Australian Clinical Trials Alliance

ADAPTIVE PLATFORM TRIALS

OPERATIONAL REFERENCE DOCUMENT

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Engagement ▪ Participation ▪ Involvement

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The Australian Clinical Trials Alliance (ACTA) is grateful for the contribution of insights and time from members of the ACTA Adaptive Platform Trial Operations Special Interest Group:

Aparna Shenoy	University of Queensland
Arlen Wilcox	NHMRC Clinical Trials Centre, University of Sydney
Cameron Green	Monash University
Enmoore Lin	The George Institute for Global Health
Gemma Blunt	NHMRC Clinical Trials Centre, University of Sydney
Grace Currie	University of Sydney
Grace McPhee	University of Melbourne
Jane Parker	Monash University
Jennifer Griffiths	Monash University
Jocelyn Mora	Orygen Youth Health
Kara Brady	University of Queensland
Kelly Fredell	Murdoch Children's Research Institute
Lauren Barina	University of Melbourne
Mitch Messer (consumer)	The Kids Research Institute
Naomi Kmetyk	Hunter Medical Research Institute
Nicole McKay	NHMRC Clinical Trials Centre, University of Sydney
Nuria Zamora Solano	NHMRC Clinical Trials Centre, University of Sydney
Richard Hall	Murdoch Children's Research Institute
Roberta Littleford	University of Queensland Clinical Trials Centre
Susan Goulding	University of Melbourne
Tracey Meares	University of Sydney
Vickie Xie	NHMRC Clinical Trials Centre, University of Sydney

DEFINITIONS AND TERMINOLOGY

The following terms, acronyms, abbreviations, and their associated definitions will be used throughout this framework:

ACTA	Australian Clinical Trials Alliance
ANZCTR	Australian and New Zealand Clinical Trials Registry
APT	Adaptive Platform Trial
CALD	Culturally And Linguistically Diverse
CRG	Consumer Reference Group
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HREA	Human Research Ethics Application
HREC	Human Research Ethics Committee
ICH-GCP	International Conference on Harmonisation Guidelines for Good Clinical Practice
IMP	Investigational Medicinal Product
MPRP	Master Protocol Research Programs
PICF	Participant Information and Consent Form
PSP	Personnel Support Package
RAR	Response Adaptive Randomisation
RCT	Randomised Controlled Trial
RGO	Research Governance Office
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
TMF	Trial Master File

For additional terminology used in this field, readers are directed to **The ACTA Innovative Trial Design Glossary** which offers detailed explanations of innovative trial designs, including APTs.

01 INTRODUCTION

Adaptive designs and Adaptive Platform Trials (APTs) represent advancements in clinical trial methodology, enhancing flexibility and efficiency compared to traditional trial designs.

Traditional clinical trials have often been characterised by rigid structures and fixed protocols, offering limited flexibility to respond to new information as it arises. In contrast, adaptive trial designs permit real-time modifications based on interim data, thus enhancing the trial's efficiency and effectiveness. Among these innovations, APTs represent significant advancement, providing a more dynamic and responsive research framework.

Adaptive designs allow for predetermined adjustments to be made during a trial based on the outcomes observed at various points. These modifications can involve changes in sample size, treatment allocations, or endpoints, enabling researchers to refine their strategies and improve success rates. Essentially, adaptive designs empower investigators to remain responsive to emerging findings, fostering a more agile and efficient pathway to effective treatments.

APTs expand upon the principles of adaptive designs by integrating multiple interventions within a unified trial framework. This innovative approach employs a single master protocol to simultaneously evaluate multiple interventions across one or more disease populations; APTs enable continual optimisation of the trial design based on accruing data. This allows interventions to be dynamically added or dropped from the platform based on pre-specified decision criteria while sharing infrastructure and control participants across intervention-specific domains, ultimately streamlining the trial process and enhancing the potential for successful outcomes.

However, the very features that make APTs so appealing from a scientific and operational perspective also introduce unique challenges in the planning and conduct of these complex trials. The dynamic nature of the trial adaptations requires robust statistical modelling and simulation to optimise decision criteria and operating characteristics, along with thoughtful consideration of trial governance and stakeholder coordination that may differ substantially from conventional trial designs.

The evolving roster of interventions under study, potentially across multiple disease domains, necessitates innovative approaches to informed consent, protocol amendments, and safety monitoring to protect participant rights and ensure the integrity of the trial. Data management systems must be designed with the flexibility to accommodate the addition or removal of data elements while ensuring data quality and integrity. Furthermore, regulatory and ethical submissions must account for the overarching governance of the trial while enabling the seamless integration of new domains and interventions over time.

To support clinical trialists in navigating these complex challenges, the Australian Clinical Trials Alliance (ACTA) commissioned its Adaptive Platform Trials Operations Special Interest Group (APTO SIG) to develop this operational guidance document. The document represents the collaborative effort of a multidisciplinary team, including statistics, trial operations, and database management, who have pooled their collective experience and generated recommendations spanning all stages of the APT lifecycle. Crucially, the development process has incorporated feedback from consumer representatives to ensure that the guidance remains firmly grounded in the perspectives and priorities of the participant communities these trials ultimately aim to serve. The resulting guidance document is organised into chapters addressing key domains in the planning and conduct of APTs:

- General operational considerations such as scope, planning, useful documents and tools
- Establishing an APT governance structure and managing trial leadership, sponsors, and oversight committees
- Resource management, including staffing, budgeting, and vendor/contract management
- Statistical considerations, including stakeholder management, trial design, simulations, and managing adaptations
- Data management guidance on stakeholder involvement, system selection, design considerations, and documentation
- Approaches to consent, patient information and re-consent as the trial evolves
- Navigating the ethics submission and amendment process
- Risk-based monitoring approaches tailored to APTs.

In developing this guidance, the writing group aimed to deliver a comprehensive yet practical roadmap for executing successful APTs to accelerate therapeutic progress for patients and populations in need. We hope this document will serve as a foundation for the continued advancement and uptake of APTs by the clinical trials community while promoting rigorous methodological standards that uphold these innovative designs' scientific and ethical integrity.

We invite readers to engage with these recommendations and to join us in refining best practices through the shared experience of planning and conducting APTs across diverse disease areas and healthcare settings.

Through such collaboration, we can fully realise the transformative potential of APTs to build a more agile, responsive, and impactful clinical trial ecosystem.

ARLEN WILCOX & ROBERTA LITTLEFORD
EDITORS ▪ CO-CHAIRS, ADAPTIVE PLATFORM TRIAL OPERATIONS SPECIAL INTEREST GROUP, ACTA

REGULATORY AND ETHICAL FRAMEWORK

This Operations Manual has been developed in alignment with current Australian standards, laws, and ethical guidelines governing the conduct of clinical trials. It is informed by:

- **The National Statement on Ethical Conduct in Human Research (2023),** issued by the NHMRC, which provides the ethical framework for all human research in Australia. An **updated version** is expected to take effect early 2026 (date to be confirmed).
- **The Australian Code for the Responsible Conduct of Research (2018)**, which outlines principles of research integrity, including honesty, transparency, and accountability in research practice.
- **The ICH Guideline for Good Clinical Practice E6(R2),** currently adopted in Australia as the operational standard.
- **The ICH-GCP E6(R3) guideline**, endorsed in January 2025, introduces a more flexible, risk-based approach to clinical trial design and conduct. Several ICH member countries—including the European Union, Switzerland, United States, Canada, and Japan—have announced implementation timelines or begun operationalising the guideline. In contrast, the Therapeutic Goods Administration (TGA) will undertake public consultation in 2025 before formally adopting E6(R3) in Australia. Given this evolving regulatory landscape, special consideration must be given when designing and conducting APTs that are led from Australia but involve international jurisdictions already operating under ICH-GCP E6(R3).

02 GENERAL OPERATIONAL ASPECTS

Adaptive Platform Trials (APTs) offer greater potential for efficiency and community benefit compared to traditional clinical trials.

However, successfully operationalising this trial design presents unique challenges. In this section, we aim to outline key considerations for those planning an APT, including establishing governance structures, resource and contract management, and other essential considerations for APT project management.

2.1 GENERAL PROJECT MANAGEMENT CONSIDERATIONS

SCOPE

Understanding the overall scope of the APT from the outset is crucial. Project teams should consider the complexity of the protocol and how planned adaptations may impact trial operations. While some flexibility in the project scope may be possible, any changes must not deviate from the trials original intention.

Examples:

In-scope adaptation: Addition of new domains

Out-of-scope adaptation: Changing the condition(s) on which the platform focuses

PLANNING

Planning an APT presents challenges, because project management requirements vary depending on the adaptive elements included and the adaptation conditions met during the trial's lifecycle.

In linear projects, factors such as resourcing, finances, and meeting schedules follow a predictable pattern and are typically only altered in response to specified triggers or issues.

When planning an APT, adopting an agile project management approach can be highly beneficial. This can lead to the up- or down-regulation of communication, data cleaning, system implementation, drug delivery, coordination, documentation, and procedures and financial management activities throughout the trial. This methodology enables dynamic adjustment of key trial activities throughout the study, including:

- Communication frequency and channels
- Data cleaning processes
- System implementation timelines
- Drug delivery logistics
- Cross-functional coordination
- Documentation requirements
- Procedural workflows
- Financial management strategies

This flexible approach allows for the strategic scaling up or down of these activities in response to evolving trial needs, emerging data, and changing circumstances.

Table 1 below compares the main characteristic differences between Non-Adaptive Platform Trials and Adaptive Platform Trials.

USEFUL DOCUMENTS AND TOOLS

The use of templates and checklists is recommended (refer to Section 2, Appendix A: Quick Reference Checklist as an example). Comprehensive manuals and standard operating procedures (SOPs) provide essential guidance for consistent trial execution. Well-structured management plans and budget templates are invaluable tools for effective planning and financial oversight.

Consider implementing a two-tiered approach with an overarching platform project plan and budget, complemented by domain-specific plans and budgets for more detailed operational control. Various project management tools are available to support these processes- these may be accessible through your administering institution or sponsor, or available via subscription or purchased online. When considering online purchases, institution's and sponsor's guidelines related to approved vendors and cybersecurity policies should be followed.

Table 1: Non-Adaptive Platform Trial and Adaptive Platform Trial Comparison Table

FEATURE	NON-APT	APT
Trial Structure	Two or three “arms”	Multiple “domains”. Each domain can have several “arms” or “interventions”
Design Flexibility	Fixed design	Adaptive design allows for modifications based on interim results
Protocol Type	Single protocol	Core (master) protocol, supplemented by multiple sub-domain protocols (or appendices)
Governance Model	Simple governance model	Complex governance model
Control Group	Single control	Common control group shared across domains
Activation of Arms	All arms active simultaneously	Domains can start and stop independently
Randomisation	Fixed randomisation	Re-randomisation to alternate domains if futility conditions are met
Stoppage Conditions	Early stoppage is unusual	Domain stoppage is expected and built into design
Budgeting	Single budget	Budget developed to inform multiple scenarios
Intervention Forecasting	Intervention re-forecasting based on low/high enrolment	Intervention forecasting to inform multiple scenarios allowing for proactive adjustments in response to evolving trial dynamics, enrolment patterns, and interim results
Sample Size	Fixed Sample Size	Variable sample size
Trial Duration	Fixed end date/ recruitment target	Variable

2.2 APT GOVERNANCE

APTs require more sophisticated governance frameworks than traditional clinical trials due to their dynamic nature. While all clinical trials need strong leadership, APTs demand specialised structures to handle their evolving protocols, multiple treatment arms, and continuous data evaluation. Each APT governance framework must be customised to match its specific scientific goals, therapeutic area, and operational scale while meeting requirements from sponsors, funders, and national and international regulators. This tailored approach facilitates efficient decision-making about adding or removing treatment arms, conducting interim analyses, and modifying protocols. Successful APT governance achieves a crucial balance between centralised oversight and distributed expertise, creating systems that can respond to new evidence while maintaining methodological rigor, regulatory compliance, and ethical standards.

Governance structure examples can be found on several APT websites, including: **Staphylococcus aureus Network Adaptive Platform (SNAP)** and **Governance of Adaptive Platform Trials.**

SPONSORSHIP

APTs remain relatively new to many sponsor institutions and can adopt a variety of sponsorship models to support their flexible and evolving nature:

- **Single Sponsor Model:** One organisation sponsors the entire platform. Suitable for smaller or simpler trials.
- **Multi-Sponsor Model:** Multiple sponsors jointly support the platform, sharing governance and financial responsibilities. Common in large-scale, international trials.
- **Domain-Specific Sponsorship:** Each domain has its own sponsor responsible for funding and oversight. This allows targeted investment and easier onboarding of new domains.
- **Public-Private Partnership (PPP):** Combines public institutions and private companies to co-sponsor the platform. Balances public health goals with industry innovation.
- **Hybrid Sponsorship Model:** A core sponsor oversees the platform infrastructure, while individual domains are co-sponsored by different organisations. Offers centralised coordination with domain-level flexibility.

APT sponsorship presents unique contractual and financial challenges due to the dynamic, multi-institutional, and long-term nature of these trials. Unlike traditional clinical trials, APTs require sponsors to commit to flexible funding models that can accommodate the addition of new research questions, treatment arms, or collaborating institutions over time. This adaptive design creates several key challenges:

Contract Structuring: Agreements must comprehensively address intellectual property rights across multiple interventions and stakeholders, while clearly delineating responsibilities for pharmacovigilance, regulatory compliance, and safety reporting throughout the trial's evolution. These contracts require exceptional flexibility while maintaining clear accountability.

Financial Management: Sponsors must establish sustainable cost-sharing mechanisms among multiple funders, plan for uncertain timeframes, and create transparent processes for resource allocation when new domains are added. This requires sophisticated financial planning beyond what's typically needed for conventional trials.

Attribution and Governance: The collaborative nature of APTs necessitates careful navigation of academic credit and recognition systems, ensuring appropriate acknowledgment for all contributing parties while maintaining the cohesive identity of the overall platform.

Institutional Readiness: Many sponsor institutions are still unfamiliar with APTs, creating additional challenges in risk assessment and management. The adaptive nature of these trials may have implications for insurance coverage and typically requires enhanced sponsor support, particularly in legal and contract management areas.

Funding Structure Clarity: Sponsors often have questions about trial duration and funding arrangements, especially when certain domains may be financially managed by other institutions. Early communication about the APT concept, scope, and financial considerations is essential for building institutional confidence.

Geographic Considerations: Depending on the trial's geographical reach, additional local or regional sponsors may be required, further complicating the governance structure.

PROJECT LEADERSHIP

Every APT establishes a tailored leadership structure to support its specific design, scope, and operational needs. At the core of this structure is a central leadership committee responsible for the overall strategic direction of the trial. This committee may also oversee operational aspects, or these responsibilities may be delegated to a separate operational oversight committee, depending on the complexity of the platform.

In addition to central leadership, APTs typically form a range of specialised committees and working groups to lead and coordinate key functional areas. These may include, but are not limited to:

- **Domain Leadership:** Oversees the design, implementation, and adaptation of specific intervention domains.
- **Consent and Ethics:** Ensures ethical conduct, participant protection, and regulatory compliance across all sites and domains.
- **Data Management:** Manages data integrity, security, and flow across the platform.
- **Health Economics:** Evaluates cost-effectiveness and economic impact of interventions.
- **Follow-up and Outcomes:** Coordinates participant follow-up and outcome assessment strategies.

This distributed leadership model supports the adaptive and modular nature of APTs, enabling efficient decision-making, domain-specific expertise, and robust trial governance.

MEMBERSHIP

Membership across all levels of an APT should be informed by a diverse range of factors to ensure robust, inclusive, and effective trial governance. Key considerations include:

- Regional representation to reflect the geographic scope of the trial.
- Relevant expertise in clinical trial conduct, statistical analysis, health economics, and data science.
- Content knowledge of the disease area and interventions under evaluation.
- Lived experience, including individuals with direct experience of the condition being studied.
- Indigenous health perspectives and cultural competence, particularly in trials involving Indigenous populations.

Membership should be viewed as dynamic and expected to evolve over the lifespan of the trial. As new domains are introduced or trial priorities shift, the composition of committees and working groups should be reviewed and adapted to ensure continued relevance, inclusivity, and effectiveness.

2.3 RESOURCE MANAGEMENT

STAFFING

APTs involve a complex coordination of various individuals with specific expertise. For successful trial execution, it is highly recommended that grant applications submitted for APTs include sufficient funding to ensure that the trial is appropriately staffed with personnel with relevant expertise.

Appropriately trained statisticians are vital to the conduct of an APT, given the role of statistical simulations in informing design decisions and the need for ongoing statistical analyses.

APTs typically require more robust project management support than a traditional RCT, particularly during the initial design phase when establishing adaptation parameters and at critical decision points when implementing adaptations. Additionally, the need to ensure that data is appropriately prepared for frequent interim analyses may require additional personnel throughout the trial's lifespan. This is crucial to ensure that data is monitored and cleaned on an ongoing basis.

Early identification of expertise gaps is crucial, enabling proactive planning and implementation of necessary steps to outsource and meet required needs when appropriate.

Investment in comprehensive resourcing significantly enhances the likelihood of successful APT implementation and reduces the risk of operational delays during critical adaptation periods.

BUDGETING

Adaptive Platform Trials (APTs) present unique resource management and budgeting challenges that distinguish them from conventional randomised controlled trials (RCTs). While APTs offer long-term efficiency gains through simultaneous evaluation of multiple research questions, their establishment requires substantial upfront investment in platform infrastructure, with ongoing costs that scale with complexity and duration.

INFRASTRUCTURE INVESTMENT REQUIREMENTS

Two-Phase Infrastructure Development

Preparatory Development Phase: The foundation phase encompasses trial design, comprehensive statistical simulations, protocol development, and extensive stakeholder engagement involving consumers, clinicians, and participating sites. This phase requires significant investment in methodological expertise and community consultation processes.

