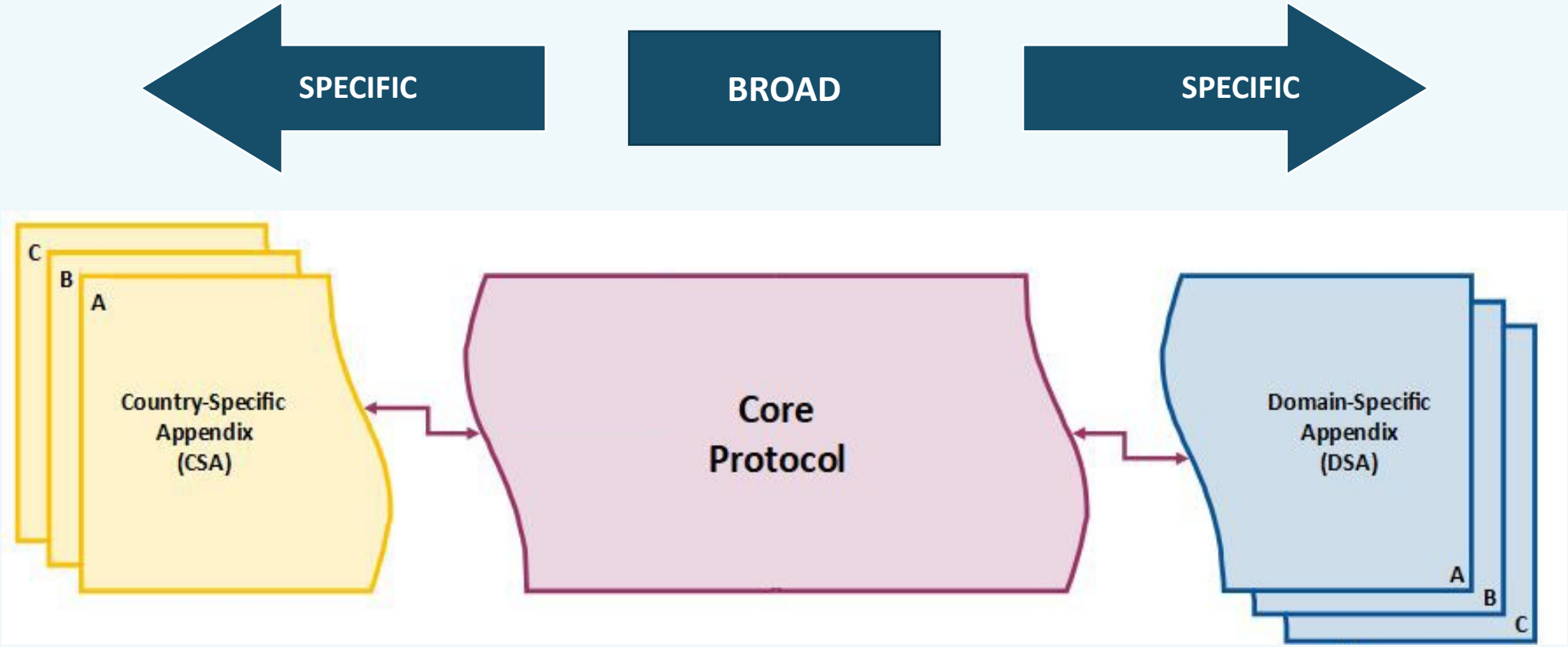
Modular Protocol

1. Core Protocol:
Applies to all trial components – domains, states, comparisons, & countries / regions.
Contains broad information that is common to the entire platform.

2. Domain/State/Comparison Specific Appendix: Applies to a particular Domain/State/Comparison & the interventions that are evaluated within it.
Contains information relevant to the delivery of that component.

3. Country/Region Specific Appendix: Applies to a specific to the country or region.
Contains information relevant to the delivery of the study within that specific region.

Modular Protocol



Where to put what?

What content would be held within a Domain Specific Appendix?

Go to **www.menti.com** and use the code **21529209**

Where to put what?

What content would be held within a Country/Region Specific Appendix?

Go to **www.menti.com** and use the code **21529209**

Content Example

Core e.g.

- Platform background & rationale Framework structures
- Adaptations summary
- Platform eligibility / target population
- Platform schedule of assessments
- Primary endpoint
- Platform statistics
- Governance model

etc.

Domain e.g.

- Background & rationale of specific evaluations
- Domain specific eligibility
- Domain randomisation/strata
- Domain specific Schedule of assessments
- Treatment schedules
- Additional
- Dose adjustments
- Safety Management
- Blinding/unblinding
- Sample size

etc.

Country e.g.

- Local ethical requirements
- Local regulatory requirements
- Local sub studies
- Local data Linkage projects
- Local biobanking procedures

etc.

Mock Core Protocol Excerpt 1

Inclusion Criteria

1. Adults ≥18 years
2. Documented clinical diagnosis of Chronic Kidney Disease according to the KDIGO definition
3. eGFR ≥ 25 to ≤ 90ml/min/1.73m^2
4. The participant and treating physician are willing and able to perform trial procedures

Exclusion Criteria

1. Have a known allergy to no more than one of the interventions
2. Be unable, or refuse, to cease concomitant open label treatment of any of the interventions prior to commencing the trial
3. Be unable, or refuse, to cease concomitant treatment with a known antagonist of any of the interventions during the trial
4. Be a participant in other trials involving active treatments used in this trial
5. Have an active malignancy
6. Be currently pregnant or breast feeding

Mock Core Protocol Excerpt 1

Inclusion Criteria

1. Adults ≥18 years
2. Documented clinical diagnosis of Chronic Kidney Disease according to the KDIGO definition
3. eGFR ≥ 25 to ≤ 90ml/min/1.73m^2
4. The participant and treating physician are willing and able to perform trial procedures
5. Eligible for randomisation in at least one recruiting domain (see Domain-Specific Appendices)"

Exclusion Criteria

Nil

Other exclusion are perhaps Domain Specific? In this example related to a studies pharmacotherapy domain.

