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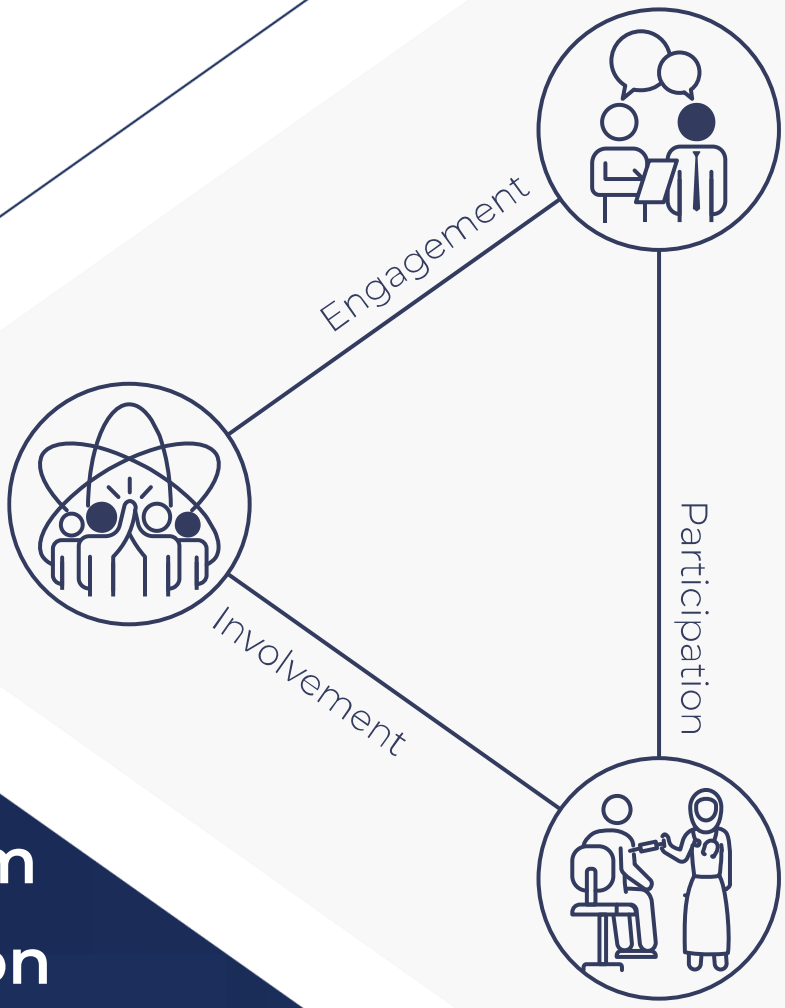

Funding Adaptive Platform Trials: A discussion paper

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Purpose of this document

This document is intended to identify issues and, where appropriate, provide options and recommendations for how adaptive platform trials (APTs) might be funded in Australia. The primary audience is federal and state or territory government agencies that fund clinical trials, including but not limited to the MRFF and NHMRC, although this document also has relevance for philanthropic organisations and the healthcare system more broadly.

This document has been developed by the Innovative Trial Designs Working Group convened by the Australian Clinical Trials Alliance. Although the scope of this working group includes all types of innovative trial design, this document is limited to issues related to funding of APTs. It is acknowledged that there are particular challenges associated with using the existing clinical trial funding models for APTs, by nature of their design features, implementation and longevity.

Issues related to funding that are distinctive for adaptive platform trials

APTs focus on a disease or condition rather than an intervention and permit more rapid generation of evidence than conventional trial designs because a large number of clinical questions can be addressed within a single platform. The flexible designs and use of common control arms are attractive to both researchers and funding agencies but add complexity in terms of trial design, statistical modeling, trial conduct and operations, digital technology and trial governance. Relevant issues include:

- The cost of the '*central infrastructure*' for an APT is more than for a conventional clinical trial. The central infrastructure can be divided into two sequential components comprising *preparatory development* and *ongoing trial execution*. Components that contribute to *preparatory development* include initial design; statistical simulations necessary to understand operating characteristics of the platform; protocol development; and engagement with consumers, sites, and clinicians. Components that contribute to *ongoing trial execution* include subsequent adaptations; protocol amendments for new questions as well as their regulatory and governance approvals, and their implementation; dynamic data flow (i.e. almost real-time data availability); frequent analyses with review by a data safety monitoring board; and multiple "final" analyses that provide a published answer for each question posed. With an APT, the '*central infrastructure*' fixed costs can be distributed over a larger number of research questions, creating efficiency compared to addressing each question in separate sequential or concurrent trials. Currently, substantial preparatory development needs to occur prior to an application to fund a new APT, as this information is necessary for peer-review for funding.
- The higher (absolute) cost of APTs argues for a prioritisation process that supports these designs being applied to health conditions that are common with high public health impact, or high healthcare expenditure, or both. It is also noted that adaptive designs make maximum use of the available sample size and can also have a role in rare disease settings.
- In Australia, there are capacity and capability limitations in relation to some elements of the workforce that are necessary for APTs, including statistical, health economics and data management support. Currently, many APTs utilise overseas statistical support and data management from other countries including USA, Europe, and New Zealand. It is key that APTs funded in Australia build national capacity in APTs for the future.
- Although widely accepted that APTs can be more efficient compared to separate sequential trials that answer the same research questions, the magnitude of efficiency gains and factors that influence efficiency have not yet been quantified.
- International collaboration(s), within the same or a 'federated' platform, can provide a pathway for more rapid evidence generation, capacity building, and dissemination of results. However, international collaboration can also create challenges in relation to funding pathways and equitable access to opportunities and academic credit.