Ongoing Execution Phase: The operational phase involves continuous adaptations, protocol amendments, regulatory and governance approvals, real-time data flow management, and frequent interim and final analyses for each research question. This perpetual operational state demands sustained resource allocation throughout the trial lifecycle.

Digital Infrastructure Requirements

APTs require sophisticated electronic data capture (EDC) platforms with capabilities far exceeding conventional trial systems. Essential features include:

- **Real-time data entry and validation** with immediate quality checks
- **Dynamic allocation algorithms** supporting complex randomisation strategies
- **Integrated safety reporting systems** with automated adverse event monitoring

Each software update, domain addition, or protocol modification necessitates comprehensive validation testing, cybersecurity assessments, and potential expansion of cloud-hosting capacity. Consequently, licensing and maintenance costs are recurring expenses that scale proportionally with scientific complexity and trial duration.

ADVANCED RANDOMISATION STRATEGIES

APTs frequently employ sophisticated randomisation methodologies including Response Adaptive Randomisation, covariate-adaptive allocation, and Bayesian hierarchical models. These approaches enhance trial efficiency and ethical balance by dynamically adjusting allocation probabilities based on accumulating efficacy and safety data or participant characteristics.

However, these advanced methods introduce substantial statistical and operational complexity requiring:

- **Specialised statistical expertise** for algorithm development and validation
- **Advanced programming capabilities** for real-time implementation
- **Enhanced data processing infrastructure** for continuous adaptation
- **Rigorous validation protocols** to ensure statistical integrity and reproducibility
- **Comprehensive documentation** for regulatory submissions and ethics approvals

Budget allocations must therefore include specialised statistical support, software engineering resources, and enhanced computational infrastructure. Additionally, regulatory and ethics submissions require more detailed documentation and justification, potentially increasing approval-related costs and timelines.

VARIABLE COST MANAGEMENT

Challenges of Adaptive Sample Sizes

Unlike conventional trials with predetermined sample sizes, APTs conduct regular interim analyses against pre-specified statistical stopping rules. This adaptive approach creates budgeting uncertainties in several key areas:

- **Participant recruitment costs** including per-patient site payments with unpredictable total numbers
- **Trial duration expenses** encompassing ongoing staff costs and data management support
- **Resource utilisation** varying with interim analysis outcomes and domain additions/closures

RECOMMENDED PLANNING STRATEGIES

To manage these uncertainties effectively, comprehensive planning should include:

Domain-Specific Feasibility Assessments: Conduct thorough evaluations for each potential domain or intervention prior to commencement, assessing both likely uptake by participating sites and realistic recruitment rates based on target population characteristics and competing studies.

Statistical Simulation Modeling: Perform extensive statistical simulations prior to trial commencement and review periodically to estimate the likely upper limit of participants required to reach specified statistical thresholds under various scenarios.

Operational Futility Provisions: Include protocol specifications for discontinuing domains or interventions due to operational futility, with pre-defined criteria for poor recruitment, safety concerns, or resource constraints.

REGULATORY AND GOVERNANCE BUDGETING

Human Research Ethics Committee (HREC) Considerations

APT budgets must account for elevated HREC-related costs including:

- **Enhanced submission fees** reflecting the complexity of adaptive protocols
- **Multiple amendment costs** as trials evolve and adapt over time
- **Participant information development** requiring clear explanation of adaptive trial concepts
- **Translation and distribution costs** for multi-site and diverse population studies

Research Governance Requirements

Governance-related budget allocations should include:

- **Elevated review fees** for complex adaptive trial protocols
- **Legal consultation costs** for inter-institutional agreement development and negotiation
- **Multi-jurisdictional compliance** particularly for international collaborations
- **Ongoing governance maintenance** as protocols evolve

Clinical Trial Notification (CTN) Management

CTN-related costs encompass:

- **Initial preparation and submission fees** including registry costs
- **Regulatory resubmission expenses** for protocol adaptations and updates
- **Multi-jurisdictional submissions** where applicable
- **Ongoing compliance monitoring** and documentation

Monitoring and Oversight

Comprehensive monitoring budgets must include:

- **Data Monitoring Committee (DMC) fees** for regular safety and efficacy reviews
- **Internal and external monitoring costs** with potentially increased frequency due to the adaptive nature
- **Travel and accommodation expenses** for monitoring personnel
- **Enhanced quality assurance** procedures for complex adaptive protocols

FUNDING STRATEGY AND PLATFORM SUSTAINABILITY

Grant Funding Challenges

Traditional grant funding models present significant challenges for APTs:

- **Pre-specification requirements** limiting ability to fund future, unspecified domains
- **Fixed-term funding conflicting** with ongoing platform needs
- **Domain expansion funding** requiring separate grant applications for each addition

Platform Infrastructure Maintenance

Established APT platforms require ongoing financial support including:

- **Core infrastructure maintenance** regardless of active domain numbers
- **Personnel retention** for specialised roles
- **System updates and security** for digital platforms
- **Regulatory compliance** maintenance

Each new domain addition should contribute proportionally to platform infrastructure costs, ensuring sustainability while leveraging existing investments for cost-effectiveness.

Financial Management Strategies

Single Administering Institution Approach: Centralising funding management through a single sponsor institution reduces complexities in vendor contracting, invoicing, and institutional overhead management, while streamlining financial oversight.

Proportional Cost Allocation: Develop clear frameworks for allocating platform costs across multiple funding sources and domains, ensuring equitable contribution while maintaining operational efficiency.

SPECIALISED PERSONNEL REQUIREMENTS

Critical Skill Sets

APTs require personnel with specialised expertise in:

- **Adaptive trial methodology** and statistical analysis
- **Complex project management** across multiple domains and stakeholders
- **Advanced database design** and real-time data management
- **Regulatory affairs** for complex adaptive protocols
- **Biostatistics** with expertise in interim analyses and stopping rules

Compensation Considerations

Competitive compensation packages are essential for attracting and retaining qualified personnel:

NHMRC Personnel Support Package (PSP) Limitations: While PSP funding provides higher support levels than other grant opportunities, it may not fully cover comprehensive salary packages including employer superannuation contributions, leave entitlements, and other benefits. Negotiations with employing institutions may be necessary to address coverage gaps.

Professional Development Investment: Budget allocations should include training and development costs to ensure personnel maintain current expertise throughout the trial lifecycle, enhancing overall trial effectiveness.

Retention Strategies: Long-term platform sustainability requires competitive compensation strategies that acknowledge the specialised nature of adaptive trial expertise and the ongoing commitment required.

RISK MANAGEMENT AND CONTINGENCY PLANNING

Funding Model Constraints

While contingency funding is theoretically ideal for managing APT uncertainties, practical implementation faces significant challenges:

- **Funding source restrictions** often prohibit contingency allocations
- **Unforeseen expense management** without budget flexibility
- **Trial conduct compromise** when unexpected costs arise

Advocacy for Flexible Funding

The dynamic nature of APTs necessitates advocacy for more flexible funding arrangements that can accommodate:

- **Adaptive budget reallocation** as trials evolve
- **Emergency funding provisions** for critical operational needs
- **Cross-domain resource sharing** to optimise efficiency

COMMUNICATION AND DISSEMINATION

Multi-Stakeholder Engagement

Effective communication and dissemination are critical components of APTs, particularly given their dynamic and multifaceted nature. As APTs often generate multiple outcomes throughout their lifecycle, it is essential to allocate adequate resources for communicating these findings to a wide range of stakeholders, including researchers, healthcare professionals, policymakers, and the public.

2.4 VENDOR AND CONTRACT MANAGEMENT

GENERAL

The increased complexity of APTs compared to standard, linear trial designs can multiply the challenges of navigating relationships and contract management with vendors.

The standard, linear design of an RCT is to have a fixed number of investigational products, a predetermined schedule and treatment plan, and a finite start and end date based on outcomes or other milestones. The purchasing of supplies and logistical management can be managed using basic product forecasting tools, supply agreements and contract management principles. Conversely, APTs encompass multiple interconnected domains, each possessing its unique components and dependencies.

As conditions evolve—such as the potential dropping of a domain during a trial—this can impact the operational requirements and necessitates early consideration to mitigate risks associated with vendor expectations.

Key Considerations for Vendors: To facilitate smooth communication and ensure that vendor agreements are aligned with the uncertainties inherent in APTs, consider incorporating the following elements into vendor contracts:

- **Demand Flexibility Triggers:** Clearly define and communicate conditions that may lead to fluctuations in demand or orders, such as the addition or removal of interventions or the initiation of new domains.
- **Flexible Contract Structures:** Incorporate provisions within contracts that facilitate variation in predefined supply amounts. A recommended approach includes establishing a comprehensive service agreement with the vendor, supplemented by specific work orders or appendices tailored to individual products or domains.
- **Early Engagement with Legal Advisors:** APTs often require specialised legal support tailored to their unique structure. Consult your organisation's legal team early in the process to ascertain their experience with APTs.
- **Educational Resources for Legal Teams:** Offer the legal team specific examples or guidance documentation that illustrate the variable nature of APTs compared to traditional trials. This can foster a better understanding of the associated risks and contractual requirements.

INVESTIGATIONAL MEDICINAL PRODUCTS

Given the unique nature of APTs, standard templates and reporting patterns may not sufficiently address trial requirements.

It is important to clarify that when pharmaceutical companies use the term "Study," they may be referring to the entire clinical trial rather than just the specific investigational medicinal product/s (IMP) they are supplying. This distinction can lead to misunderstandings in data sharing agreements. Therefore, it is crucial to ensure that any agreements explicitly differentiate between the broader study context and the specific safety and reporting requirements related to the particular product(s). Clear definitions will help prevent misinterpretation and ensure that all parties understand the scope of data sharing, focusing on the relevant safety reporting for the supplied product while maintaining compliance with regulatory and pharmacovigilance requirements.

Transparency regarding how participant data may be shared is a legal and ethical obligation, which must be explicitly detailed in the Participant Information and Consent Form (PICF). Please refer to Section 5.

An APT can have multiple domains and within each domain investigational medicinal product (IMP). There may be a single source/vendor for all IMPs in a study, or multiple separate suppliers depending upon availability and the manufacturing status of the product. If using the same supplier for multiple interventions, it may be beneficial to have a single agreement that captures the supply for all products rather than separate agreements for each product individually.

2.5 ESSENTIAL DOCUMENTATION MANAGEMENT

TRIAL MASTER FILE

When designing the Trial Master File (TMF), it is important to keep in mind the unique requirements of an APT. These trials may have a large number of amendments, modulated protocols, appendices, governance entities, and other important components that require documentation. It is crucial to establish a clear documentation plan from the beginning, specifying how each aspect of the study will be documented and where each document can be located.

One way to achieve this is by using a TMF index, which can systematically list each component of the TMF in chronological order, organised into pre-, during, and post-study sections. Additionally, each domain, adaptation, or similar requirement may require its own subfolders. For instance, you may have a 'Protocol Folder', accompanied by an additional folder that stores any amendments, appendices, or adaptations.

For further information: **The Trial Master File (TMF) Reference Model Version v3.3.1** (account required) provides a standardised framework for organising and managing essential documents in clinical trials, ensuring compliance and facilitating efficient trial conduct.

In addition, there are several software platforms available for managing electronic Trial Master Files (eTMF) and Investigator Site Files (ISF), which are essential for the efficient and compliant conduct of clinical trials. These platforms, such as **Flex Databases**, **Florence**, **Trial Docs**, and **Zelta**, offer comprehensive solutions for organising, storing, and managing trial documents in a digital format.

They provide features like real-time document management, automated workflows, and built-in compliance tools to ensure data integrity and regulatory adherence. Additionally, these platforms support remote access and collaboration, making it easier for clinical teams and sponsors to work together seamlessly.

However, it is important to consider the budget when selecting an eTMF and ISF software solution, as costs can vary significantly among platforms. By leveraging advanced eTMF and ISF software solutions, organizations can streamline their trial processes, reduce administrative burdens, and enhance overall trial efficiency.

EXAMPLE
RECOMMENDED NAMING FRAMEWORK

A consistent naming convention enhances document traceability and supports efficient collaboration across teams and sites. Below is a naming framework tailored for an oncology APT (e.g., **ONCOPLAT**):

1. **MASTER PROTOCOL**
   Format: [Platform]_MP_[Version]_[Date]
   Example:
   - ONCOPLAT_MP_v3.2_FINAL_20250526
2. **ARM-SPECIFIC PROTOCOLS**
   Format: [Platform]_ARM[ID]_[Treatment]_[Version]_[Status]_[Date]
   Examples:
   - ONCOPLAT_ARM01_Placebo_v1.3_CLOSED_20250501
   - ONCOPLAT_ARM02_Carboplatin_v2.0_ACTIVE_20250610
   - ONCOPLAT_ARM03_Pembrolizumab_v2.1_ACTIVE_20250615
   - ONCOPLAT_ARM04_Nivolumab_v1.0_PENDING_20250620
3. **AMENDMENT TRACKING**
   Format: [BaseProtocol]_AMD[Number]_[Scope]_[Date]
   Examples:
   - ONCOPLAT_MP_v3.2_AMD05_Statistical_20250526
   - ONCOPLAT_ARM03_v2.1_AMD02_Dosing_20250515

4. **STATISTICAL ANALYSIS PLANS (SAP)**
   Format: [Platform]_SAP_[Domain/Scope]_[Version]_[Date]
   Examples:
   - ONCOPLAT_SAP_CORE_v2.0_20250530
   - ONCOPLAT_SAP_Breast_v1.1_20250605
5. **INFORMED CONSENT FORMS (ICF)**
   Format: [Platform]_ICF_[Domain/Population]_[Version]_[Date]
   Examples:
   - ONCOPLAT_ICF_Breast_v1.0_20250520
   - ONCOPLAT_ICF_Lung_v1.1_20250601
6. **CASE REPORT FORMS (CRF)**
   Format: [Platform]_CRF_[Domain]_[Version]_[Date]
   Examples:
   - ONCOPLAT_CRF_Breast_v1.0_20250525
   - ONCOPLAT_CRF_Lung_v1.0_20250525

2.6 COMMUNICATION AND REGISTRATION

STAKEHOLDER ENGAGEMENT

Regular meetings with stakeholders offer opportunities for engagement and contribution to trial design, development and operationalisation. These meetings can be study-led or fit within existing meeting forums such as workshops and conferences.

WEBSITES

Websites are great opportunities to grow visibility for APTs. Sponsor institutions will be able to provide website options, including the potential for co-branding on independent website builds. There are several excellent examples of APT websites that provide information and resources for a range of audiences, including:

- **BEAT-CF Trial Website**
- **SNAP Trial Website**
- **ASCOT Trial Website**

REGISTRATION

Clinical trials should be prospectively registered. It is a requirement of the National Statement on Ethical Conduct in Human Research (2023, p. 27). The two main registries for clinical trials in Australia and New Zealand are ClinicalTrials.gov (website: **www.clinicaltrials.gov**) and the Australian and New Zealand Clinical Trials Registry (ANZCTR, website: **www.anzctr.org.au**). The former may be preferred for international trials involving participating sites in countries outside of Australia and New Zealand.

Please note that clinical trials with Australian and New Zealand recruitment sites registered on ClinicalTrials.gov are also displayed on the ANZCTR.

The format of these clinical trial registries is currently not well-suited to the registration of multi-domain APTs, and it may be challenging to appropriately describe a platform trial that may include design features such as multiple domains and interventions; potential interactions between domains; eligibility criteria that may be applied at the platform- and domain-level; stratification of participants; non-sequential randomisation; and endpoints that may vary by domain. In addition, registry entries for APTs may need to be updated frequently, to reflect any modifications over time (e.g., addition or removal of a domain, arm or intervention).

ClinicalTrials.gov identifies APTs as Master Protocol Research Programs (MPRPs) and recommends entering separate study records for each subsequently enrolled 'arm' or 'sub-study' of the APT, with one core (master) protocol record that is used to provide reference to each of the domains/arms/interventions within the platform **(Williams et. al., 2022)**. Text should be included in the detailed descriptions of both the core (master) protocol and each additional domain/arm/intervention record to clearly describe their relationship, and the nature of shared placebo group usage between domains/arms/intervention (if relevant).

Despite this, many APTs have opted to register the entire trial (including all domains/arms/interventions) as a single entry. This may be to reduce the workload associated with maintaining multiple entries for APTs with multiple domains and adaptations over time (e.g., REMAP-CAP), avoiding unnecessary duplication of key information across multiple entries, or emphasise that all domains/arms/interventions are being conducted as part of a single trial. Where an APT is registered as a single entry, efforts should be made to clearly explain the nature and design of the trial in a transparent way that is clear to the reader.

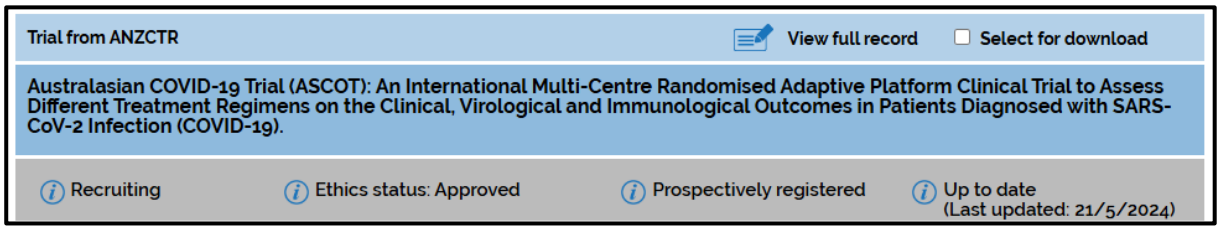
Figure 1: Example: ClinicalTrials.gov record


NOT YET RECRUITING

PLatform for Adaptive Trials In Perinatal UnitS- [Core Protocol]

ClinicalTrials.gov ID NCT06461429
Sponsor University of Melbourne
Information provided by University of Melbourne (Responsible Party)
Last Update Posted 2024-06-17

Figure 2: Example: ANZCTR record


Trial from ANZCTR — View full record — Select for download

Australasian COVID-19 Trial (ASCOT): An International Multi-Centre Randomised Adaptive Platform Clinical Trial to Assess Different Treatment Regimens on the Clinical, Virological and Immunological Outcomes in Patients Diagnosed with SARS-CoV-2 Infection (COVID-19).