Mock Core Protocol Excerpt 2

The platform component of the trial allows for a number of domains of care to be individually assessed, with competing interventions and domains added as they became scientifically appropriate and operationally feasible for assessment. Comparisons within the platform will have a sample size of 50, with participants randomised in a 1:1 ratio between the intervention & comparator.

The platform component of the trial allows for a number of domains of care to be individually assessed, with competing interventions and domains added as they became scientifically appropriate and operationally feasible for assessment. ~~Comparisons within the platform will have a sample size of 50, with participants randomised in a 1:1 ratio between the intervention & comparator.~~ Individual comparisons sample size considerations will be described in detail within the individual DSA. When initiated, platform domains will begin with a randomisation ratio consisting in an equal allocation between all arms within that domain, unless described otherwise within the relevant DSA.

Mock Core Protocol Excerpt 3

Allocated research treatment should start promptly after randomisation, and continue until a trial stopping point is reached. Research treatment should be paused if a Grade 2 or worse adverse event, according to the CTCAE, is experienced, and not resumed until it has resolved to Grade 0.

Allocated ~~research treatment~~ intervention should start promptly after randomisation, and continue until a trial stopping point is reached, or the responsible physician deems it in the participant's best interest to stop treatment. ~~Research treatment should be paused if a Grade 2 or worse adverse event, according to the CTCAE, is experienced, and not resumed until it has resolved to Grade 0.~~ Procedures for the management of the intervention-related side effects of interventions will be defined in the respective DSA and should be used by the responsible physician to guide their clinical practice.

Mock Core Protocol Excerpt 4

Data will be collected as per the Schedule of Assessments below (Table 3). The data variables listed in this Core Protocol will be collected for all domains. Additional domain-specific visits and data variables are outlined in Section 5.4.1 of each Domain Specific Appendix.

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Mock Core Protocol Excerpt 5

In participating countries, there will be a separate consent form for participants to consent to the trial staffs' access to their relevant local routinely-collected health databases/registries, such as the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data in Australia. Consent to data linkage in this manner is not mandatory for trial participation but will be discussed during the trial consenting period.

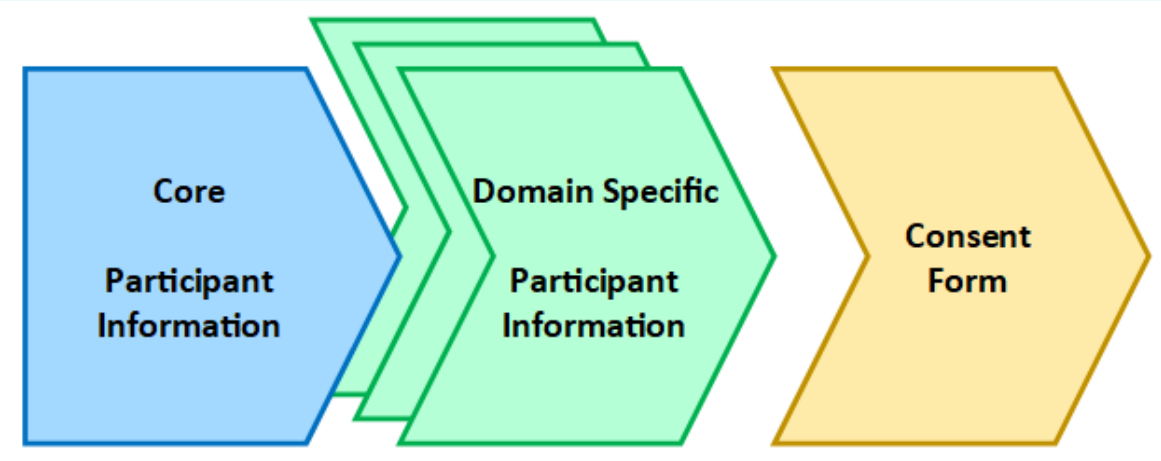
→ Move to Country/Region Specific Appendix & rewrite

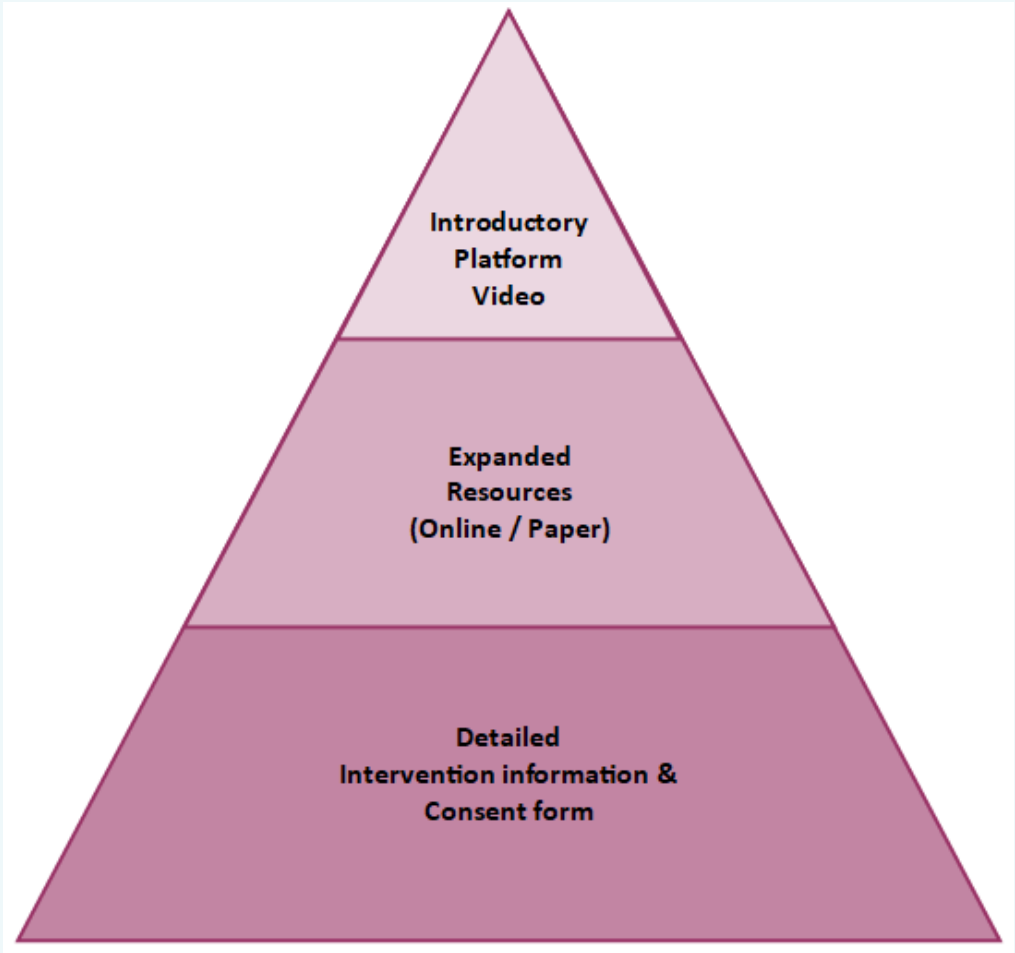
To facilitate economic evaluations and ancillary studies specific to the Australian context, the BEAT-Calci investigators will seek to link Australian-recruited trial participants to their data held within various routinely-collected health databases. In Australia, this will include the Australian Government Department of Human Services' Pharmaceutical Benefits Scheme and Medicare Benefits Schedule records as well as state-based hospital and emergency department admission databases. Data will be obtained for the duration of the trial at regular intervals. Consent to access health data & perform linkage is not mandatory for trial participation but will be discussed and documented during the trial consenting period.