- APTs have the flexibility to add new research questions, over time. Within the research community, an unresolved issue relates to how researchers can have equitable access to submission and acceptance of new questions within an ongoing APT.
- There are challenges associated with developing valid and appropriate budgets for APTs. This occurs for several reasons including:
    - Uncertainty about sample size necessary to reach conclusions. This contrasts with conventional designs in which the sample size is fixed for each question. A fixed sample size makes budgeting easier but comes at the cost of greater uncertainty regarding whether or not a definitive answer to each research question will be achieved.
    - The central costs can be assigned across all questions being addressed by the platform, but there can be uncertainty, particularly during earlier phases, about how many questions will be addressed. It is often the case that an APT commences with a small number of domains (sets of alternative intervention options that are evaluated within the platform) and interventions, and the speed with which additional domains and interventions can be added may be variable.
    - Some APTs utilise a 'per participant' funding model in which there is a 'platform' payment for every randomised participant with supplementary payments for each question (domain) of the APT that the patient participates in. However, this creates challenges with budgeting as there can be uncertainty about the mean number of questions-per-participant.
    - National capacity building in APTs would be facilitated by including a mechanism and funding component for training and mentoring of early career researchers.

Recommendations

We recommend three sequential and integrated funding schemes to accelerate, initiate, implement, and maintain APTs that are led from Australia. Firstly, an *APT Incubator Scheme*, designed to evaluate feasibility, significance, and research impact of a proposed APT. Secondly, an *APT Launch Scheme* to establish the required infrastructure for an APT and initial launch domain(s). Finally, an *APT Expansion Scheme* to fund and sustain established APTs growth in terms of new questions.

1. APT Incubator Scheme

The Incubator Scheme would be a competitive scheme that provides funding for the generation of a mature proposal for the design and implementation of a subsequent APT. Modest funding would be available to support design development and plan implementation, including:

- consumer and end-user engagement
- clinical consensus on prioritisation of research questions and choice of initial interventions within the APT
- statistical simulations necessary to guide the trial design and understand the operating characteristics of the platform
- plans for digital infrastructure and data management
- assessment of feasibility, including site participation and feedback
- trial management and governance structures
- evaluation of potential public health impact

A similar scheme to accelerate the development of APTs has been established in the United Kingdom by the National Institute for Health and Care Research (NIHR) with considerable early success (see https://www.nihr.ac.uk/documents/22104-hta-application-acceleration-award-platform-studies-in-areas-considered-strategic-priorities-commissioning-brief/31088). An expectation would be that an application for the APT Incubator Scheme includes, as one of their milestones, the submission of an application to the APT Launch Scheme.

2. APT Launch Scheme

The APT Launch Scheme would be a competitive scheme that provides funding for core infrastructure and sufficient *launch* domains (i.e., the questions and interventions that will initially be evaluated) to establish an APT. This could be structured to include a pilot phase with a series of 'stop-amend-go' evaluations, and iterative involvement of the funder, or delegate, regarding progress, pre-specified decision points and budget reviews. We recommend a mandatory requirement that if funding is used off-shore for statistical or other support services, it must include training of Australian-based statisticians, data managers and/or trialists in APTs, so that on-shore capacity is developed. Additionally, given the potential longevity of successful APTs, we also recommend that involvement of early- and mid-career researchers is an essential requirement. Furthermore, APTs might also need to demonstrate how they provide equitable access to the APT to a range of researchers within the discipline.

3. APT Expansion Scheme

The APT Expansion Scheme would comprise competitive funding for new questions (domains) to be added into an established APT. The funding would include support for central infrastructure with matching between duration of confirmed core infrastructure support and anticipated duration for the new question(s). This APT Expansion Scheme could include applications to existing schemes that fund clinical trials, and a new scheme for renewal of an established APT, as well as partnership with industry or philanthropy, or both.

Implementation of Recommendations

The following section outlines some principles that might be considered for how these three schemes would be implemented.

Peer-review of APT-specific schemes should include individuals with previous statistical and operational experience of APTs. High quality peer-review likely includes an assessment of the capability of the team to deliver a successful APT, the feasibility and validity of the proposed design, and the appropriateness of the proposed budget. It is acknowledged that because the current community of practice with experience of APTs is relatively small in Australia, this may create issues around the management of conflicts of interest. Accordingly, international expertise should be considered as part of the peer review process.

APTs are of particular interest to industry because of their potential to accelerate, and reduce the cost of, product development. Demonstration of partnership with and capacity to meet industry or regulatory requirements may be a desirable feature, although not necessarily essential, as an evaluation criterion. Similarly, APTs are likely to be attractive to philanthropy and the healthcare delivery system, and partnership with these organisations might also be considered as an evaluation criterion.

The high cost of APTs argues strongly that applications for funding should include both economic quantification of the potential value of the APT in terms of lives improved and healthcare expenditure, as well as integrated health economic evaluation of interventions tested within the APT.

Additional criteria that might be considered in the evaluation of proposed APTs include:

- the incidence and impact of the disease that the APT is proposed to serve
- evidence of variation within standard care and likelihood that such variation influences one or both of patient outcome and healthcare expenditure
- that outcomes can be established in a clinically meaningful manner so that useful adaptation can be implemented
- evidence of support from consumers and relevant clinical groups.

Evaluation of efficiency of APTs over conventional trial designs

As a separate proposal, it is noted that work to quantify the efficiency of APTs over conventional trial designs would be highly useful. This could include evaluation of the cost of answering questions and the speed with which evidence is available within an APT, compared to the counterfactual of evaluating the same questions within a series of conventional clinical trials. This methodological research on APTs could occur via a competitive funding application or as work commissioned by a funder.

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