Recruiting | Ethics status: Approved | Prospectively registered | Up to date (Last updated: 21/5/2024)

SECTION 2 APPENDIX A: PROJECT MANAGEMENT QUICK REFERENCE CHECKLIST

ITEM	APT VARIATION FROM TRADITIONAL TRIAL	GUIDANCE/COMMENTS
CTN (For international trials, follow local competent authority requirements)	Adding a new arm, dropping an existing arm, or adding a new site, requires an amendment to CTN, or a new CTN	Are there specific considerations for this design?
Communication	Higher volume of trial management bodies and subcommittees	Stakeholders, sites, vendors Committees, Community Communication strategy for each stakeholder group; tools for explaining complex design decisions; regular update mechanisms
Data Monitoring & Analytics	Continuous data analysis required throughout trial	Specialised statistical expertise for interim analyses, stopping rules, and adaptive randomisation; data visualization tools for complex decision-making
Essential Documentation	Higher volume of documentation, protocol amendments and manuals	Drug Information Association and adaptive trials Maintaining clear records of decision-making processes to support transparency during audits and inspections.

ITEM	APT VARIATION FROM TRADITIONAL TRIAL	GUIDANCE/COMMENTS
Financial	Variable needs over the life of the trial and depending on number, success of domains	Is there a central budget? Are there funds with specific conditions (e.g. only to be expended in one jurisdiction)? How are per domain costs managed?
Feasibility and Site Selection	More complex site selection criteria Continuous training needs as protocol evolves	Training program that can be rapidly updated; site support tools for implementing complex protocols; regular site engagement sessions
Governance	Higher volume of Trial Management bodies and subcommittees	Data Safety Monitoring Board, TSCs with demonstrated adaptive design experience Management group Domain & Jurisdiction-specific working groups
Milestone Mapping	More detailed milestone tracking required	Project Management Tools
Monitoring and Reporting	Increased frequency and detail in reporting	Provide regular updates and use automated reporting tools to streamline the process
Patient Recruitment & Retention	Dynamic recruitment needs as arms open/close	Flexible recruitment strategies: communications plan for explaining changes to participants; site support for explaining adaptive design to patients
Project Management	Complex and variable milestones Unknown end dates Variable resourcing, financial, product needs	Create flexible platform infrastructure (plans, budgets, agreements) Use agile principles
Staff Resourcing	Increased need for specialised staff Variable needs over the life of the trial and depending on number, success of domains	Are staff members experienced in adaptive designs? Is further training required? What training is available? How many staff members will be required and for what outcomes? What areas of expertise are needed?
Risk Assessment	Dynamic risk profile throughout trial	Frequent risk assessments; scenario planning for different adaptation outcomes; contingency plans for each major decision point
Technical Infrastructure	Specialised systems/processes for adaptive randomisation and data capture	Validated systems for handling adaptive elements; integration planning between clinical, statistical, and supply chain systems

ITEM	APT VARIATION FROM TRADITIONAL TRIAL	GUIDANCE/COMMENTS
Trial Registration	Multiple domains within the platform	Ensure timely updates to trial registries and provide comprehensive information about each sub-study or arm within the trial. Check the registries of the available resources. Meet with registry administrators to discuss options. Provide additional information or guidance on adaptive trials. Confirm if singular/multiple submissions. Have you listed the trial as adaptive? Consider the nomenclature. Consider the process by which changes are made (opening/closing domains)
Vendors	Variable needs over the life of the trial and depending on number and success of domains	Is there flexibility built into the scoping and agreements? What will the structure of the contract and have you minimised administrative burden if changes arise? Does the vendor understand the degree of variability in supporting an APT? Will you include provisions in the contracts and work plans for increased/decreased supply?

03 CONSUMER INVOLVEMENT AND ENGAGEMENT

3.1 WHAT IS CONSUMER INVOLVEMENT AND ENGAGEMENT?

Consumer involvement is where patients, carers, and other people who use health care services or are impacted by a particular disease or condition, actively work with researchers and research organisations to help shape decisions about health research priorities, ideation, design, dissemination, implementation strategy policy and practice.

Consumer engagement is where information and knowledge about research is shared with consumers and the community so that they are better informed on why, how, where and by whom research is conducted. Engagement is about creating a dialogue with consumers and the community to improve research literacy and increase trial awareness to encourage trial participation as a routine care option. Some examples of consumer engagement include sharing research findings, consumer training on product or protocol development, and research open days.

Due to the complexity of APTs, it is particularly important that consumers have an active role in all stages of the study, from design and planning, in changes/adaptations that occur during the trial, trial reporting and outcomes and implementation. Researchers should work closely with consumers to ensure their voices are heard and that they are included as valued members of the research team.

For more detail and practical advice about involving consumers in clinical trials, please refer to the **ACTA and CT:IQ Consumer Involvement and Engagement Toolkit**.

HOW CAN ADAPTIVE PLATFORM TRIALS INVOLVE CONSUMERS?

The degree of consumer involvement will vary with each study, and each APT can consider whether consumer involvement requires a consumer reference group (CRG) or similar (if required for the scope/design of the trial), or if individual representation is more appropriate. For example, if multiple diverse patient groups are to be recruited for the study, these types of consumers (e.g. adults, children, pregnant people etc.) could form one or several consumer groups. Generally, as APTs are large studies involving disease-specific groups, a CRG will likely be formed. However, involvement can also be informal or include a research buddy – one or two as consumer advisor/s, depending on scope.

It is also important to re-evaluate the level of consumer involvement throughout the life of the project and amend as required.

WHAT IS THE ROLE OF A CONSUMER REPRESENTATIVE IN AN APT

A consumer representative voices consumer perspectives and takes part in the decision-making process on behalf of consumers. Consumer representatives can be patients, former patients, family members, carers and friends of patients. Ideally, they will have a lived experience of the health disease or condition that is being studied in the research project.

In an APT, their role is to advocate for the interests of consumers and present how consumers may feel and think about certain study components, approaches, and issues. Their goal is to ensure the clinical trial staff and steering committee recognise and engage with consumer needs and concerns. Consumer representation can help ensure maximum success for the study team, by identifying participation issues or practical barriers that may impact patients (e.g. no mobile phone reception in outpatient clinics may prevent people from answering a survey). They can provide very practical guidance to the research team in relation to patient-facing material for APTs and study design and implementation, including prioritisation of aims and outcomes that are most relevant to consumers.

WHEN SHOULD WE SEEK CONSUMER INVOLVEMENT?

Due to the complexity of APTs, consumer involvement should occur from inception and consumers should ideally be involved in design and development of protocol and patient-facing documentation. Consumers should be integrated into funding applications, whenever feasible for the consumer(s), ensuring their involvement is both properly resourced and recognised. This collaborative approach not only enriches the research with lived experience but also produces more patient-centred and impactful outcomes.

Figure 2 presents a timeline of an APT, and suggestions of when/how to include consumer representation.

Figure 2: APT Timeline

GRANT: PRE-AWARD	▪ Include funding for consumer representation: Meetings, travel, substance, consumer focus groups etc. ▪ Consumer review of the grant application, consider a consumer representative as co-applicant
GRANT: POST-AWARD	▪ Confirm the trial-specific level of consumer involvement ▪ Confirm consumer representative(s) involvement in relevant committees, and outline any expectations or commitments ▪ Advertise for consumer representation ▪ Conduct consumer focus groups on trial protocols and consent forms
PROTOCOL DEVELOPMENT	▪ Provide ATP-specific training opportunities for the consumer representative(s) ▪ Allow time for consumer representative(s) review of: ▫ The protocol, patient-facing documents/materials ▫ Input into patient reported outcomes
DURING THE TRIAL	▪ Allow time for the consumer representative(s) review of any amended patient documents ▪ Include consumer representative(s) in regular oversight committee meetings ▪ Provide consumer representative(s) APT-specific training opportunities ▪ Trial management group meet with consumer representative(s) regularly to discuss progress and any issues ▪ Review level of consumer representation in the ATP and adjust as required.
END OF TRIAL	▪ Include consumer representation in dissemination plans

3.2 HOW CAN CONSUMER REPRESENTATIVES BE INVOLVED IN APTs?

Levels of involvement or roles include:

- Member/Chair of the Trial Steering Committee (global or national)
- Member/Chair of project-specific CRG (consumer reference/working group)
- 'Research buddies' with informal out of session feedback e.g. reviewing patient-facing material and social media feeds
- Wider community conversations/seminars
- Consumer advocates as investigators on grant applications

3.3 HOW TO FIND CONSUMER REPRESENTATIVES

There are many avenues to recruit consumers for your APT. Below are some suggested contacts to assist with recruitment of a consumer representative in Australia. However, the list is not exhaustive, and each trial should liaise with their sponsor and steering committees to explore all avenues to recruit appropriate representation.

- **Health Issues Centre**
- **Consumers Health Forum of Australia**
- Telethon Kids Institute
- Advertise on your Institute Website and/or LinkedIn page:
  - Example advertisement
  - Twitter, X, etc

[Your Institution Here]

Consumer Representative for the [Trial Name] Trial Steering Committee

We are looking for [#] consumer(s) to join the [Trial Name] Trial Steering Committee, commencing as soon as possible.

[Insert Lay Background of Trial]. The [Trial Name] trial aims to determine [XXX].

We are looking for a consumer representative to join [monthly] meetings to discuss trial progress, review patient-facing documents, and provide input from a consumer perspective.

The applicant will ideally have had a previous diagnosis of a [XXX].The consumer will be reimbursed for their attendance at meetings ($XX/hour) and where meetings occur in person, will be compensated for travel and sustenance provided.

Please send a brief cover letter outlining your interest and CV to the Clinical Trial Manager:

[Name]
[Institute]
[Email]

Further information: [Insert Link]

3.4 BEST PRACTICE FOR CONSUMER INVOLVEMENT AND ENGAGEMENT IN APTs

The points below are recommendations only, and each research team should liaise with the sponsor and steering committees to ensure the needs of the APT are met.

RECOMMENDATION 1: ENGAGE THE WIDER COMMUNITY WITH GENERAL TRAINING ON APTs

APTs are complex and require some degree of education on how they work, their methods and how these methods may impact involvement of participants and consumer representatives over time. The research team should advertise training opportunities, including seminars, presentations and workshops in an environment and format where your target audience may benefit from participating (e.g. outpatient clinics, CALD). This may also be a good opportunity to find consumer representatives that may want to be formally part of the research team. Sending additional educational resources such as the ones below may be helpful to provide to community members so that they understand the differences in complexity and the different phases of APTs.

HELPFUL RESOURCES FOR THE CONSUMER REPRESENTATIVE:

- **What is an adaptive clinical trial? – YouTube**
- **Response Adaptive Randomisation – YouTube**
- **Sample size for APT designs – YouTube**
- **What are the benefits of APT designs? – YouTube**

RECOMMENDATION 2: PROVIDE MORE DETAILED TRAINING TO CONSUMER REPRESENTATIVES TO UNDERSTAND THE METHODS OF APTS AND WHAT YOUR STUDY IS AIMING TO ACHIEVE

An overview should be given to representatives about how platform trials differ from traditional trials and to make clear that there is often a more intensive and longer set up phase, with frequent changes to the protocols throughout the life of the trial. This is to advise them that their involvement may potentially be longer than may be required in traditional trials.

Time should be dedicated to training within the agenda of consumer meetings, with opportunities for members to ask study investigators and study staff questions to clarify understanding. The research team should also consider holding informal catch ups with consumer representatives to allow the consumer(s) opportunity to raise any concerns or queries in a more relaxed environment.

RECOMMENDATION 3: CONSUMER REPRESENTATIVES SHOULD BE TREATED AS VALUED MEMBERS OF THE RESEARCH TEAM

Ideally, consumer representatives should be paid members of the research team. Some institutions do not offer options for volunteer/honorarium payments which are tax free. In these cases, you may need to contact your organisation to discuss potential options for payment including recruiting representatives as casual employees or setting them up as contractors (which usually require an ABN). There are no standards for national payment rates that exist; however ACTA have developed a **Consumer Reimbursement and Remuneration Policy.** Each institution may have their own guidelines and recommendations.

RECOMMENDATION 4: DEVELOP A PROCEDURE TO NOTIFY CONSUMERS, PUBLIC AND PARTICIPANTS OF TRIAL-SPECIFIC CHANGES OR OUTCOMES THAT AFFECT THEM

Each APT should have a clear procedure in place to ensure that consumers, participants, and the public are informed of any trial results or changes to the trial which are relevant to them.

All communication with consumers/public/participants should be presented in an appropriate format i.e. ensure the correct media is used and in a format that is easily accessible to the relevant patient groups. Consumer and patient confidentiality should be maintained at all times.

Research teams may consider using the following media formats to release updates relevant to these patient groups:

- A trial website with a consumer/patient specific section (e.g. **The SNAP trial**)
- Blogs from the research team
- Newsletters to participants or consumers on updates or changes that have direct impact on their involvement in the study.

ADDITIONAL RESOURCES FOR THE APT TEAM

- **NHMRC: Consumer and Community Engagement**
- **Clinical Trials Alliance - Consumers**
- **VCCC Alliance: Consumer Remuneration**
- **ACTA Consumer Involvement & Engagement Toolkit**
- **The Kids Research Institute Australia** - training for both researchers and consumers

04 STATISTICAL OPERATIONS

In the ever-evolving landscape of clinical trials, adaptive methodologies offer promising avenues for efficiency and responsiveness. However, navigating the operations of the more statistically intricate space of adaptive trials demands careful planning and meticulous execution.

This section will provide guidance for managing the statistical operations of adaptive trials, emphasizing the critical role of statistical planning and the necessity for a comprehensive approach within the complex landscape of adaptive designs.

At the outset of an adaptive platform trial, it is important to understand the differences in operational planning and delivery of these trials compared to those with traditional designs. This includes considering statistical stakeholders, timelines, finances, and governance. Biostatisticians play a vital role throughout the lifecycle of all research projects, and it is essential for the APT team to work closely with the designated lead statistician to effectively plan and manage this component of the research.

4.1 STATISTICAL STAKEHOLDER MANAGEMENT

A cross-functional team with appropriate skills and expertise is critical to managing the dynamic nature of adaptive clinical trials.

Within the Australian context, key stakeholders often have diverse perceptions and understandings of adaptive designs. Stakeholders should understand the implications of adaptive designs on the conduct of the trial and have clear role-based expectations for successful trial delivery.

Investing time in communicating the design and outlining simulation results as appropriate to the specific stakeholder improves the overall understanding within your team. Statisticians play a key role as educators, providing opportunity for engagement where questions can be raised, design aspects clarified, and the benefits and risks of the trial design understood.

Due the additional complexity of adaptive trials, additional statistical time and expertise is required compared with traditional designs. Statisticians are heavily invested in developing efficient design.

They work collaboratively with a variety of key stakeholders (e.g. clinicians, operational staff, and investigators) at the planning stage to workshop the platform/adaptive needs of the trial and explore opportunities for efficiency. In addition to defining the research question, statistical input is needed to ensure research questions can be answered. A significant investment of time is made in running simulations and iterating until the trial decision rules are clearly defined.

IDENTIFICATION

Investing time in scoping and identifying the main stakeholders and decision-makers within your institution is a key initial step toward building a cross-functional team. It is important to identify gaps in expertise early and plan these needs, including outsourcing if necessary.

Adaptive designs require a multidisciplinary team of stakeholders from internal and external sources, including:

- Clinical & Academic: Lead/Co Investigators
- Statistics: Adaptive statistical expertise/ Blinded & Unblinded teams
- Data: Data Systems Developer/ Programmer/ Data Manager
- Operations: Project Manager/Other
- Trial steering committee/Data and Safety Monitoring Board
- Regulators: Ethics committee/Regulatory agency

Once a potential list of key stakeholders has been identified, it is important to prioritise their influence, contributions, and plans for engagement.

The benefits of peer-to-peer learning opportunities are well documented and may be an ideal strategic development opportunity for your organisation in upskilling around the niche topic of adaptive trials. This is particularly important for developing statistical expertise.

If there is a knowledge gap within your organisation and the long-term goal is to upskill your organisational statisticians in this area, then there are the following peer-to-peer learning opportunities.

1. Incorporate peer-to-peer learning opportunities as part of overall costings when outsourcing statistical expertise. This ensures that current trial requirements are met and that the investment in your organisation begins with statisticians gaining knowledge from external experts during the build. Share knowledge broadly across the organisation by investing time in future training initiatives, documenting work processes and developing standard operating procedures (SOPs) at both the team and organisation levels. This ensures the knowledge spans several staff and minimises the impact of staff changes.
2. Mid-career statisticians new to the adaptive trial space may seek support and collaboration from relevant experts. Initiatives such as the **Statistics in Trials Interest Group (STInG) – ACTA**, the Data and Safety Monitoring Board (DSMB) mentoring program, and statistician directories offer peer support and collaboration opportunities.

ENGAGEMENT

Establishing a solid foundation for engagement begins with defining your group structure, outlining the roles and responsibilities of your team, and identifying key decision makers. Prioritize key stakeholders appropriately and engage them early in the design and development process. Engaging regulators early in the planning stage is crucial. Trial steering committee/DSMB members also require early engagement as they need to understand the adaptive design to perform their roles.