Modular Protocol Development Top Tips

1. Review & adapt ‘standard wording’ from your institutions template
2. Plan ahead
3. Critically evaluate where information is described (Core vs Appendices)
4. Add a glossary of terms
5. Frame your language appropriately
6. Apply terms consistently
7. Remove redundant specifics
8. Clearly describe the links to appendices / core
9. Develop a template for appendices
10. Individualise based on needs of the trial

Modular PIS/CF





Adaptivity in PIS/CF

In the background…

- Establish your structure
- Think through potential future changes
- Prepare upfront for planned adaptations

In the PIS/CF…

- Be clear about the design of the study
- Keep information limited to what is relevant to a participant

2. Dynamic Database Development & Management

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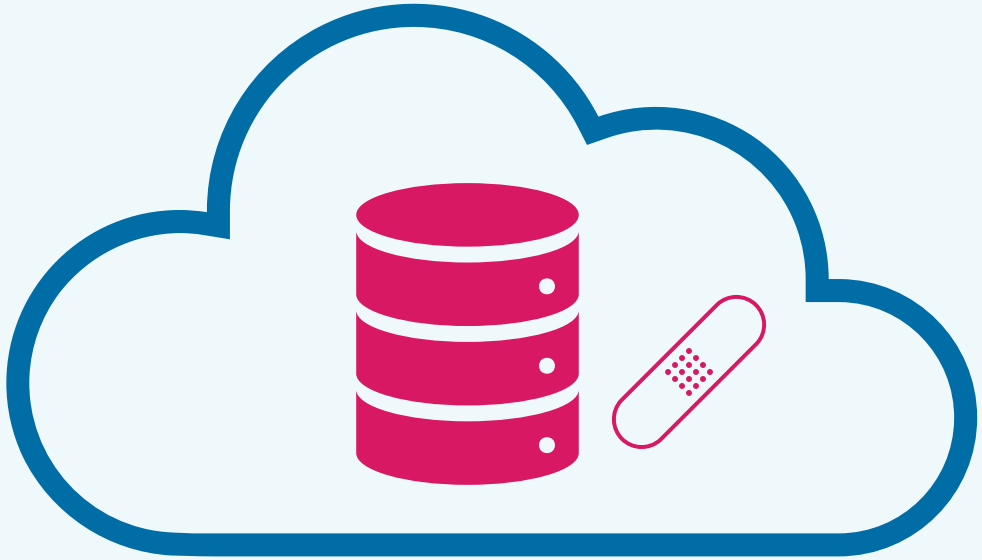
Clinical Trial Database

Traditional Database



Adaptive Platform Database

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Clinical Trial Database

Adding / Removing Domains

Adding / Removing Interventions within Existing Domains

Adding / Removing Domain Specific CRFs

Adjusting Existing CRFs

Adding / Removing Domain Randomisation

Adjusting Existing Randomisation Options

Ability to have Comparison Specific Data Locks

Adjusting Existing Randomisation Ratios

Systems Development → Systems Usability

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e/CRF Development

1. CRF development and maintenance
2. Databases
a. Design, including incorporating new CRF, question and validation requirements
b.Table structure
c. Support
e. Electronic[a] data capture
f. Randomisation system
3. Training and documentation
4. Competing, concurrent tasks: data queries and CRF chases
5. Competing, concurrent tasks: opening new comparisons while managing existing comparisons

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Hague, D *et al.* Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. *Trials* 2019.