Cross-functional influencers should be engaged broadly. The data systems developer should engage the statistician early in the development process, as data system decisions influence statistical output and vice versa. Ensuring statistical input and collaboration at all the key touch points of the data system build is critical to ensure the electronic data capture (EDC) design and data collection address the adaptive needs and the study research questions and outcomes.

More detailed discussions and collaboration between the data systems developer, trial statistician, and the wider team are required due to the additional complexity around the randomisation build of adaptive trials. Additional statistical time will be needed to discuss and clarify proof-of-concept builds to ensure adaptive specifications are delivered. This may also involve additional review of test data and outcomes leading up to the initial and subsequent rounds of user acceptance testing.

It is important that the bodies within the governance structure are planned to evolve with platform growth in mind. For example, this may include:

- Having a mix of junior and senior researchers.
- Defining a minimum number/mix of members
- Having a plan for evaluating additional members or replacement of retiring members over time.
- Providing training and development for those with developing, or without specialist, expertise.

Investing time in communicating and training staff ensures that there is a clear expectation of roles and responsibilities throughout the trial's duration.

WORKING

Building meaningful working relationships and collaborations with internal and external stakeholders is crucial for the successful delivery of an adaptive trial. Ongoing, open, and collaborative communication throughout the duration of the trial further strengthens the organisational culture within the adaptive trial landscape.4.2 Financial & Time Management of Statistics

It is important to understand the time and financial investment that will be required to support the statistical design and implementation of the trial. Although each trial differs in size and complexity, Adaptive Platform Trials require significantly more statistical support than traditional trials that use frequentist statistics.

STATISTICIANS

Additional funding outside of trial-specific grants maybe required to support statistics resourcing. The pool of statisticians with expertise in APTs in Australia, and globally, is limited. The cost of external statistical consultants with clinical trial and Bayesian statistical expertise can be high. If there is an effort to build statistical expertise in-house, the cost of training and development over several years of both blinded and unblinded statisticians must be factored in.

TRIAL DESIGN

The design of Adaptive Platform Trials may require the creation of Bayesian statistical models to simulate the trial. These simulations require substantial investment.

The statistical design will inform costs for other aspects of the trial, such as the randomisation system and EDC build. Additional complexity can increase costs and time. Consideration should be given to whether aspects of the trial's design can be modified to reduce costs whilst retaining the benefits of the adaptive design. It may be possible to minimise statistical and resourcing requirements by reducing the number of interim analyses, modifying the pre-specified decision rules, and adjusting the types of adaptations that can be implemented. Factors that can impact resourcing and costs include:

- **Sample size re-estimation:** This allows the sample size to be increased or reduced based on accumulating data at interim analyses. Sample size re-estimation can prevent the trial from being underpowered or overpowered if the assumptions underlying the initial sample size calculations were incorrect. An underpowered trial will not recruit sufficient patients to fully answer the research question, while an overpowered trial will recruit more patients than necessary. If the target sample size is changed at an interim analysis to ensure adequate powering, this will change the trial's duration and costs.
- **Triggering of a pre-specified stopping rule:** The probability that the treatment arm is effective or futile is assessed against pre-specified stopping rules at interim analyses. If a stopping rule is met, a definitive answer about the effect of the treatment arm is available and the treatment arm is stopped early. Early stoppages can reduce the cost of the trial and free up resources.
- **Changes to the EDC system:** A change request or mid-study update may be required to the EDC system to accommodate trial adaptations, such as changes to randomisation ratios or early termination of a treatment arm. Any changes to the EDC system will incur costs and require resourcing.
- **Changes to recruitment timeframe:** The time needed to recruit remaining participants may be affected by trial adaptations. For example, if recruitment to a treatment arm is stopped early based on pre-specified decision rules, the research question could be answered with fewer patients and thus a shorter recruitment timeframe.

It is also useful to consider whether the trial simulations and design rules will apply to all domains or if some domains will require modifications to the existing statistical design. Modifications may require additional trial simulations and costs.

MANAGING UNCERTAINTIES & COMPLEXITIES

Given the uncertainties around what trial adaptations may occur and what statistical design is required for new domains, it can be difficult to predict the cost and resource impacts. Increased resourcing maybe required to manage this uncertainty. Budgets should be stress-tested for worse case scenarios to ensure adequate funding.

Adaptive designs are highly variable in cost which can present difficulties when preparing funding applications. It is important to clearly communicate costs to the funder and explain how the trial's design influences the resources required.

Considerable planning is required to manage the initial extended timelines and increased costs associated with the complexities inherent in Adaptive Platform Trials. How resource planning is managed will be dependent on the organisation's size, workforce experience and number of staff.

4.3 MANAGING STATISTICAL OPERATIONS DURING STATISTICAL DESIGN & SIMULATIONS

Without diving into the statistical intricacies of research, it is important that operational leaders of adaptive clinical trials have a basic understanding of the adaptive techniques planned to be implemented and the downstream effects they have in operational planning and delivery.

STATISTICAL PLANNING

During initial statistical design planning, it is paramount that the statistical team is given time to workshop the platform and potential for adaptations with relevant investigators. As with traditional designs this involves understanding the scientific and design challenges, and defining research questions, yet in this case, we should also evaluate the opportunity to cost for utilising various adaptive techniques. Clinical leads will need to provide information that underpins the merit for the simulations work.

This might include clinical parameters like estimating treatment effects, via providing a range of best expected and worst cases of the primary outcome for the control and interventional arms of the research, and whether there is any potential for compounding treatment effects of any two interventions across different domains. Additionally, the group may discuss and document strategies for managing unexpected changes efficiently, ensuring adaptability without compromising trial integrity. Operational leaders should support and plan with the statistical team, to ensure appropriate discussions occur and relevant information is obtained and documented.

TRIAL SIMULATIONS

Working towards a finalised trial protocol for an APT requires considerably more complex statistical work when compared to a traditional design. Statistical planning lies at the heart of adaptive trial design, with statistical simulations used to generate a series of predefined decision rules for the trial protocol. While these simulations demand significant upfront investment and time, they pave the way for informed decision-making. Early and extensive planning is essential, encompassing comprehensive testing of design rules to determine appropriateness and understand the potential gains and losses of adaptations. Decisions regarding adaptation must undergo rigorous risk-benefit assessment across multiple scenarios, ensuring that scientific and ethical considerations outweigh biases and inefficiencies. This statistical planning and simulations work could take around 6 months depending on the complexity of the project, expertise of those involved and influence of other surrounding standard processes.

To perform simulations work, statisticians need access to data, including treatment effect estimates and recruitment rates. In some cases, patient-level data may be required to build these models. These statistical simulations are critical as they inform trial adaptation and decision rules. The statistical design process is iterative as multiple rounds of statistical simulations are presented and adjusted. At the end of the design process, the statistician must provide a statistical design report that documents the statistical properties of the trial and the simulations. This report is typically submitted with the protocol for ethics and regulatory approvals. Governance bodies may have additional queries about the statistical design that require clarification or amendments and re-submission, which can extend timelines for approval.

TRIAL RESOURCES

Wason et al., 2022 (p2-12) outlines a practical five-step process for estimating resources required for adaptive trials, providing a valuable framework for planning and budgeting. Tasks required for adaptive design significantly impact time and cost, necessitating a thorough understanding of the workload involved. Appropriately costing an adaptive trial entails outlining key tasks from design to analysis and reporting, considering the increased resource utilization, particularly in terms of statistician time and specialist expertise.

DOMAIN SPECIFIC NEEDS PLANNING

Standard trial documentation or oversight structures may become modulated in an APT. For example:

1. A robust statistical analysis plan (SAP) is indispensable for adaptive trials, encompassing both interim and final analyses to optimize efficiency and draw conclusive insights. Domain specific SAPs may be developed to describe the differential adaption rules or statistical properties for each domain.
2. Central to the oversight of adaptive trials is the Data and Safety Monitoring Board (DSMB), responsible for monitoring the trial's progress and ensuring participant safety. While the DSMB functions for the entire trial duration, the nature of DSMB meetings may vary based on the domain-specific considerations.

Careful consideration should be given to deciding the need for catering for domain specific differences in the trial delivery.

RANDOMISATION SET UP

Standard randomisation systems may need customized coding to accommodate the complexities of adaptive designs. Careful planning should be performed with the relevant personnel to ensure the systems capabilities meet the trial's needs.

4.4 MANAGING STATISTICAL OPERATIONS DURING DELIVERY & ANALYSIS

In summary, managing statistical operations in adaptive trials requires a multidimensional approach, encompassing meticulous planning, robust resource estimation, and tailored statistical methodologies. By adhering to these guiding principles, researchers can navigate the complexities of adaptive trial design and simulation, ushering in a new era of efficiency and responsiveness in clinical research.

05 PARTICIPANT INFORMATION AND CONSENT

As Adaptive Platform Trials (APT) are constantly evolving, it is important that the associated information and consent documents can change accordingly.

This section provides initial guidance for developing consent forms and keeping participants informed of any changes to the trial that could affect them. It is important that each trial liaises with the lead HREC to ensure that HREC or jurisdictional-specific requirements are met.

This section will outline two main approaches to obtaining consent for APTs:

One-Stage Consent Process – consent is obtained for the trial and associated domains at the one timepoint using a single consent form. This may be prior to, or after, eligibility assessment of one or more domains.

Multi-stage Consent Process – consent to the trial is obtained first, with consent to each domain obtained as the participant becomes eligible using separate consent forms.

5.1 GENERAL SUGGESTIONS

When designing Participant and Consent Forms (PICFs) and Withdrawal Forms for APTs, it is important to consider how to best communicate the multiple aspects and complexity of this trial design to participants, and how to make the adaptability of the design easy for sites to modify, based on the particular aspects they will be participating in.

MODULAR APPROACH

Many APTs allow for modifications to domains/treatments at a regional an/or site level. Therefore, it is important to keep the PICFs as modular as possible. Placeholder text is already widely used in PICF design to denote aspects of the PICF that need to be modified on a site level to ensure that the PICF complies with local requirements and contains important local contacts.

In the case of APTs, the use of placeholder text can be extended to include aspects of the trial that can be modified on a site level. This will allow the PICF to be adapted specifically for each site, resulting in improved readability. Any aspect of the APT that could vary from site to site, such as domains, treatment arms, sub studies, etc., should include placeholder text.

Examples of placeholder text can include:

- *[Site to delete treatment domains they are not participating in. For each domain include only information relevant to interventions that your site has selected.]*
- *[Site to delete information about this domain, if not participating]*
- *[Site to delete information relating to this intervention/arm, if not participating]*

The site will then modify their PICFs to only include the domains, treatment arms and sub studies, that they are specifically participating in. This does not allow for the PICF to be modified on a patient level (i.e. removing information from the PICF for participants that are not eligible for a certain aspect of the trial). This type of patient-level modification may be possible using an e-consent model.

SIMPLIFIED DESIGN

A simplified design should be considered, due to the complexity of Adaptive Platform Trials (Symons et al, 2022). This includes providing information that a 'reasonable person would want to have in order to make an informed decision about whether to participate'. In this layered approach to consent, each participant can view as much information as they feel they need to make an informed choice about participating in the trial. The consent process makes use of a range of different types of information, including written material, videos, and access to more detailed information to assist participants in understanding the complexity of an adaptive platform clinical trial.

This gives the participant the control to decide how much information they want to read to make their decision. A layered approach can reduce the number of pages of information the participant will be provided with initially and allow them to seek this information if they wish to, in order to make their decision.

Symons et al (2022) provide examples of layers to use:

1. SIMPLIFIED PICF/LAYERED CONSENT

These forms contain only the essential trial information; they have been shortened to make the information more digestible for the reader.

They can contain links to the additional layers if the patient wants to further understand aspects of the trial prior to consenting to take part in the study.

- **CTIQ Project Resource**
- **INFORMED Project**

2. WEBSITE INFORMATION

A clinical trial website can be created to house additional information the participant might want to know such as more detailed information about the interventions and side effects, data linkage, storage and shipment of their information, and links to the additional layers listed below.

3. INFORMATIONAL VIDEOS

Informational videos can be used as another tool to provide additional information to participants. These can be videos that already exist, that you can link to, or if created, these videos could be uploaded to the clinical trial website for easy access. Links to these videos can also be added into the PICF.

Examples of Useful Video Resources for APTs:

- **What is an adaptive clinical trial?**
- **Response Adaptive Randomisation**
- **Benefits of APT Designs**

4. EXTERNAL LINKS

Further detailed information can be provided to those who are interested in additional scientific or a more comprehensive explanation about the study. These additional detailed documents include links to external information, such as drug information sheets or investigator's brochures, other related studies, previous publications, overarching governance, regulatory information and approvals, etc.

eCONSENT

Electronic informed consent may be used to either supplement or replace paper-based informed consent processes to best address the participant's needs throughout the course of the study.

Participants should have the option to use paper-based or electronic informed consent methods completely or partially throughout the informed consent process.

As the e-consent process is more adaptable, this method provides an opportunity to format PICFs on a patient level, to allow the patient to navigate through information that is only applicable to their specific participation in the trial. This allows for the PICFs to be tailored one-step further than the modularising the form as parts that are available on the site level but are irrelevant to the particular participant can be omitted entirely.

The participant level modular architecture will require to be clearly outlined in the HREC application, allowing for the PICF template to be approved.

Suggestions for good platforms and resources:

- **Australian Genomics – Dynamic Consent and Control**
- **CTIQ – Implementing Consent**
- **Consent IC Australia**

It should be noted that dynamic consent is a technology-led approach that allows for ongoing communication and consent management, ensuring participants remain informed and engaged throughout the trial. This approach can provide practical, sustainable, and future-proof solutions to challenges related to participant recruitment, retention, and consent management. It is currently being utilised within Genomics England and Australia Genomics and European Union 202 Projects and is being explored at the National University (ANU) in collaboration with other institutions. These platforms will evolve, and their utilising will be implemented within the evolvable APT ecosystem.

5.2 ONE-STAGE CONSENT PROCESS

Consent is obtained for all domains at the one timepoint using a single consent form. This may be prior to, or after, eligibility assessment of one or more domains.

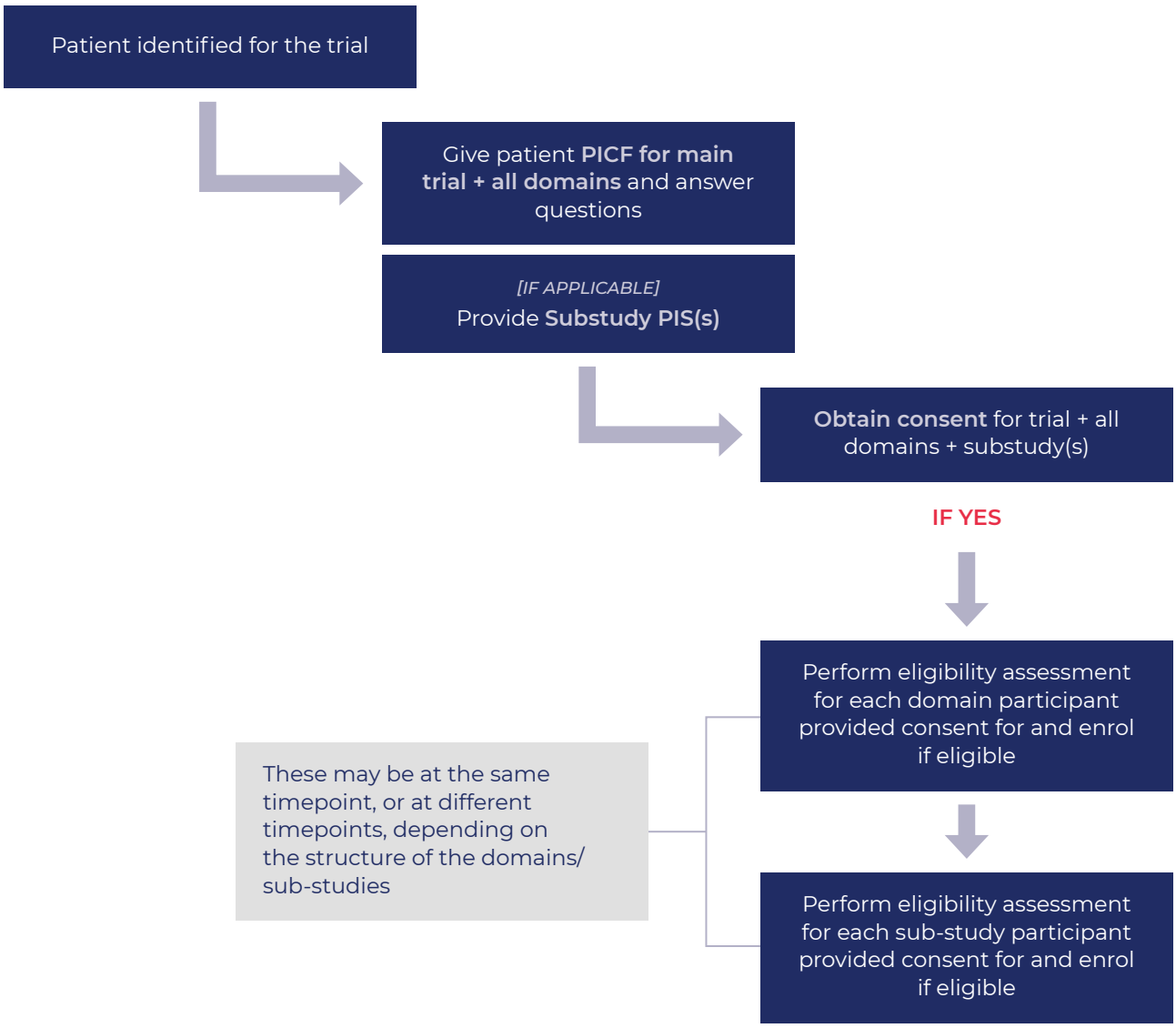
The one-stage consent method allows all information for the participant to be contained in the one consent form. It can simplify and streamline consent discussions.

The one-stage consent process can occur prior to, or after, the assessment of domain eligibility. As the PICF is modified at a site level, site investigators need to ensure they are clear about which domains the participant is eligible for when discussing domain consent.

- If consent is obtained once eligibility is determined, only relevant domains are discussed with the participant allowing them to process relevant information. This method is recommended where it is likely not all domains are relevant to each participant.

- If consent is obtained for all domains at an upfront consent process, the study team can gather information about whether a patient would have consented if they were eligible, this allows study teams to determine acceptability of a domain at a patient level. This method may be more useful for domains with broad eligibility criteria, where it is expected that most participants will be eligible for all the domains.

Figure 3: One-Stage Consent Flowchart



PARTICIPANT INFORMATION DESIGN

The Participant Information design for one-stage consent requires that all domains be explained in the one document; therefore, a simplified and layered approach to consent may be required to ensure that the information can be digested by the reader, particularly if there are multiple domains they will need to be consented to.

It is recommended that the PICF contain the following sections: Overview of the trial

- Brief explanation of the structure trial, explaining that the domains are independent aspects of the trial
- Separate section explaining each domain and the interventions involved.

CONSENT FORM DESIGN

As the participant will be consenting to multiple aspects of the trial at one time, it is recommended that the consent form contain a matrix to document their consent to each different aspect of the trial.

If it is preferred to assess eligibility for each domain prior to undertaking the consent process, please ensure that a N/A option is included so that it can be clear that a domain was never discussed with a patient, rather than documenting if the patient did or did not consent to the trial.

An example has been provided below:

I AGREE TO PARTICIPATE IN:	
All study domains available at this site	☐ Yes ☐ No
OR	
I agree to participate in Domain 1	☐ Yes ☐ No ☐ N/A*
I agree to participate in Domain 2	☐ Yes ☐ No ☐ N/A*
I agree to participate in Domain etc.	☐ Yes ☐ No ☐ N/A*

**Only include if the participant will be advised of domains, they are NOT eligible for, and as such, do not need to provide consent to.*

INCORPORATING SUB STUDIES

It may be preferable to consent to any sub studies during the one-stage consent process. If so, a separate section of the main consent form should include details for documenting consent to each of the sub studies available.

As only a particular subset of patients is likely to be eligible for a sub-study, it is advised that a separate PICF is created for each sub-study and provided to the participant as a separate document, or as an appendix to the main PICF. Sub studies are often approved after the main trial, so it may be easier to create this new document when the sub-study has been approved and so as not to need an amendment to the PICFs for each new trial sub-study.

To streamline the consent process, additional wording on the main consent form can be included as:

"I have read the relevant sub-study(s) Participant Information Sheet(s), or someone has read it to me in a language that I understand, and I agree to participate in the following sub-study(s):"

	NAME OF SUB-STUDY	PIS VERSION #	PIS DATE	PATIENT TO COMPLETE
N/A ☐ (Patient not eligible)	{short name}			☐ Yes ☐ No

[Repeat next rows for each of the sub studies the site is participating in]

OBTAINING AND DOCUMENTING CONSENT

Once they have been assessed as eligible for the trial, the participant can be approached for consent to the trial and all its domains in one streamlined consent process.

This means that consent may be obtained:

- Prior to knowing a patient's eligibility for a domain
- Once domain eligibility has been determined
- With the knowledge that the participant may be ineligible for a domain

During the eligibility screening for each domain, the participant will be excluded from participating if they meet any of the exclusion criteria or do not meet any of the inclusion criteria.

If the patient agrees to participate, the investigator should follow the regular informed consent process for clinical trials, with the additional points in mind:

1. Confirm which domains within the trial the patient agrees to participate in
2. Obtain sub-study consent (if applicable and available)

CONSENTING TO SUB STUDIES

To streamline the process for the participant, consent to the relevant sub-study(s) can be undertaken at the same time as the main trial consent process, if possible. If the participant eligibility for a sub-study is not known at the time of trial consent, this process can be undertaken at a time suitable for the participant and their consent documented on the same master consent form.

ONGOING ASSENT TO PARTICIPATE

At the time of initial consent, the participant provides their consent to participate in one or multiple domains within the trial. However, depending on domain eligibility, the participant may not be aware of their randomised treatment allocation within a domain until a later time point, if the domains are temporally staggered.

As such, it is vital that the investigator confirms the patient provides ongoing assent to participate in all domains to which they initially consented and are still happy to be randomised within that domain. This discussion does not require a consent form but should be documented in the patient's medical records or study notes.

The investigator should:

- Make the participant aware that the eligibility assessment for a domain is approaching
- Remind the participant of the treatments they may be randomised to within the domain
- Confirm that the participant is still happy to continue
- Ask the participant if they would like to see any of the information resources available about the domain, prior to continuing.

WITHDRAWAL FORM DESIGN

Withdrawal forms can be structured in a similar way to the consent forms, with all aspects that the participant can withdraw from contained in one form. This reduces the number of documents for sites and participants and streamlines the discussion to ensure each aspect of the adaptive platform trial is discussed with the participant when they withdraw.

As an adaptive platform trial, it can be important to segregate withdrawing from the treatment/intervention from withdrawing from data collection/other aspects of the trial. A participant may no longer wish to receive treatment in a particular domain without necessarily wishing to withdraw from the other aspects.

OBTAINING AND DOCUMENTING WITHDRAWALS

Due to the streamlined consent process, all withdrawals can be documented using the one withdrawal form. If a participant requests to withdraw from the trial, the aspects of the trial they withdraw from and agree to continue with should be documented in the single withdrawal form.

If the participant then later chooses to withdraw from additional aspects, the original withdrawal form should be updated to reflect this (assuming the withdrawal form accommodates signing and dating of withdrawal from each aspect).

An example has been included below of some aspects to keep separate in the withdrawal:

I WISH TO WITHDRAW FROM PARTICIPATION IN THE FOLLOWING ASPECTS OF THE TRIAL:			
Domain 1 Treatment	☐ Withdraw	☐ Continue	☐ N/A*
Domain 2 Treatment	☐ Withdraw	☐ Continue	☐ N/A*
Domain etc. Treatment	☐ Withdraw	☐ Continue	☐ N/A*
Follow up contact	☐ Withdraw	☐ Continue	
Ongoing data collection	☐ Withdraw	☐ Continue	
Storage of samples for future research	☐ Withdraw	☐ Continue	☐ N/A*
Data Linkage	☐ Withdraw	☐ Continue	☐ N/A*
I agree to participate in Domain etc.	☐ Withdraw	☐ Continue	☐ N/A*

**This should be selected if the participant did not participate in a particular domain*

5.3 MULTI-STAGE CONSENT PROCESS

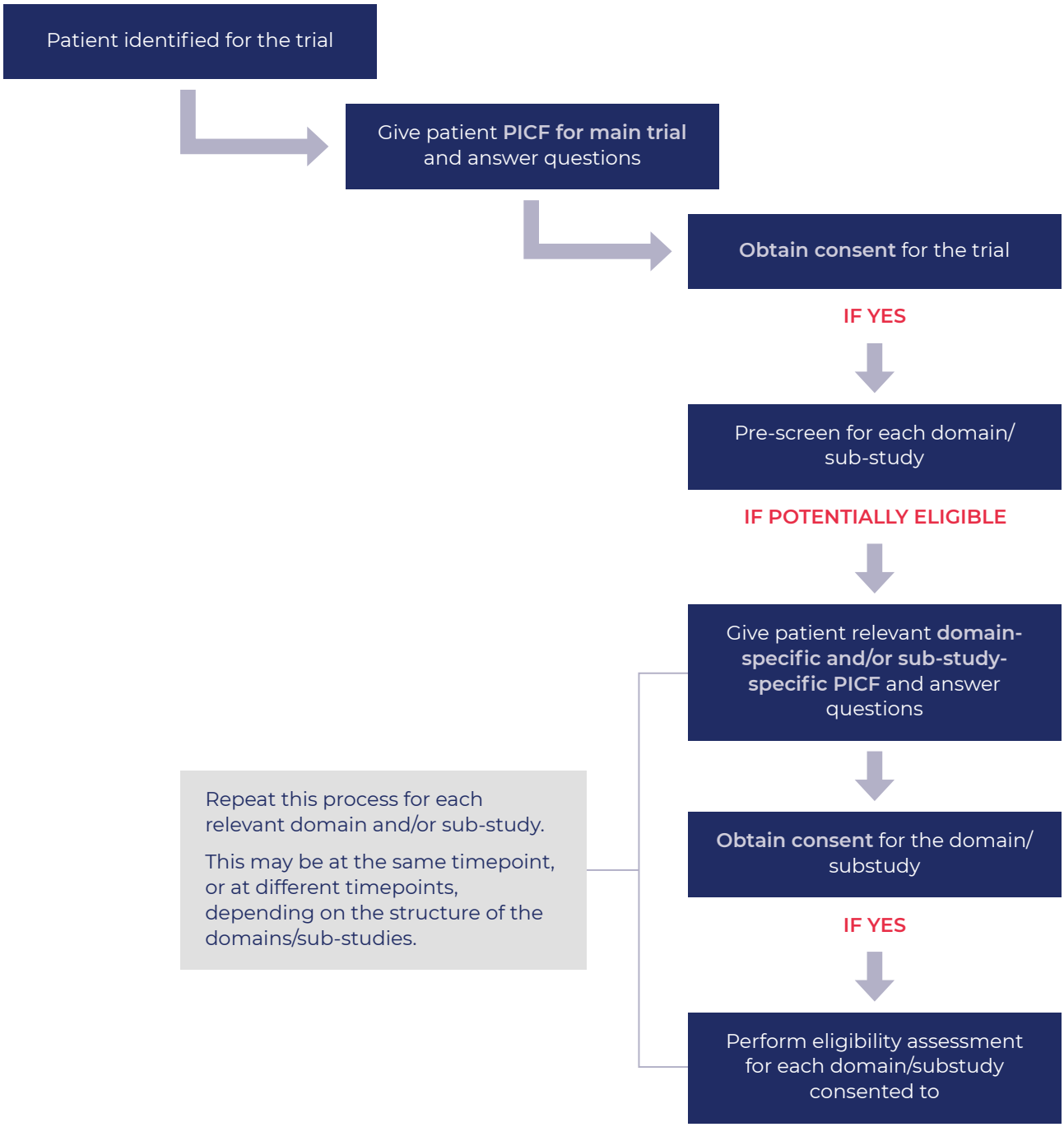
Consent to the trial is obtained first; consent to each domain is only obtained once the participant is determined to be eligible for that domain.

The multi-stage consent method requires that the participant is provided with multiple PICFs – one describing each aspect of the adaptive platform trial. At a minimum, this will include a trial-level PICF and a separate domain-level PICF. The participant must then provide their informed consent to each individual aspect of the trial.

The multi-stage consent process should occur after the assessment of domain eligibility, to reduce the burden of consent on the participant. As a separate signature and consent discussion is required for each domain, it is important to consider the impact on the participant when using this approach.

As each aspect of the trial is contained within its own PICF, site investigators can simply omit the use of a PICF if it is not relevant to a participant and/or if the site is not participating in that aspect of the trial.

Figure 4: Multi-Stage Consent Flowchart



PARTICIPANT INFORMATION DESIGN

As the participant may be given multiple PICFs at the same timepoint, or at multiple timepoints, it is important to consider the information contained in each document is sufficient for the participant to make an informed decision, but remains digestible to the reader; therefore, a simplified approach to consent may be considered to ensure that the information provided to the participant is not overwhelming, particularly if there are multiple domains they will need to be consented to.

INCORPORATING SUB STUDIES

If trials are using the multi-stage consent process, participants will be provided the option to consent to the sub-study/ies if they are eligible.

- If containing information about the sub-study within the main PICF, each sub-study should be separated into a defined different section on the PICF and should allow the option of consent for each separate sub-study.
- If choosing to create a separate PICF for each sub-study, a separate consent form should also be included for the participant to consent to the sub-study.

OBTAINING AND DOCUMENTING CONSENT

During the eligibility screening for the trial/ each domain, the participant will be excluded from participating if they meet any of the exclusion criteria or do not meet any of the inclusion criteria.

If the patient agrees to participate in the trial, the investigator should follow the regular informed consent process for clinical trials, with the additional points in mind:

1. Obtain domain consent (for each domain within the trial the patient is eligible for and agrees to participate in)
2. Obtain sub-study consent (if applicable and available)

WITHDRAWAL FORM DESIGN

In general, a separate withdrawal form should be associated with each consent form, containing information about withdrawing from the aspects the participant consented to using that particular consent form.

OBTAINING AND DOCUMENTING WITHDRAWALS

If a participant chooses to withdraw from the trial or one of its domains, it is important that the withdrawal form corresponding to their signed consent form is used.

1. If a participant consents to the trial using the main trial PICF, they must only withdraw from the trial itself using the trial Withdrawal Form
2. If a participant consents to domain 1 using the domain 1 PICF, they must only withdraw from that domain using the domain 1 Withdrawal Form
3. If a participant consents to one or more sub-studies using a Sub-Study PICF, they must only withdraw from the sub-study(s) using the corresponding Sub-Study Withdrawal Form

Therefore, if a participant decides to withdraw from one aspect of the trial initially, and then later from other aspects, there will be multiple withdrawal forms to document this.

5.4 INFORMING PARTICIPANTS WHEN NEW INFORMATION ARISES

A participant must be made aware of any new information that arises within the platform that may affect their decision to continue to participate.

New information includes, but is not limited to, changes to:

- The available interventions or domains
- The available safety information
- The use of the participant's information or samples
- The protocol or the schedule of assessments

These changes may arise when amendments are made to the trial or domains after the trial has begun, and the participant has consented to documentation that has been superseded.

Participants should be made aware of changes that are substantive in nature and those that increase burdens or risk to the participant. Due to the modular nature of Adaptive Platform Trials, this may not be relevant to all participants and could only require the contacting of participants randomised within a particular domain, or to a particular intervention.

If required, site investigators should be notified that all currently enrolled participants should be contacted in a timely manner and provided with the relevant new information.

- Updated consent may be required, depending on the nature of the changes to the trial.
- The participant should be reminded of how to initiate the withdrawal process, if the new information changes their willingness to continue in the trial and/or the domains.

5.5 TRAINING INVESTIGATORS IN CONSENT

As the consent process for Adaptive Platform Trials can be different to consent for regular trials, it is advisable to provide training to site investigators, who may not be as familiar with the modular approach, and the different approaches to consent available for these sorts of trials.

Detailed SOPs or training videos are ways to communicate the requirements for the consent process for the adaptive platform trial, and to educate the investigators on the approach taken for your particular trial.

Reference examples:

- **SNAP trial training video**
- **What is an adaptive clinical trial?** by Adaptive Health Intelligence. This video provides a clear and concise explanation of adaptive clinical trials and how they differ from traditional designs.
- **What are adaptive clinical trials?** by the MRC Biostatistics Unit, University of Cambridge. This animation explains the benefits of adaptive clinical trials in an easy-to-understand format.
- **GCAR Video Resources** by the Global Coalition for Adaptive Research. This resource includes several videos that discuss adaptive trials and their advantages, focusing on patient-centered approaches.

06 ETHICS SUBMISSIONS

This section is divided into three sections: pre-approval, during the study, and post-study. It is important that each trial liaises with the lead ethics review bodies to ensure that ethical and jurisdictional-specific requirements are met.

In Australia, this is typically the Human Research Ethics Committee (HREC), while in New Zealand, it is the Health and Disability Ethics Committee (HDEC). Additionally, it is important to recognise that international organisations may use different terminology. For clarity and consistency, the terms ethics committee or HREC will be used throughout this document.

It is well recognised that Adaptive Platform Trials comprise a significant number of protocols and associated documentation. Therefore, it is crucial that sponsors and trial teams plan their ethics applications well in advance, with a clear outline of the trial structure, documentation, and operating procedures.