e/CRF Development

CRF type	Generic	Comparison-specific
Advantages	• Efficient if data requirements are similar across comparisons • Data are captured consistently across comparisons • Capacity to still make sections specific by arm, comparison, sites, patient sub-group, etc. • CRF changes need to be made on only one set of CRFs, reducing time taken for development/amendments • Generally fewer CRFs overall	• Efficient if data requirements are substantially different across comparisons • Only data required for a single comparison is captured • Not likely to become as complex as generic CRFs. May therefore be easier for site staff to use. • Each CRF is easier to maintain for comparison-specific changes • Not all changes across life of the trial must be included, only those during the lifespan of the CRF
Challenges	• Adding comparisons/questions. - Increasing length and complexity as additional data requirements are added - Question numbering can become unwieldy if new questions are needed within the existing CRF - Unanticipated changes may require existing CRF to be redeveloped or a new CRF to be developed[a] - Shared control arm participants may be affected by new comparisons requiring conditional questions/sections to be added[b] • Less flexibility in collecting data - Must ensure CRFs can be relevant for all comparisons • Changes external to the trial may be more likely to impact generic CRFs[c] - Universal coding lists changing the names or values of items on the list[d] - Changes in standard of care	• Generic changes will need to be made across specific CRFs separately, increasing maintenance time and risk of errors. • More CRFs in total - Can take longer to train site staff on each individual CRF if they are different from each other - Version control/CRF tracking. Multiple similar versions with differing version numbers. Data management staff must be more careful to ensure correct version is used. • If a shared control arm is being used, CRFs for this arm must still capture data required for multiple comparisons whilst ensuring this does not introduce bias; additional questions may lead to events being more likely to be reported or introduce other biases. Some questions may need to be added to all comparison-specific CRFs to avoid this.

Hague, D *et al.* Changing platforms without stopping the train: experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. *Trials* 2019.

Randomisation Challenges

Potential challenging needs:

- Participants randomised in only one or multiple domains, according to individual participant eligibility
- Output of randomisation with a mix of open label & Blinded domains
- Finely adjust the randomisation allocation ratio according to statistical model / planned analysis points.
- Add or drop interventions within a domain / whole domains with a live study
- Sequential randomisations / re-randomisation within domains, adjusting treatment regimen
- Integration with eCRF software

Randomisation & Trial Supply Management Mock Example

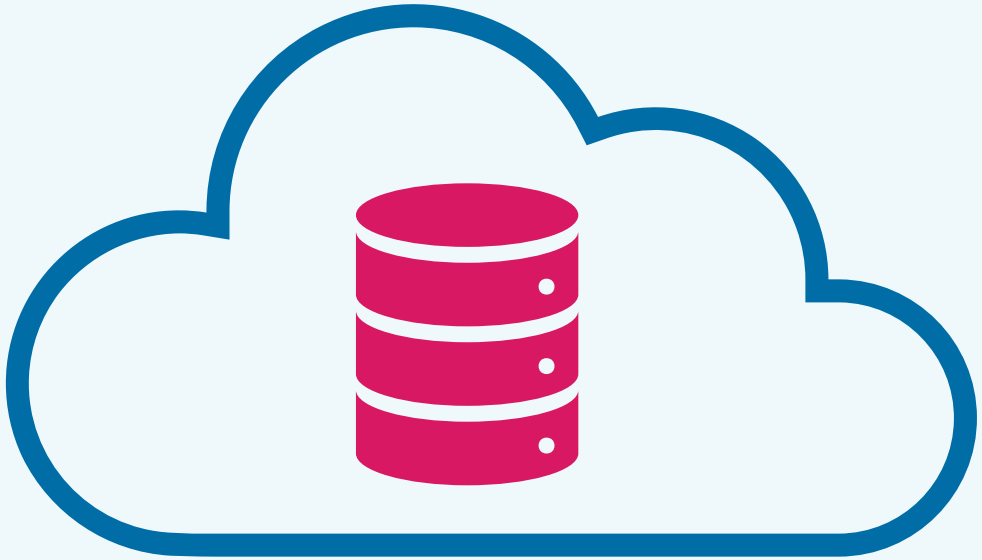
- Very Rare condition → slow recruitment expected
- Large number of sites in multiple countries
- Adaptive Sample size across all domains
- Blinded kit management is required
  - Device domain - Active #1 vs Active #2– unblinded site, blinded central staff
  - Drug domain – Active #A vs Active #B vs Active #C vs Placebo (+ sequential adaptive randomization & response adaptive randomisation)
- New domain in development, active v placebo
- Site have limited storage capacity for bulky stock

Trial Supply Management Mock Example

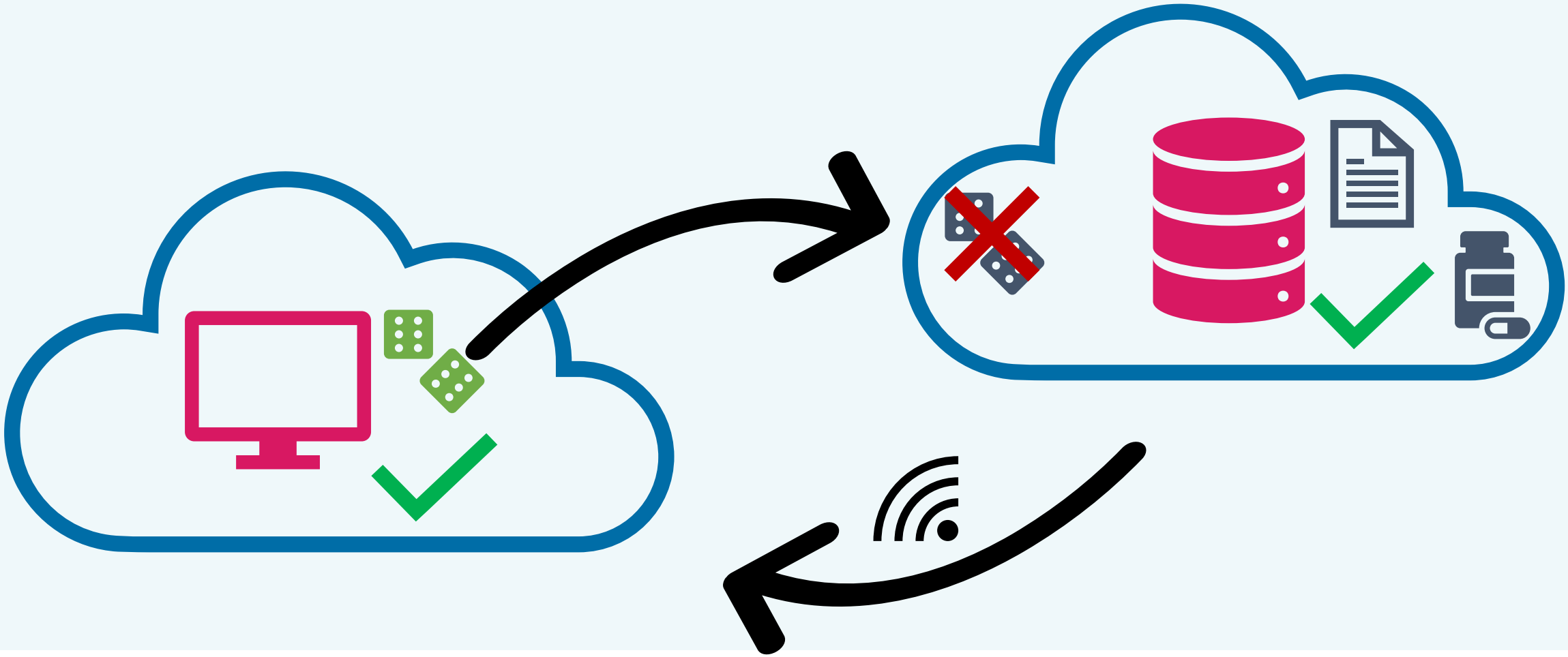
Database capable of all eCRF requirements (i.e dynamic nature, framework & domain specific CRFs)