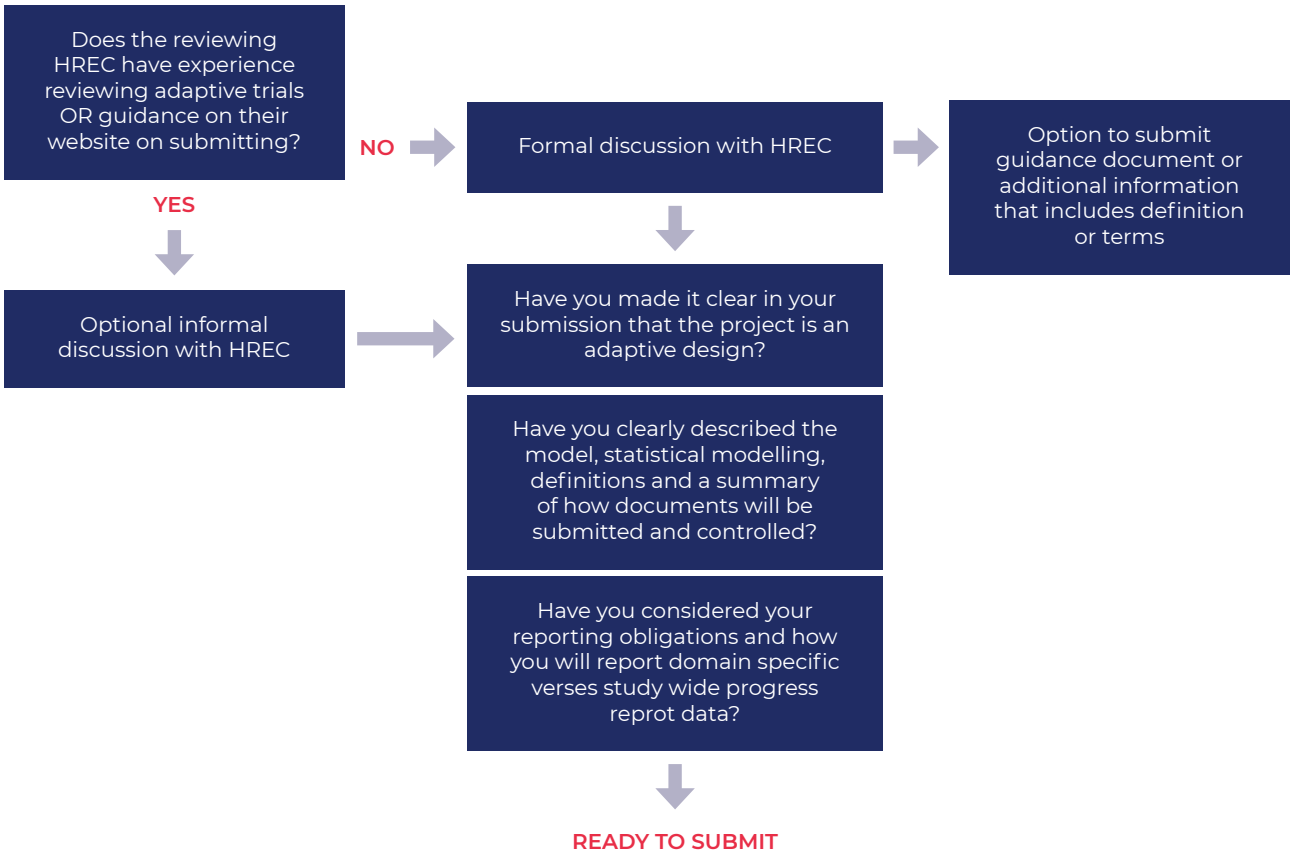
The authors have also provided some checklists that may be useful when planning an ethics committee submission.

6.1 PRE-APPROVAL (UP TO INITIAL ETHICS COMMITTEE SUBMISSION)

APPROACHING THE ETHICS COMMITTEE

Whether you are transitioning from a frequentist protocol or starting your trial with an adaptive protocol, it is important to approach the reviewing HREC early to discuss the submission and understand the review process for your trial. Below are some suggestions to consider when approaching the ethics committee to review an adaptive platform trial.

Figure 5: Flowchart for Ethics Submission



MEETING AND PRESENTING TO THE LEAD HREC

Some committees allow for presentations during their review sessions, where lead investigators can present their trial to the committee and answer questions. This would be especially useful for an HREC that is new to reviewing APTs and would allow them to ask questions and obtain feedback.

HRECS WITH EXPERIENCE REVIEWED APTS

If your HREC is new to reviewing APTs, it may be useful to offer to link them in with an HREC who has previous experience in reviewing these sorts of trials.

See below table of HRECs familiar with APTs who may be able to provide guidance/support to other HRECs conducting a first review of an adaptive platform trial:

Table 3: List of HRECs with experience reviewing APTs

COMMITTEE NAME	COMMITTEE CODE	TRIALS REVIEWED
Sydney Local Health District Ethics Review Committee (RPAH Zone)	EC00113	
Royal Melbourne Hospital HREC	EC00243	
Concord Repatriation General Hospital Ethics	EC00118	
Bellbery Ltd	**https://bellberry.com.au/about-us/hrec/**	

REQUEST FOR EXTERNAL REVIEWERS

If your trial employs unique statistical modelling or trial design, you may be required to obtain an external review of your trial protocol prior to submission to the reviewing HREC. Check with your local HREC in advance if this would be required, as it can take some time to confirm a reviewer and obtain the review.

TRANSITIONING FROM A FREQUENTIST TO ADAPTIVE DESIGN

If you are looking to transition from a frequentist trial design to an adaptive trial design, you may be required to submit this as a new study, or as a major amendment to your protocol, depending on your HREC. Where possible, it is recommended that studies aim to transition by submitting an amendment, allowing the study to retain its original project ID/study number, which will reduce workload on both the central and site teams. Maintaining open communication with your HREC about how this process can and should occur will be key to facilitating this process.

It is important to note that some changes may reach outside the scope of the original frequentist approval; changes of a significant nature to the research questions, interventions, and outcomes may no longer be relevant to the original ethics approval received for the frequentist trial. It is important to consider key aspects of the study when deciding if the transition to an adaptive design makes sense as an amendment, or if the scope of changes requires a new ethics submission.

Some of these factors are listed below:

- Statistical Analysis Changes: Are the analytical methods fundamentally different (e.g., Bayesian vs. frequentist inference)?
- Ethical and Safety Implications: Do the changes introduce new risks or alter the risk-benefit profile for participants?
- Study Outcomes: Are the primary or secondary endpoints being modified?
- New Interventions and Risk Profiles: Are new treatments being introduced, and what is their phase (e.g., early-phase investigational drugs)?
- Scope of Changes: How extensive are the modifications to the trial design, procedures, or population?
- Insurance and Sponsorship Implications: Will the changes affect trial insurance coverage or sponsor responsibilities?

TRANSITIONING TO AN APT BY AMENDMENT

If submitting as a major amendment, documents and notifications that may require updating (in addition to the core study documents) include:

- Regulatory Submission (CTN, etc.)
- Trial Registrations (ClinicalTrials.gov, ANZCTR, etc.)
- Ethics Submission Portals (ERM, REGIS, GEMS, RGS, etc.)
- HREA – if requested by the HREC
- Victorian Specific Module /Western Australian Specific Module /New South Wales Civil & Administrative Tribunal / Queensland Civil & Administrative Tribunal
- Indemnity and Insurance
- Sponsor/Third Party Agreements (Research Agreements, etc.)

TRANSITIONING TO AN APT BY SUBMITTING AS A NEW STUDY

If submitting as a new study, you will need to complete site closure/project closure processes for the previous non-adaptive trial, including ongoing standard of care, and commence a new project submission with each site under the new adaptive protocol. This means a site closure process for each site, and a new governance submission for each site. If submitting as a new study, it is vital that the workload on central staff, the burden on sites, and the cost implications are considered prior to undertaking this process.

DOCUMENTS FOR SUBMISSION

As there are often many documents involved in a submission, it is important that these are named, version controlled and collated with clarity, and that sufficient explanation of each document's purpose is provided for HREC review.

NAMING OF DOCUMENTS

To streamline the ethical review of APTs, we recommend using the 'standardised terminology' currently used across other active trials. For guidance on naming documents using the standardised terminology, please refer to the **ACTA Innovative Trial Design Glossary**. Some definitions and terms that will be of particular relevance to the documentation involved in the ethics submission of an APT include:

1. Core Protocol
2. Domain-Specific Appendix
3. Statistical Appendix

PICFS AND OTHER PATIENT FACING DOCUMENTS

Please refer to Section 5 of this document for further guidance on developing the participant information and consent forms (PICFs) for APTs.

Depending on the consent approach taken, you may have one trial PICF, or multiple PICFs (one for each aspect/domain of the APT).

As there are many documents to localise in an APT, it is suggested that other patient facing documents (patient diaries/participant cards/ GP letters, etc.) are provided in a format in which site-specific details can be added by wet-ink and therefore, do not need to be localised for governance submission. This will reduce the burden of the documents for the sites participating. For example:

- All domains listed on participant card, and site ticks which domains the participant is enrolled in and adds contact details using a pen prior to providing to participant
- GP letter contains blank areas to be completed by the site:

> Your patient, _____ ,
>
> has been enrolled in the *Example Trial* in the following domains:
>
> _____

COLLATION OF DOCUMENTS

Please refer to Section 2.5 of this document for further guidance Essential Documents/TMF. Due to the number of documents involved in an APT ethics submission, it is suggested that documents are collated into subfolders, to facilitate easier navigation. An example collation is provided below:

1. Core study documents = all protocols/ appendices
2. PICFs & Patient Facing Documents = all PICFs and patient facing resources
3. Region-Specific = VSM, WASM, NCAT, QCAT, etc.
4. Other = insurance, CTN, other regulatory documents, external reviews, HREA

HREC COVER LETTER

It is highly recommended that a detailed cover letter is included in the HREC submission. The cover letter should not conflict with any information provided in the HREA and study protocol and instead utilised as a summary of the key information contained within these documents.

This purpose of the cover letter is to provide an overview of the study and highlight aspects of the APT that make it unusual / different to other clinical trials. Additionally, it is recommended that your cover letter includes a detailed lay summary. This is to ensure that non-research-based staff and consumer representatives can understand the trial and its domains. To make your cover letter more effective, visual aids and flowcharts are also highly recommended.

A summary of aspects to include in the cover letter is listed below and refer to Table 6: HREC Submission Check List:

1. Overview of the study and what aspects make it an adaptive platform trial
2. Detailed lay summary
3. Summary of present and potential future domains; this could also include a visual summary/flowchart of the trial interventions/ domains and or the 'patient journey'
4. How domain changes will be communicated with the HREC and sites
5. A brief summary of scheduled/interim analyses – how frequently they will occur and the timelines around communicating trial decisions that arise from these analyses
6. Details about Response Adaptive Randomisation (RAR), if being implemented, and how the initiation of RAR will be reported to the HREC
7. An overview of the consent process – how will consent for the platform vs domains be obtained?
8. If the 'platform' will be perpetual
9. Link to resources on APTs – where possible, providing educational material alongside the submission may be useful so as to provide education about APTs for their review. Some useful resources include:
    - **Adaptive Health Intelligence YouTube Channel**
    - **ACTA**
10. An offer to present the trial to the HREC and answer any questions members may have.

DETAILED LIST OF DOCUMENTS/ TABLE OF CONTENTS

As APTs usually require many documents, having a summary sheet that clearly lists all documents, with a brief description of their purpose, version number, and date, will be very useful.

If using any online/multimedia resources as part of the trial consent/participant facing documentation, ensure to check how the HREC would like these listed and how any changes to these resources will be documented/submitted/reviewed.

Table 4: Example Table of Contents/List of Documents (for HREC Submissions)

DOCUMENT NAME	VERSION	DATE	TYPE OF DOCUMENT
Core protocol	1.0	31 Jan 2025	Protocol
Domain 1 Appendix	1.0	31 Jan 2025	Domain-Specific Appendix
Master PICF – Adult Providing Own Consent	1.0	31 Jan 2025	Patient-Facing Document
Pregnancy Appendix	1.0	31 Jan 2025	Other Appendix
Victorian Specific Module (VSM)	–	31 Jan 2025	Region-Specific Document – VIC
HREA	–	31 Jan 2025	Other Document

ETHICS & REGULATORY SUBMISSION PLATFORMS

It is recommended to keep all domains under a single project, to simplify the process of submitting to ethics and regulatory platforms.

ETHICS PLATFORMS (ERM/REGIS/RGS/GEMS/ETC.)

It is recommended that an APT and all its domains are contained within one project listing on the ethics platforms. Not only does this provide further emphasis that all parts of the study are to be considered as one trial (i.e. all documents should be considered components that make up the overall trial protocol), but also allows for domains and interventions to be added/changed/closed by the submission of an amendment.

This follows a similar structure to the way that sub studies are commonly submitted under the umbrella of a parent trial.

REGULATORY SUBMISSION PLATFORMS (ANZCTR/CLINICALTRIALS.GOV/TGA)

It is important to note that the regulatory websites are not well established for platform trials, and it is often difficult to fit the required information into the sections provided; this has been noted as a topic for development within those spaces. However, Section 2.6 provides considerations when registering and submitting results for an APT.

6.2 DURING THE STUDY (POST APPROVAL)

PLANNING ETHICS AMENDMENTS

Given the extensive range of documents and the complexity inherent in APT designs, amending the trial naturally involves considerable effort. Therefore, minimising the number of amendments is advantageous, as it can simultaneously alleviate the administrative burden on sites and streamline the communication of multiple changes. To achieve this goal, it is advisable to engage with the HREC to discuss the process for submitting changes—differentiating between significant and minor amendments and notifications for clarification only —and to reach an agreement on what will be permissible as part of the trial.

Below are some suggestions for maintaining trial integrity whilst reducing the number of amendments required.

MAJOR AMENDMENTS VS MINOR AMENDMENTS

One way to reduce the burden of amendments is to group amendments into major and minor amendments.

1. **Major Amendments –** updates to the core trial/study documents that are significant in nature, affect a large number of documents, or are applicable to a large number of sites.

   Examples of major amendments include a transition to a new version of a protocol, addition of a new trial domain/intervention, updates to the PICFs, or any combination of these changes.

2. **Minor Amendments –** updates to the trial/study documents that have minimal/no ethical implications, are pertinent to only a small number of trial documents, and/or are only applicable to a small number of sites.

   Examples of minor amendments include the addition of a sub-study being run at only a few select sites, protocol clarifications or administrative updates, addition of sites, changes of principal investigators, submission of paediatric PICFs (where only select sites will recruit children).

If any changes are non-urgent, they should be considered for incorporation into the next major amendment.

SUBMISSION OF 'NOTIFICATIONS'/'ACKNOWLEDGMENT ONLY' CHANGES WHERE POSSIBLE

Some HRECs allow for documents containing minor changes to be communicated/provided to sites after being acknowledged by the HREC, and do not require full committee review. Acknowledgments from the HREC are provided when the changes are deemed to have minimal/no ethical impact and therefore do not need to undergo full review by the committee. Examples of these could include operational updates to the study documents that do not have ethical implications or minor wording changes that do not affect the content that was approved by the HREC.

Utilising documents such as memos, protocol clarification letters, or other forms of notification may be useful to implement small operational changes that are important to communicate to sites. These changes can then be formally incorporated into the next planned amendment, as required.

Be sure to discuss with the lead HREC if notifications/acknowledgements are allowed and how these will be submitted.

‘INTERIM’ PROTOCOLS

Some trials have implemented the use of an ‘interim’ protocol, which is a running document that incorporates changes between major amendments. This protocol is provided to sites for reference but is not considered an official document until approval from the ethics committee. This document may be posted to the trial website/online for transparency and utilises minor version updates (v1.1, v1.2, etc.) between full versions that are submitted for ethical review. These ‘interim’ protocols can be watermarked as ‘not yet approved’, or something similar, to note that the document has not undergone ethical review.

CHANGES TO TRIAL DOMAINS AND INTERVENTIONS (CLOSING/ ADDING/SUSPENDING)

As an adaptive trial, it is crucial that the changes to interventions and domains are able to be implemented quickly. It is important that your trial has a clear pre-defined process for making decisions regarding adding, closing or suspending treatment arms or domains, and informing and implementing these decisions with the HREC. Some important ethical aspects to consider for each type of change is listed below.

ADDING A DOMAIN OR INTERVENTION

Adding a domain or intervention is a considered process; unlike other situations in which changes to the trial may need to be implemented more urgently, the integration of a new domain or intervention may not need to be handled in the same expedited manner. Generally, individual sites will not be able to enrol into a new intervention/domain, until all approvals (HREC and local) and training pertinent to the new domain/intervention are finalised. An amendment to the HREC should be submitted with a clear outline of the changes, an updated list of trial documents (with versions/dates), and any changes to the study/participant risk profile and statistical analysis.

An addition of a domain or intervention could involve updates to/submission of:

1. Core protocol
2. Domain-specific appendix
3. Statistical Appendix/Statistical Analysis Plan (SAP)
4. PICF incorporating new information about this domain/intervention
5. Investigator’s Brochure (IB)
6. Patient facing documents
7. CRFs and data collection
8. Regulatory approvals/listings
9. Multimedia/digital resources

It is also recommended that the addition of the domain or intervention should be announced publicly where appropriate.

TEMPORARILY SUSPENDING A DOMAIN OR INTERVENTION ARM

For example, following safety concerns that arise from trial data, preliminary advice from the DSMB, loss of clinical equipoise due to emerging evidence regarding efficacy or safety, temporary loss of availability of an interventional product globally/regionally, other operational or budgetary constraints.

In the case where a domain or intervention will be temporarily suspended, it is recommended that this change to the trial is submitted to the HREC as a notification. It is also recommended that the HREC be consulted and request that a formal acknowledgment from the HREC is not required for the suspension of the domain or intervention to take place. This allows for the suspension and the notification to the HREC to occur simultaneously.

As an adaptive trial, it is crucial that temporary suspension of the interventions and domains are able to be implemented quickly, particularly if the suspension is due to safety concerns. We recommend this is discussed clearly with your HREC early on in the trial.

Generally, affected sites will have enrolment into this domain/intervention suspended on the study database (where possible), and this suspension will not be lifted until a decision has been made to resume recruitment or to close the study domain/intervention.

When a domain or intervention is suspended, it is recommended that the following steps are taken:

- A notification to the HREC is submitted containing the following information:
  - Reason for the suspension, and who was involved in making this decision
  - Date/time of the suspension
  - Date/time of any changes to study database
  - The number of participants enrolled at the time of suspension, and implications for participants who are still in follow-up

- How this change will be communicated to participating sites

- If there is a significant safety concern and the treatment domain/intervention must be ceased for all active participants and/or impacts participants who are no longer active in the trial, it is recommended that a letter to participants is provided as part of the acknowledgment submission to HREC.
- If required, HREC-approved study documents should be amended and formally submitted as part of an amendment, as soon as reasonably possible, subject to the final decision regarding the suspended arm.

CLOSING A DOMAIN OR INTERVENTION ARM

For example, a pre-specified stopping rule is met, confirmed safety concerns that arise from trial data or external sources, recommendation from the DSMB, sufficient external evidence regarding the superiority/inferiority or futility of a domain/intervention, permanent unavailability of an interventional product globally/regionally, or other permanent operational or budgetary constraints.

In the case where a domain or intervention needs to be closed, it is recommended that this change to the trial is submitted to the HREC as a notification in the first instance. It is also recommended that the HREC be consulted and request that a formal acknowledgment from the HREC is not required for the closure of the domain or intervention to take place. This allows for the closure and the notification to the HREC to occur simultaneously.

As an adaptive trial, it is crucial that closure to the interventions and domains are able to be implemented quickly, particularly if the closure is due to safety concerns. We recommend this is discussed clearly with your HREC.

Generally, affected sites will have enrolment into this domain/intervention permanently suspended on the study database where possible.

When a domain or intervention is closed, it is recommended that the following steps are taken:

- A notification to the HREC is submitted containing the following suggested information:
  - Reason for the closure, and who was involved in making this decision
  - Date/time of the closure
  - Date/time of any changes to study database
  - The number of participants enrolled at the time of closure, and implications for participants who are still in follow-up
  - How this change will be communicated to participating sites
- If there is a significant safety concern and the treatment must be ceased for all active participants and/or impacts participants who are no longer active in the trial, it is recommended that a letter to participants is also provided as part of the acknowledgment submission to HREC
- It is recommended that study documents are amended and formally submitted with the next amendmentIt is recommended that the closure of a domain or intervention is announced publicly via the trial website, and via media release where appropriate.

GOVERNANCE SUBMISSIONS, AMENDMENTS AND COMMUNICATIONS

As per Section 6.1 (documents for submission) it is important that study documents are named and collated with clarity, and that sufficient explanation of the document's purpose is provided for review at a governance level. In addition to the guidance provided above, some additional recommendations are provided below to assist in streamlining governance submissions and amendments for Adaptive Platform Trials.

COVER LETTER TO THE RGO

It is recommended that a cover letter to the RGO is provided, explaining the trial design and or the nature of the changes and how the trial documents apply specifically to that site and/or region. It is suggested that this cover letter be based on the cover letter provided to the HREC to ensure consistency in information. If helpful, this cover letter can include placeholder text for the site to adapt/remove, to ensure that the cover letter only contains information that is relevant and pertinent to that particular site

For example, if the site is not participating in any paediatric aspects of the trial, the part of the cover letter that describes the paediatric aspects could be removed, as is not relevant for that site.

SUMMARY OF CHANGES

This document is commonly included in ethics and governance submissions, but is particularly relevant for large, adaptive platform trial amendments. A clear and easy to read Summary of Changes will assist the research office and the site teams to be able to understand all the changes to the multiple documents involved in the trial and maintain a clear audit trail of documentation. It is recommended that this summary of changes document include: A table of contents

10. A section for each document that is amended, with version updates
11. An explanation for the changes, either per change (line-listing), or comprehensive explanation of changes per document, and clear reference to the relevant section of the document.

DETAILED LIST OF DOCUMENTS/ TABLE OF CONTENTS

It may be useful to provide sites a summary list of the documents, and if they relate to that site.

In the case of an initial governance submission or amendment, there may be particular documents that are not relevant to a participating site, due to their recruitment population, region/location, or domain preferences.

As there can often be a large number of documents involved in the governance submission or amendment of an APT, this document can provide a clear guide for the sites of what they need to localise and submit for local approval. An example is provided below.

Table 5: Example List of documents/Table of Contents (RGO Submissions)

DOCUMENT NAME	VERSION	DATE	TYPE OF DOCUMENT
Core protocol	1.1	31 Jan 2025	All sites
Domain 1 Appendix	1.1	31 Jan 2025	Sites participating in Domain 1
Master PICF – parent/legal guardian	1.1	31 Jan 2025	Sites recruiting <18 years
Pregnancy Appendix	1.1	31 Jan 2025	Sites recruiting pregnant patients
Victorian specific module (VSM)		31 Jan 2025	VIC sites only

6.3 POST-APPROVAL (STUDY REPORTING AND CLOSURE)

STUDY REPORTING

Safety reporting in APTs that incorporate multiple domains presents distinct challenges and considerations compared to traditional clinical trials.

There are several key aspects related to safety reporting in these complex settings:

COMPREHENSIVE SAFETY SURVEILLANCE

In APTs featuring multiple investigational products across different domains, it is crucial to establish a comprehensive safety surveillance system. This system must ensure that adverse event (AE) data is collected for each treatment arm and domain. Consistent data collection is necessary to facilitate a holistic assessment of safety across the entirety of the trial.

STANDARDISED REPORTING PROCEDURES

Implementing standardised procedures for documenting and reporting adverse events is vital due to the complexity of managing multiple domains. This ensures that all sites follow the same processes for classifying, recording, and reporting AEs and serious adverse events (SAEs). Consistency in reporting will enhance the ability to aggregate and analyse data efficiently, enabling the prompt identification of safety signals.

INTERIM SAFETY ANALYSIS

APTs generally include interim analyses to evaluate safety and efficacy data. It is essential to establish clear protocols that dictate when and how these interim safety analyses will occur across different domains. Predefined criteria for stopping or modifying trial arms based on safety outcomes need to be outlined. Regular interim safety assessments can help identify potential issues early, allowing for timely intervention.

DATA SAFETY AND MONITORING COMMITTEE (DSMB) OVERSIGHT

An independent DSMC Committee should be convened to provide oversight of the safety data across all domains. The DSMC will routinely review AE and SAE data to ensure participant safety and determine if changes to the trial design (e.g., dropping an arm or modifying a treatment strategy) are warranted. Their role is crucial in maintaining trial integrity and ensuring that any safety concerns are promptly addressed.

INTEGRATION OF PHARMACOVIGILANCE PRACTICES

Robust pharmacovigilance practices should be integrated into the safety reporting framework. This involves assessing the relationship between adverse events and investigational products utilised within different domains. All AEs need to be evaluated in the context of their respective products, considering the unique safety profiles associated with each.

PARTICIPANT INFORMATION AND CONSENT

It is vital to ensure that the Informed Consent Forms clearly outline the potential risks associated with participation in APTs involving multiple domains. Participants should be made aware of the various investigational products and domains, as well as the safety reporting process that will be followed.

TRAINING AND EDUCATION

All clinical site staff should receive comprehensive training on the safety reporting procedures specific to multi-domain APTs. This training should cover the complexities of collecting and reporting safety data, the importance of timely reporting, and the use of standardised forms and systems. Such preparation will help ensure accuracy and compliance across all participating sites.

REGULATORY AUTHORITIES

Reporting must be conducted by the protocol and regulatory requirements, ensuring that serious adverse events (SAEs) are reported promptly, and regular safety updates are provided. Clear communication is key to maintaining compliance and fostering confidence in the trial's safety oversight.

Where the APT has been submitted as one listing on an ethics platform (ERM/REGIS, etc.), only one study report should be submitted. For APTs submitted as separate projects (for example, a different project listing for each domain), a report will be required for each project.

The recommendation is to report overall trial numbers and platform status in the specified fields, whilst include a breakdown of each individual domain, including trial numbers and domain status, as additional information. It should be noted that depending on the ethics system used, some reports will only allow for direct entry of overall study; domain details and numbers may need to be outlined in the comments.

ANNUAL REPORTING

Annual reports should outline overall progress of the study with domain status and recruitment by domain also described. One report is submitted for the whole trial (with domain-specific sections). An update of the status of each domain should be included, however, the HREC should have been notified about closures as part of notification/closure

FINAL REPORTING

The final report will be submitted once all domains/interventions are closed for the APT.

6.4 DISSEMINATION OF STUDY RESULTS

The process for dissemination of study results should be outlined in the setup phase of an APT. Ensure what was agreed with the reviewing HREC is actioned regarding dissemination of results.

Table 6: APT Submission Checklist

The checklist is designed to work through considerations for each step of the ethics approval process.

RECOMMENDATION ACTION	GUIDANCE	
PRE-APPROVAL CONSIDERATIONS AND CONSULTATION		
Check the reviewing HREC's available resources	Are there reference materials or guidance documents specific to adaptative trials? **NHMRC Guidelines** HRECs may have their own website/portals where information on submitting can be obtained	☐
Meet with HREC and discuss the trial	Have you considered arranging a meeting to discuss or present to the committee the structure of the study?	☐
Provide additional information to the committee or in the application on structure, statistics and adaptations	The aim to provide clarity and content in relation to your ethics submission and how adaptivity will impact on your trial, so that it is clear to the committee any ethical impacts of this as they are reviewing the study. Could be in the form of a guidance document, reference materials, a cover letter or clearly detailed in the protocol or other submission documents.	☐
Discuss with the HREC and confirm how the progress reports will be managed (i.e. domain versus platform metrics)	Consult with the HREC and confirm their preference for reporting structures. Prepare templates to ensure that the reporting will be consistent over the course of the trial.	☐
Explain and agree upon nomenclature and document control	Consult with the HREC and discuss what nomenclature should be used to avoid confusion. If nil preference, consider providing a glossary of terms with the protocol or submission. Document if the protocol, PICFs etc will be modulated and agree on how these should be versioned and named. For example, versioning a Master or Core protocol separate to each Domain Protocol, or Appendixes	☐

RECOMMENDATION ACTION	GUIDANCE	
Investigate how portal or submission administration could be impacted	Will the HREC project/approval number remain the same for all domains? What would be considered a minor or major amendment (I.e. closure of a domain)?	☐
Confirm costs with the HREC	What HREC fees might apply to each activity? Estimate how many potential events that attract fees might occur throughout the study	☐
Confirm what would be a minor or substantial amendment	Could minor amendments be actioned between full HREC committee meetings and approvals? Does the HREC allow notifications to be submitted without review and what might fall into this category?	☐
Is there a method to handle the governance for processing protocol amendments and notifications of change or dissemination of results (for the platform or for each domain?)	Will the communications to sites be via a website, or via letter, versus all participating sites individually, via a portal etc? Consider what results need to be shared with sites, and with participants and the method that will be used to ensure participants are informed of changes that they might care about (see consumer engagement sections).	☐
DURING THE STUDY		
Use an amendment decision tree and checklist	Based on what has been agreed with the HREC, you can build a decision tree for each predicted event in your trial that might trigger a HREC notification or submission (protocol clarification, amendment, domain closure, site-specific information/unanticipated serious medical event etc). Throughout the trial for each event refer back to the agreed pathway to ensure speedy action. Include a decision on site involvement.	☐
AFTER THE STUDY		
Specify which milestone has been reached (I.e. Site, Domain and Trial Closure)	Based on what has been agreed with the HREC, you may report based on individual domain, site or whole trial milestones.	☐
Disseminate results for each milestone/event as agreed	You may publish and distribute results as domains are added or dropped.	☐

07 DATABASE/ DATA MANAGEMENT

The electronic data capture (EDC) system for any clinical trial should be developed with careful consideration to both the system of choice and the trial scope/electronic case report form (eCRF) requirements as specified in the study protocol.

When a clinical trial has an adaptive protocol with the scope to have multiple domains and the addition or removal of interventions or domains over time, this will impact the established processes and aspects of traditional database systems and data management practices. The dynamic nature of an adaptive trial design may require consideration of both 'off-the-shelf' and bespoke options.

The aim of this section is to provide key considerations for EDC design and data management for adaptive trials.

7.1 STAKEHOLDER MANAGEMENT AND SYSTEM CHOICE

Investing time in the scoping and planning stage is critical to ensure that key stakeholders are involved in the process from the beginning, and that design considerations at the higher level are well defined, guiding the decision process for the system of choice.

It is critical to involve data system developers/ programmers early in the process to:

- Identify the unique needs of the APT platform
- Understand known system limitations
- Determine whether existing systems can manage the dynamic nature of the adaptive trial or if a bespoke option will be needed

DEFINE DATA SCOPE

The source of the data to be collected needs to be considered when determining systems for data collection and storage. Data collected from various internal and/or external sources may have different requirements for retention and storage depending on:

- The data custodian
- The sensitivity of that data

If data is to be sourced externally, it is important to understand:

- What information is required for the data request
- Any linkage requirements (if applicable)
- The ease of data linkage **which** may be impacted by the systems being used and the variables required for linkage
- The frequency of data linkage **which** may be determined by project requirements including planned analyses and the availability of that data over the time course of the project

If any manual linkage is required, a risk assessment should be conducted to determine:

- The risk to data and project outcomes
- Any mitigation strategies that may be required

As with all clinical trials, data storage and back-up measures should be considered from the outset to ensure that all jurisdictional, ethical and regulatory requirements are met.

SYSTEM CONSIDERATIONS

An initial consideration in planning for an adaptive platform trial is whether the EDC system is fit for purpose. There are multiple EDCs available for clinical trial use, each with their own strengths and weaknesses. What might be suitable for one trial may not be fit for purpose for another trial and this is particularly the case for more complex, novel trial designs. Some institutions may have preferred EDC providers.

It is recommended that before commencing the EDC build, there is careful consideration of:

- Whether the trial design can be achieved using current EDC providers within the institution
- Whether a bespoke option will need to be considered
- Whether a hybrid approach may be considered where the institution may outsource a particular module such as the randomisation component whilst using their institutional system of choice for data collection

CHOICE OF EDC PROVIDER

Institutional policies and procedures should be followed when determining choice of EDC provider. Some additional considerations specific to Adaptive Platform Trials have been provided below for reference:

- What is the vendor's experience with Adaptive Platform Trials? What types of adaptations have they managed in the past? Are these similar to those planned in your adaptive platform trial, and if not, how would the vendor manage your requirements?
- What is the cost each time an adaptation is implemented (if applicable), and how will these be managed within your contract with the vendor? Has this been budgeted for?
- If there is a future adaptation, how will this be handled? How will new domains be added, and existing domains closed? Will new domains be costed separately to the main development budget? How quickly can the adaptation be implemented and who needs to be involved?
- Can the EDC system facilitate features such as Response Adaptive Randomisation?

7.2 PRE-TRIAL DATA SYSTEM SCOPING AND DESIGN

It is important to understand who within your institution is responsible for data system scoping and design and to engage them as early as possible. Communication that is ongoing, open and collaborative with the key stakeholders will ensure that they are involved in all phases of the eCRF design process and will increase the likelihood of a successful collaboration.

Key stakeholders and project roles will vary by institution, but may include:

- Investigators, Clinical Leads and Research Fellows
- Statisticians
- Clinical Data Systems/Development teams
- Trial Operations Team
- Clinical Data Management staff

PROJECT PLAN AND DATA DESIGN QUESTIONS

Key considerations include:

- Develop a comprehensive project plan defining days of effort, resources, key timelines, and deliverables. Be sure to include any expected delays and possible resource limitations and regularly update the project plan.
- Conduct a formal system and design scope prior to starting the EDC build. Identify the unique needs of the APT platform design, key limitations, and possible planned solutions to enable a more realistic project scope.
- Prepare documentation and have regular meetings to address all questions/ issues with key stakeholders (ongoing) through development, go live and post implementation. Keep record of all decisions and actions.

DESIGN CONSIDERATIONS

Key design principles include:

- Consider a robust design with both core elements and domain specific elements, future proof the system (where possible), consider streamlining the system design for future design updates.
- Utilise system features such as variable re-use, dynamic forms/field lists and show/ hide features.
- Define data validation and integrity rules/ edit checks as part of the development process, assisting the future data management plan.

PARTICIPANT IDENTIFIERS

Consider how participants will be identified with a unique alphanumeric attribute in the EDC. If participants can enrol in more than one domain, depending on the EDC structure, consider:

- Whether the data for each individual participant will need to be linked and how this linkage will occur
- Whether a platform ID may be required for each participant to allow linkage of data collected in different domains

TYPE OF DESIGN

The structural design of the EDC will be informed by the trial requirements and features of the system.

Key questions include:

- Is it possible to customise the EDC to allow all domains in the same study container/ URL?
- Should the study be divided into domain-specific and/or therapeutic containers due to substantial differences?

USER-ACCEPTANCE TESTING (UAT)

Considering the potential complexity of Adaptive Platform Trials and their systems, thorough testing of the EDC, including all planned adaptations, is essential. International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH-GCP) requires that all computer systems used in clinical trials are appropriately validated.

In addition to common system/instance level requirements, such as data security and disaster recovery, validation should include:

- A comprehensive UAT to ensure data collection instruments are fit for the specific requirements of the APT
- Consideration of how UAT will be conducted for the core build versus each domain-specific build
- Documentation of how user requirements and UAT will be documented
- Targeted testing rounds for additional domains or other adaptations focused on the changes and possible interactions within existing EDC structures

RANDOMISATION AND RESPONSE ADAPTIVE RANDOMISATION (RAR) CONSIDERATIONS

Allow for additional development time and effort to discuss and plan for:

- Any current and future considerations (future-proofing) for design and system requirements
- Whether the system can incorporate changes to randomisation questions, eligibility, multi-randomisation, sub-groups, randomisation tables, weighting, and stratification factors as per study protocol
- Confirmation of correct datapoint set-up and field view/entry restrictions prior to going live

DOCUMENT AND SUMMARISE KEY DEVELOPMENT SPECIFICATIONS

Best practices include:

- Keep up to date with existing/planned changes
- Document proof of concept models using an agreed template/worksheet
- Record detail on key development decisions – reasons, why/how? This will ensure that all staff (new and existing) are across the development/planned changes, serving as a key reference to understanding why decisions and approaches were made

7.3 PRE-TRIAL DATA MANAGEMENT CONSIDERATIONS

DATA CLEANING – PROCESSES AND VALIDATION

Within an adaptive trial there are often competing and concurrent tasks and the additional challenges of opening new domains while managing existing domain arms

- How will the addition of domains and/or arms within established domain/s with every protocol amendment affect the current processes of data review/cleaning? For example, new domains and/or arms may have different eligibility criteria prior to enrolment or randomisation which needs to be considered during data review/ cleaning.
- What are the processes to close/drop domains and/or arms within established domain/s? Consider the trigger points and communication plan with key stakeholders (including clinical data systems, trial operations and statistician) (Hague et al., 2019. p11-12).