→ Randomisation module cannot handle complex randomisation

→ Trial Supply Module can handle the kit management, but module designed to only work with the in-built randomisation module



Trial Supply Management Mock Example



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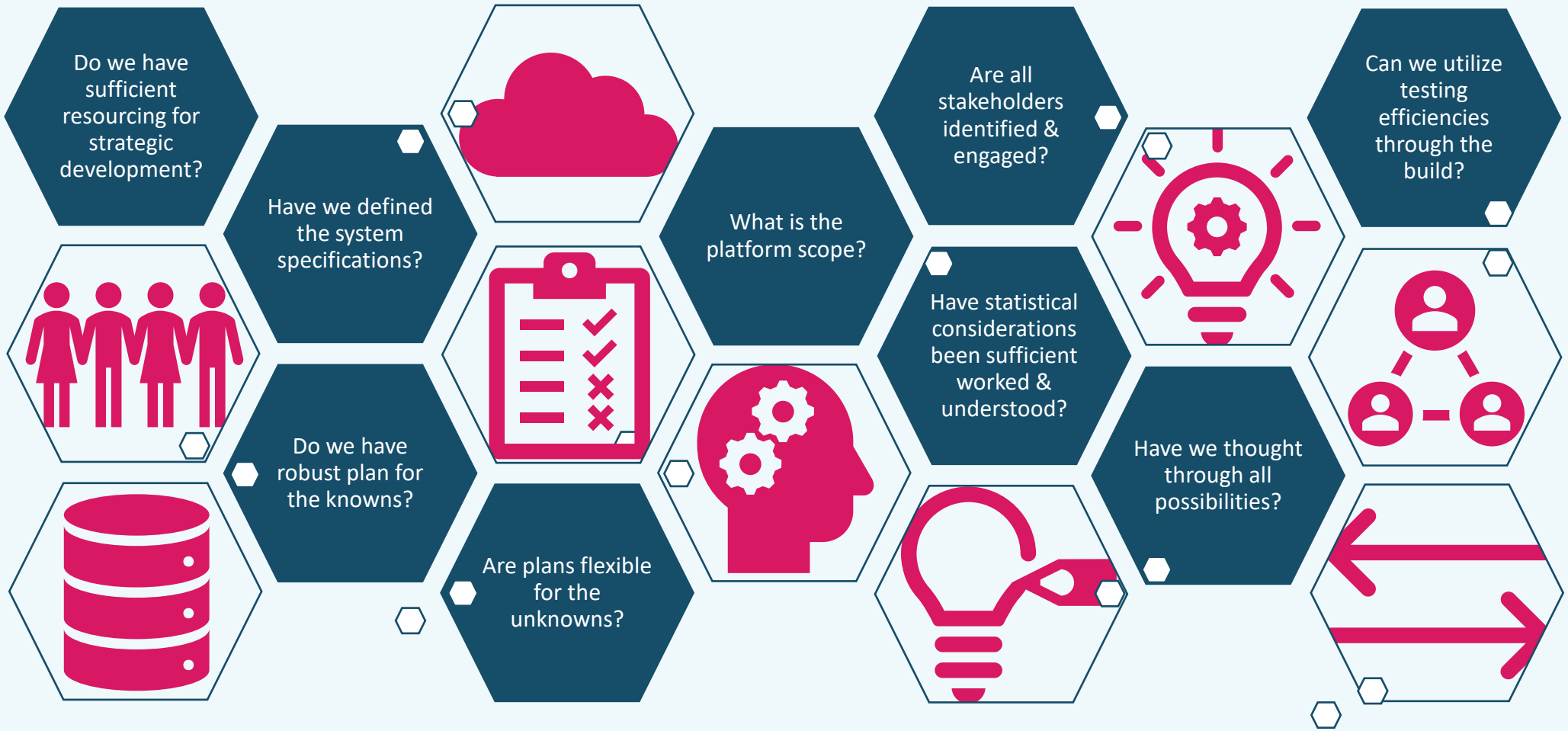
Database Development & Management