DATA MANAGEMENT PLAN AND ELECTRONIC CASE REPORT FORM (ECRF) GUIDELINE

For the data management plan, consider how the addition of domains and/or arms within established domain/s will affect the key milestones of analysis.

- How will the budget, time and resources be allocated when the trial is expanding with additional domains and/or arms? Consider the requirements for multiple rounds of UATs and database migration down-time.

- Will the data management plan and/or eCRF guidelines need to be updated with the addition of domains and/or arms for every protocol amendment?
- What are the analyses triggers to prepare and clean the data? The data manager should be in regular contact with the Statistician and use resources to communicate interim and final data lock milestones (e.g., using a 'data lock milestone' document to plan all relevant activities in the lead up to the interim analyses or final analysis).

It is important that the data management plan is developed in close consultation with the established statistical analysis plan (SAP) to ensure a comprehensive inclusion of all relevant data considerations.

7.4 POST-LIVE STUDY UPDATES

Within the adaptive trial setting, closing/dropping domains or treatment arms are expected dynamic changes in the trial design and there is an element of pre-planning and consideration in terms of additional budgeting, time, and resources.

Additional resources and attention to detail is required during the study update process to:

- Retain present data requirements
- Incorporate future data requirements
- Remove past data requirements as needed

Keeping a change log document up to date to track collective changes is recommended.

ADAPTIVE CONSIDERATIONS

Key questions include:

- How will new domains and new arms within a domain be denoted (e.g., will a new domain be considered as a separate 'group' in the randomisation module?)
- What will be the process of adding and activating new domains and arms within a domain? How will the existing domains and arms be affected?
- Communicate and plan system downtime considering existing and new domains.

DATA MIGRATION CONSIDERATIONS

Plan all stages of data migration as part of study update requirements with consideration to both systems managed within your organisation and external system requirements (as required). Be sure to have a clear set of expected outcomes with key stakeholders - consider time, resources, and expertise.

7.5 POST-LIVE DATA MANAGEMENT PROCESSES AND DATA ANALYSIS

OPERATIONAL PROCEDURES/ RESOURCES FOR INTERIM ANALYSES

Key operational requirements include:

- The Data manager should be in regular contact with Statistician regarding analyses triggers to prepare and clean the data
- Resources: data lock milestones document: this is a document used by data managers to plan all relevant activities for data lock (whether this is for interim analyses or final analysis)

Adaptive trials bring increased challenges in managing multiple often competing analysis timepoints at both interim analysis and as part of ongoing trial commitments for data safety and adverse event reporting. The adaptive features and the interim decisions incorporated in the trial design often involve one or more interim analyses whilst recruitment is ongoing and based on results changes are implemented. These activities require high quality data and therefore require intensive data cleaning activities to be performed by the data manager prior to analysis. The workload of a data manager is more complex and increased in an adaptive trial with a number of competing and concurrent data cleaning and query management activities throughout the course of the trial.

The data and safety monitoring committee (DSMB) play a critical role in reviewing the data at each interim analysis providing key recommendations on how the trial should proceed. This may include:

1. Modifications as planned by adaptive design
2. Proposing unplanned design modifications or stopping if there are serious safety concerns

DOCUMENTATION – COMPLETE LIFECYCLE

Comprehensive documentation related to data system development and management decisions, roles and processes is particularly important for APTs considering the complexity and evolving nature of these types of trials. Regular reviews of documentation and processes, as well as triggered reviews (such as upon adding new domains) are recommended to ensure that documentation remains up to date throughout the lifecycle of the project.

Version control should be maintained for all changes including:

- Documenting the nature of the change
- Documenting the reason for the change

STAFF RESOURCES AND TRAINING CONSIDERATIONS – DATA PERSONNEL

Staff resourcing and training is a key consideration for all trials but, APTs increase the complexity of both data design and management activities to set-up, conduct and report a trial.

APTs require higher levels of effort and expertise with further consideration to the provision and delivery of effective training models for both data system and data management staff, throughout the complete lifecycle of the trial and beyond. This is especially important as part of future organisational planning, growth and development initiatives.

Sample size and study duration are often not known at the time of study onset which provides an additional layer of complexity when trying to plan and quantify data resourcing needs for the trial. APTs that are not adequately resourced can compromise the advantages of the adaptive trial method itself and create a higher level of operational risk and statistical bias (Wason et al,. 2022. p2).

Adaptive trials should be appropriately resourced with experienced staff to improve the delivery of more complex trial designs. Ongoing training and upskilling of data management staff and trial support staff is required, ensuring the in-depth knowledge is spread across several staff minimising the impact of staff changes (Hague, et al,. 2019. p11).

Training documentation for data personnel needs to be:

- More comprehensive and kept up to date during the trial
- Adaptable to the dynamic needs of the study
- Updated as recruiting arms change together with updates to the data design and management plans.

08 MONITORING

Trial monitoring plays an important role in quality assurance for all trials, including APTs, by verifying the protection of participant rights and well-being, the accuracy of reported trial data and ensuring the conduct of the trial complies with Good Clinical Practice, with the approved protocol, and all regulatory requirements.

Current international standards for trial monitoring are outlined in the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH-GCP) Integrated Addendum, ICH-GCP E6(R2), Section 5.18 (2016, p29-32) and the National Health and Medical Research Council 'Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods' (2018). This section highlights additional APT-specific considerations that may be helpful when assessing risk and developing Trial Monitoring Plans for APTs.

8.1 RISK-BASED MONITORING

A risk-based approach is recommended for the monitoring of clinical trials, including APTs.

Risk assessments should be performed:

- Prior to recruitment commencement
- At each adaptation point
- At regular intervals, using a dynamic proportionate risk approach

These assessments identify potential risks to participant safety and trial integrity, requiring comprehensive management and mitigation strategies that must be continuously monitored throughout the trial's duration.

In addition to risks shared with conventional clinical trials (such as intervention safety profiles, funding challenges, recruitment difficulties, and protocol complexity), APTs introduce several unique risk factors:

- **Increased statistical complexity due to multiple interim analyses:** More frequent adaptive analyses require sophisticated statistical methodology and may introduce operational challenges in data cleaning, verification, and decision-making timelines.
- **Platform evolution through domain and intervention additions:** The dynamic nature of incorporating new research questions and treatments over time creates governance, regulatory, and operational continuity challenges.
- **Consent management complexities:** Evolving trial designs may necessitate participant re-consent processes, with potential impacts on retention and participant understanding.
- **Multi-domain participant enrolment considerations:** Participants enrolled across multiple domains introduce unique analytical challenges regarding treatment interactions and safety monitoring requirements.

Risk assessments should be used to determine:

- The frequency and intensity of monitoring activities across the whole platform
- Whether any additional domain-specific monitoring activities are required
- Site-level risk factors (such as the experience of site research personnel, recruitment rate, rate of data missingness) to inform prioritisation and selection of sites for monitoring

DEVELOPMENT OF A MONITORING PLAN

Prior to the recruitment initiation, a comprehensive monitoring plan must be established and subsequently updated in alignment with adaptations. The monitoring plan should include:

- Identification of potential risk sources related to the trial
- Detailed strategies and methodologies for monitoring
- Clearly defined expectations regarding the level of monitoring necessary to manage identified risks effectively.

For risk-based monitoring, consider the potential areas of as part of APTs:

- Informed consent procedures
- Frequency and types of analyses conducted
- Definition of primary outcome
- Management of domain-specific risks (new or closed)
- Staffing and resource requirements and allocation

Monitoring Focus:

- **Domain-Specific monitoring:** tailored oversight of particular domains
- **Comprehensive monitoring:** assessment across all domains

Risk Rating and Tailored Monitoring Strategies

Implement a risk-rating system for sites that allows for customisation of monitoring activities based on identified risks.

This framework should enable:

- Domain-specific monitoring approaches that concentrate on high-risk areas
- Flexibility to adapt monitoring intensity based on ongoing assessments and risk evaluations.

8.2 DATA CLEANING (INCLUDING FOR INTERIM ANALYSES)

To maintain data the integrity in an APT, monitoring may need to be more frequent compared to traditional trials. This increased frequency is crucial to prevent the accumulation of significant backlogs of key data awaiting cleaning, which could delay analysis and adaptation decisions. Ensuring timely and thorough data cleaning is vital for making informed adaptation choices based on accurate and reliable data.

This is especially important for APTs to ensure that:

- Triggers for analysis and potential adaptation are not missed
- Decisions about adaptations are based on appropriately cleaned data

The extent of data cleaning required for analyses must be integrated into the risk assessment process. This allows researchers to account for potential issues arising from unclean or incomplete data.

Where interim analyses are event-driven, establish:

- Clear communication lines
- Delegation of responsibilities for:
  - Monitoring the number of events
  - Determining monitoring frequency
  - Carrying out data monitoring

Additional monitoring visits may need to be scheduled if there is a data backlog and an upcoming interim analysis.

It is recommended that sites are notified in advance (for example, during Site Initiation Visit, SIV) that there may be additional monitoring prior to interim analyses due to the nature of the trial, so that this can be accommodated, and any concerns addressed from the outset.

When preparing a data monitoring for APT, address these key considerations:

- **Crosschecking between different CRF sections:** It is essential to conduct thorough crosschecks among different sections of the Case Report Forms (CRFs) during the monitoring process. This practice helps ensure consistency and accuracy across all data entries. Additionally, crosschecking should be implemented whenever updates to the CRF are made or when adaptations to the trial occur, to identify and rectify any discrepancies.
- **Identifying systematic sources of bias:** Assessing potential systematic sources of bias is a critical component of the monitoring process. Researchers should systematically evaluate data collection methods, participant selection criteria, and any external factors that may influence results. Addressing these biases early can significantly enhance the reliability of the trial outcomes.
- I**nterim analyses frequency and data cleaning requirements:** Consideration of the frequency of interim analyses and the data cleaning requirements should be considered when preparing a monitoring plan for an APT. It is important to determine how often interim analyses will occur and ensure that sufficient resources are allocated for timely data cleaning to support these analyses

8.3 CHOICE OF MONITORING APPROACH

Due to the importance of ensuring timely monitoring of key data in APTs, consider different methods when determining the monitoring strategy . Additional last-minute on-site monitoring visits for data cleaning prior to an interim analysis can be both expensive and impractical depending on the number and availability of sites and monitors.

To optimize resource allocation and ensure comprehensive oversight, the following strategies should be considered and integrated into the monitoring plan:

- **Centralised monitoring:** Implement centralised monitoring procedures that allow for continuous oversight without the need for frequent site visits. This approach can streamlines processes and enhance efficiency.
- **Validation Checks:** Build robust validation checks into the database to minimise data entry errors and reduce the need for manual queries. Automated checks can flag inconsistencies or missing data in real-time, allowing for timely corrections.
- **Institutional SOPs and guidance:** Adhere to institutional standard operating procedures (SOPs) and guidance to ensure consistency in monitoring practices across sites. This enhances the reliability of data collection and management.
- **Risk-Based monitoring:** Utilise a risk-based approach that leverages central monitoring and risk assessment to focus on high-priority sites. This may involve visiting specific sites more frequently based on their performance indicators or risk levels.
- **Robust central and statistical monitoring:** Implement strong central and statistical monitoring techniques to track key metrics, such as the rates of Protocol Deviations (PDs), Serious Adverse Events (SAEs), and overall data completeness. Monitoring these indicators helps identify potential issues early and facilitates proactive interventions.

8.4 OPERATIONALISING MONITORING

When operationalising monitoring for an APT, address the following key considerations:

- **Practical Monitoring Considerations:** Implementing monitoring for APTs often differs significantly from traditional trials. Evaluate the practical challenges in site selection, visit frequency, and resource allocation.
- **Informed Consent Documentation:** As the trial evolves, updates to informed consent forms will be necessary. Ensure clarity and accuracy in the documentation to reflect changes in the trial's design while maintaining ethical standards and participant data integrity.
- **Budget Implications:** More frequent monitoring will result in additional costs. Budgeting should account for increased resources for statistical support, programming, and data management to facilitate effective central monitoring.
- **Endpoint Selection Impact:** The choice of endpoints can influence the required level of monitoring and data cleaning. For instance, critical endpoints like mortality may necessitate more stringent monitoring than less critical assessments.
- **Monitoring Staffing Needs:** Consider the need for multiple monitors based on the required level of blinding for each domain. Determine the necessity for both blinded and unblinded monitors to ensure trial integrity and data accuracy.

8.5 MONITOR TRAINING

Typically, monitors on investigator-initiated trials already have some familiarity with the APT they are monitoring (i.e., Project Manager and Project Officers etc.) however most will benefit from targeted monitoring training in all domains active in the region they are working and/or when there is an upcoming change in therapeutic area.

When outsourcing monitoring to a Clinical Research Organisation (CRO), ensure that:

- Personnel responsible for monitoring APTs have a solid understanding of APT design and its application
- They receive documented training relevant to the domains active in the region they are working in
- They are provided with training and required access to the electronic data management system for central and/or remote monitoring

8.6 APT MONITORING PLAN TEMPLATE

Unlike monitoring plans for conventional trials, APT Monitoring Plans are anticipated to evolve throughout the trial's lifespan. The following points may be helpful when adapting Trial Monitoring Plan templates into APT Monitoring Plans:

CORE TEMPLATE COMPONENTS

- **Modular Formatting:** Design the plan to allow modular updates, enabling new domains and sectional changes to be incorporated and documented efficiently during each review.
- **Risk Assessment Documentation:** Provide a detailed description (or link to) the risk assessments conducted for each domain, including identified risks and the corresponding monitoring responses. This ensures transparency and clarity in how risks are managed.
- **Inclusion of Regional Requirements:** Highlight any regional monitoring requirements that go beyond what ICH-GCP, sponsor, and funder requirements are stipulated. This consideration ensures compliance with local regulations and practices.

PRAGMATIC APPROACH TO MONITORING

Recognise that:

- As monitoring occurs at a platform level, an increase in the number of domains may elevate the overall monitoring load
- Preparation for interim analyses may necessitate additional monitoring resources, potentially impacting or replacing other planned activities

Include:

- A clear section delineating triggers that may supersede planned activities, along with the rationale for these adjustments
- Specification of any additional monitoring procedures or checks that are required when adaptations are planned, ensuring thorough oversight during transitions

DOCUMENTATION AND CONTINUOUS IMPROVEMENT

- **Change Log:** Implement an expanded version log to document changes to previous versions of the monitoring plan, including the rationale for each modification. This provides a clear audit trail and facilitate communication about the evolution of the monitoring strategy.
- **Training and Resources for Monitors:** Include a section outlining the training and resources required for monitors to conduct their roles effectively within the evolving APT framework. This promotes preparedness and competency among personnel.
- **Feedback Mechanism:** Establish a feedback mechanism to gather insights from monitors and other stakeholders on the effectiveness of the monitoring approach. This feedback can drive continuous improvement in the monitoring process.
- **Collaboration and Communication Protocols:** Outline explicit collaboration and communication protocols among study teams, sponsors, and any external monitoring entities to ensure that everyone is aligned

09 CONCLUSION AND NEXT STEPS

This guidance document has outlined the key operational considerations for APTs, drawing on collective insights and best practices from experienced adaptive platform trialists.

As the field of APTs continues to evolve, sustained collaboration across the research community will be crucial to refine best practices, develop standardised tools, and ensure these innovative designs fulfil their potential to accelerate the delivery of effective therapies to patients.

For research teams planning or initiating an APT, the following steps are recommended:

1. Engage Early with Key Stakeholders

Initiate early discussions with sponsors, investigators, statisticians, data managers, consumers, and ethics committees to align on the trial's vision, design, and operational strategy

2. Conduct a Feasibility Assessment

Evaluate the infrastructure, resources, and expertise required to deliver the APT. Identify capability gaps and develop strategies to address them.

3. Develop a Robust Protocol Framework

Create a detailed master protocol supported by domain-specific appendices. Clearly define the scientific rationale, governance structure, and operational workflows. Engage regulators and ethics bodies early to facilitate alignment and approvals.

4. Build a Cross-Functional Team

Establish a strong cross-functional team with clearly defined roles and responsibilities. Invest in training team members on the unique aspects of APT operations.

5. Implement Flexible Data and Monitoring Systems

Deploy data management and monitoring systems capable of supporting dynamic adaptive features, including interim analyses, domain modifications, and real-time data cleaning to inform trial adaptations.

6. Establish a Communication and Engagement Strategy

Develop a comprehensive communications plan to keep all stakeholders informed of trial progress, adaptations, and results. Prioritise transparency and meaningful consumer and patient engagement throughout the trial.

7. Embed Continuous Evaluation and Learning

Continuously monitor and evaluate trial operations, identifying areas for improvement and implementing corrective actions as needed. Share lessons learned to support the broader APT community to advance best practices.

8. Connect with the APT Community

Engage with ACTA and national and international APT trialists networks to stay informed, contribute to shared learning, and access peer support.

By proactively addressing the operational complexities of APTs and leveraging collective experience of the research community, teams can unlock the full potential of this innovative trial design to deliver faster, more efficient, and more patient-centred clinical trials.

For additional guidance and support, we encourage readers to consult the referenced resources and connect with the growing community of adaptive platform trialists and experts.

Ongoing collaboration and knowledge exchange will be critical to advancing the successful implementation of APTs across diverse research settings.

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Australian Clinical Trials Alliance

Australian Clinical Trials Alliance

Suite 1, Level 2, 24 Albert Road
South Melbourne VIC 3205

T +61 3 8639 0770 ▪ **E** acta@acta.au

clinicaltrialsalliance.org.au

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