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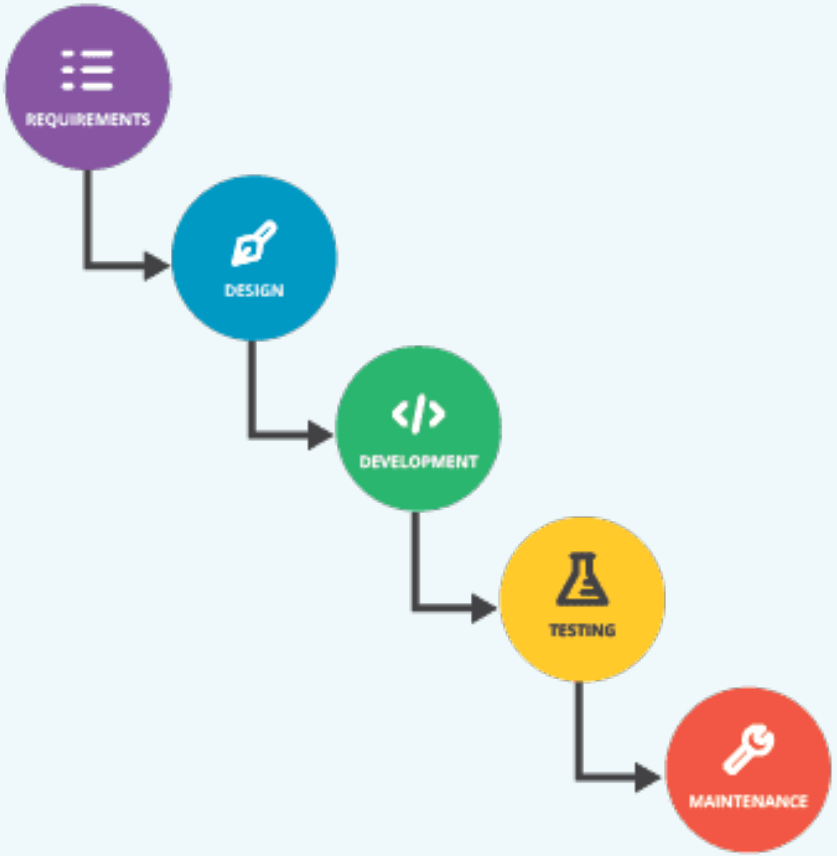
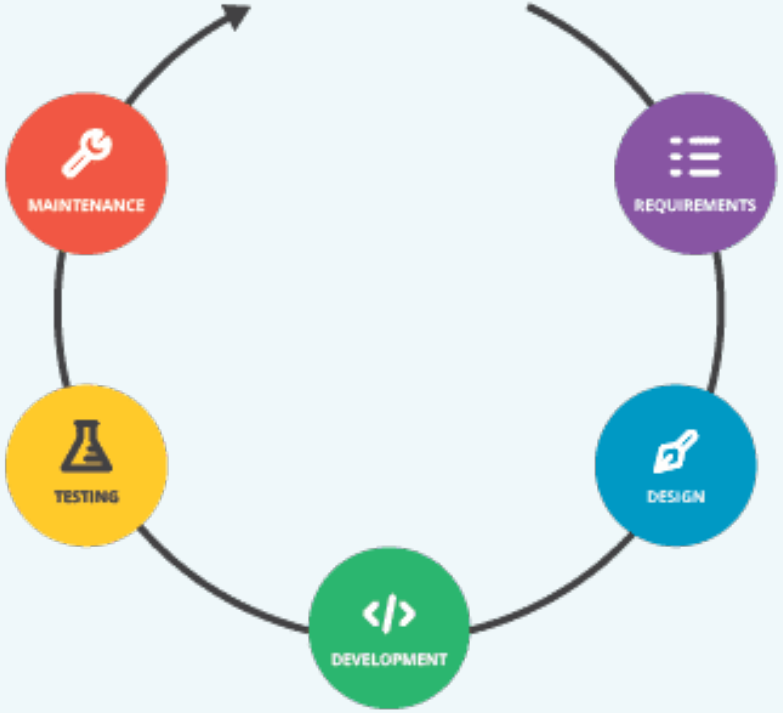
Design Approach



Waterfall Model



Agile Cycle

3. Navigating Ethics, HREC Review, Registration, & Site Set Up

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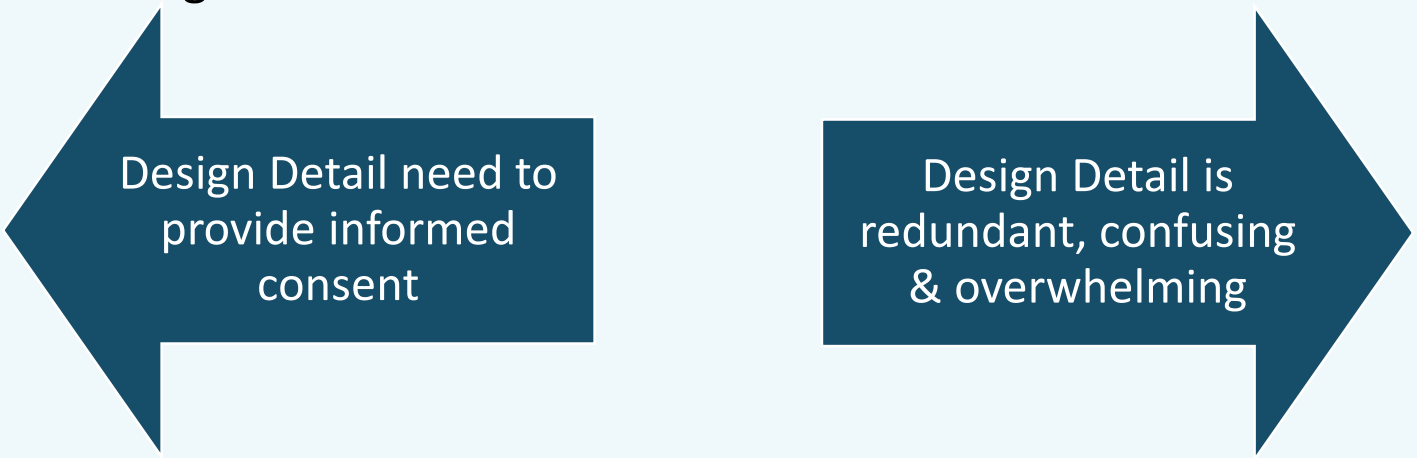
Ethical Challenges

Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative (2019)

While adaptive platform trial designs may promise greater efficiency and scientific sophistication, they raise questions about foundational research ethics principles of informed consent, clinical equipoise, and justice, in addition to practical challenges.

Ethical Challenges: Informed Consent

Debated the amount of design information shared with Pt'



"One attendee described a plan for a two-stage informed consent process for adaptive-platform trials: one consent form at the beginning of the trial that explains the general trial design, and a consent form after the participant is randomized to their specific intervention that explains the benefits and risks, and alternatives, to that particular adaptive intervention."

Ethical Challenges: Clinical Equipoise

Does an adaptive design interrupt traditional understanding of clinical equipoise, such as that within a 2 arm RCT?

"adaptive and adaptive-platform trials may uphold clinical equipoise more effectively than traditional trial designs by addressing uncertainty more frequently through periodic data analyses. If an adaptive review shows that equipoise is sufficiently disturbed, the trial can be terminated or modified accordingly."

Ethical Challenges: Justice

"As long as participants enrolling at the same time bear the same risk, and the informed consent documents are clear about what those risks are, justice is not compromised, even if the risks differ between cohorts."

Submitting to HREC

REGIS
Paving the way

ethics rm

VICTORIA
State Government

RESEARCH
GEMS SA

Australian
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Trials
Alliance

Navigating HREC Review Tips

Be explicit on the design
Explicitly flag the study may add comparisons / interventions / domains in the future in the protocol and on application forms at the initial submission.

e.g. *"The trial is designed to test multiple interventions, using an adaptive platform trial structure that can change over time using pre-specified rules. At the platform level, adaptations include the introduction or removal of comparisons, domains, or both, from the platform. Additional pre-specified adaptations are possible within specific domains."*

& how HREC is engaged throughout adaptation
Explicitly flag how comparisons / interventions / domains will be added / removed in the future in the protocol and on application forms at the initial submission.

e.g. *"Any modifications to existing domains, or the addition of new domains, will be approved by the relevant ethical body prior to implementation"*
e.g. *"….If either of these rules is met, then randomised assignment to the corresponding intervention will be ceased without formal amendment of the DSA, and HREC will be notified of this decision."*

Navigating HREC Review Tips

Open a dialogue w/ HREC

A discussion between the HREC and the CI/trial team may be valuable for the first review to understand future plans. This should involve discussion on the boundaries of what is in scope for the future and what is out of scope, and what changes might require major review for subsequent amendments.

"The investigator or a mediator commissioned by the research team should be prepared to invest significant time into helping IRBs understand unfamiliar complex designs. Researchers may be able to ease the approval process by inviting IRB members to a meeting dedicated specifically to understanding the mechanisms of and justifications for adaptive and/or platform designs."
Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative (2019)

Navigating HREC Review Tips

Seek HREC Expertise

- Sydney Local Health District Ethics Review Committee - Royal Prince Alfred Hospital (EC00113)
  - REMAP-CAP & BEAT COVID-19
- Sydney Local Health District Ethics Review Committee - Concord Repatriation General Hospital (EC00118)
  - BEAT-Calci
- Royal Melbourne Hospital Human Research Ethics Committee (EC00243)
  - ASCOT-ADAPT
- Bellbery & More

Trial Registration

1. **Submit early**

Plan for questions / feedback in the record, registrations of adaptive designs can involve multiple review and query rounds

2. **Make the design clear**

Make sure that the type of study is clearly stated in the title, e.g. a platform study, umbrella trial, etc.

3. **Submit as a single entry (in 1st instance)**

Registration of novel study designs is currently considered on a case-by-case basis

Depending upon the complexity (number of interventions, arms, cohorts, and differing study designs within a record) you may be asked to submit more than one record for registration

4. **Open a dialogue with reviewer**

If you are willing to provide a copy of the protocol this will assist us in determining how best to register

Draft guidance is in development and ANZCTR will seek input from ACTA

Contracting

Site Contracts

Relatively similar to traditional trials approach, though with additional revisions / addendums / amendments through time.

Challenges;

- Unknown Sample Size Targets
- Unknown Research Stop Date
- Flexible payment structures
- Structure for new equipment / intervention supply.

Funder / Collaborator Contracts

- Industry Partnership Funding / Support
- Commercial Body Grant Funding
- Government / Other Grant Funding

Challenges;

- Lengthy
- Definitions of the trial / data set
- Ensuring parameters on data sharing
- Intellectual Property ownership
- Legal understanding of the platform
- New templates

Site Set Up - Initiation / Training

Quality Content

- ✓ Fit for purpose
- ✓ Within the right model
- ✓ Delivered at the right time
- ✓ To the right audience
- ✓ Available for refresh

4. Utilisation & Adaptation of Sponsor / Coordinating Centre Processes & Procedures

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Process & Procedures

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Standard Operating Procedures

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www.clinicaltrialsalliance.org.au

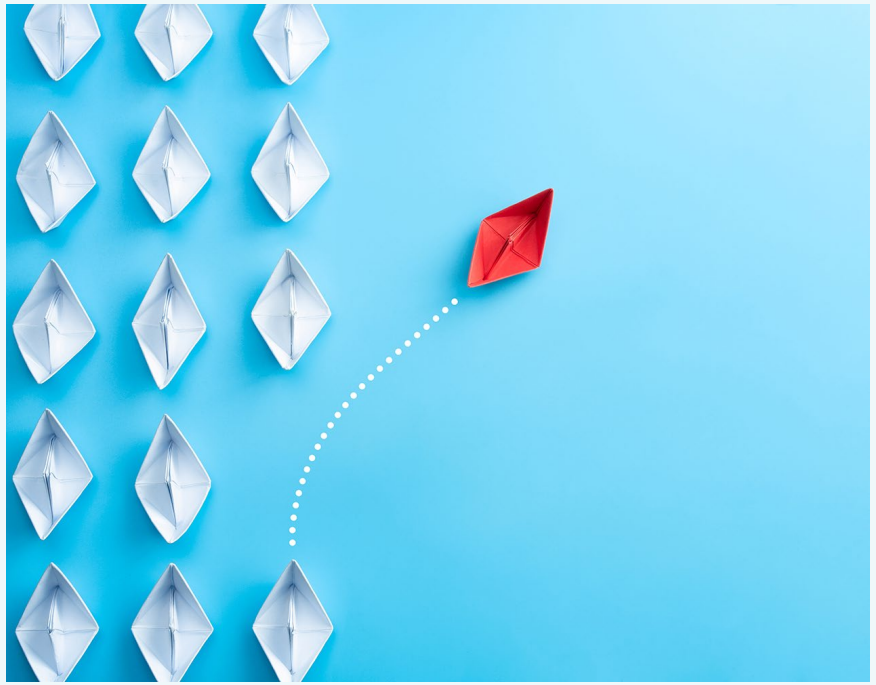
Review Templates, Checklists & Plans

- Protocol Template
- Protocol Review Checklists
- Project Plan
- PIS/CF Template
- PIS/CF Review Checklists
- Quality Management Plan
- Budget Template
- Activation Checklist
- Data Management Plan
- Tracker Templates
- Essential Documents Checklist
- Site Manuals

Development of new SOPs

Potential new processes surrounding adaptive platforms e.g.

- How to evaluate new candidate interventions & document that assessment?
- How to perform domain specific training & activation for new domains of live studies?
- How to perform major database changes to a live study with the addition of new domains, and what review processes are needed?
- How to manage & track which domains are active in which sites?
- How to implement closure of a domain or arm within a domain?
- How to ensure consistent use of nomenclature?
- And more..



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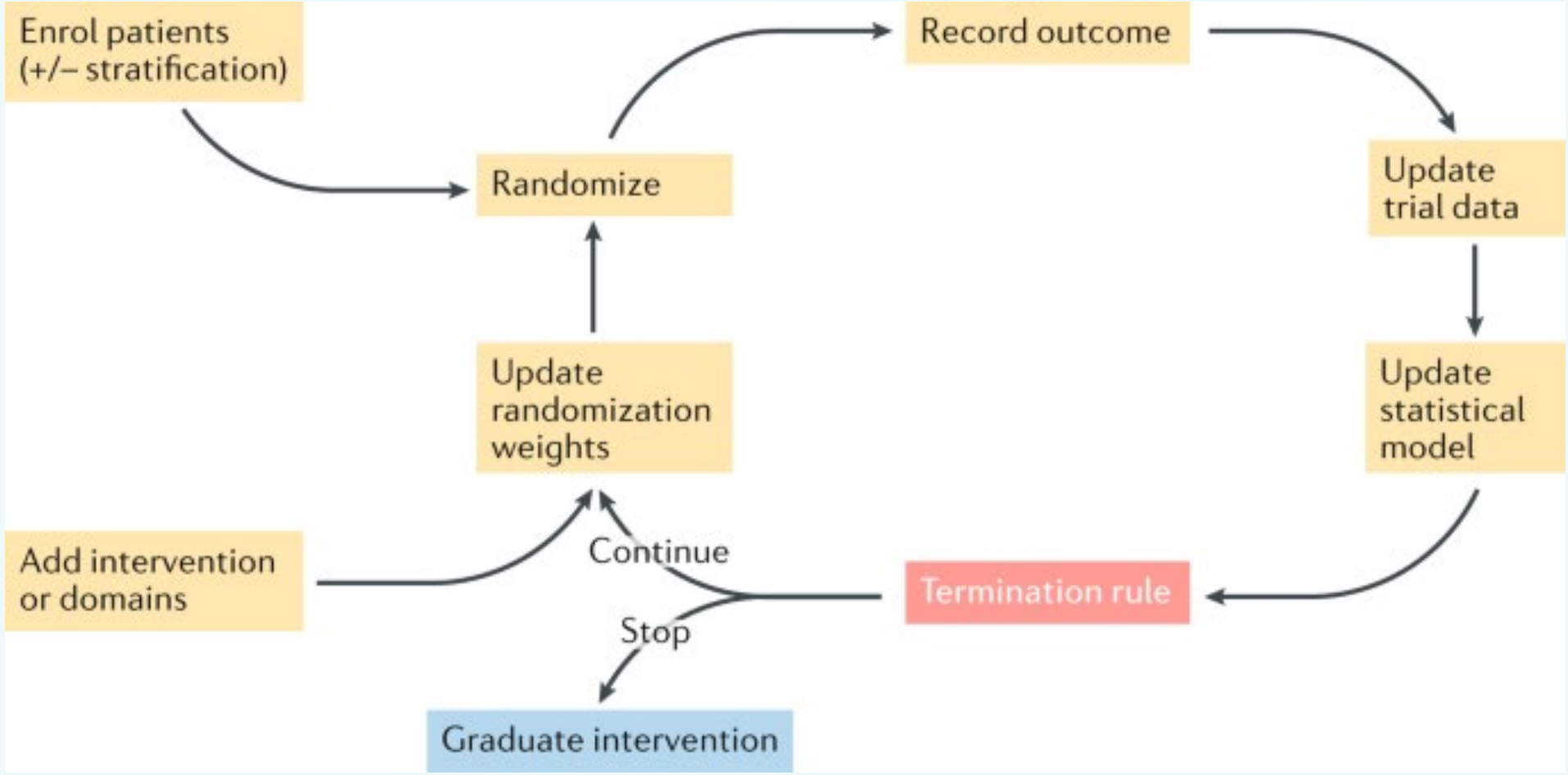

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Acknowledgements

- ACTA Adaptive Platform Trials Operations SIG (Co-chaired w/ Jocelyn Mora)
- ACTA Innovative Trial Designs WG (Co-chaired by Ian Marschner & Katherine Lee)
- NHMRC Clinical Trials Centre's Adaptive Designs Working Group

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