DCRI **THINK TANKS**

FROM INSIGHT TO ACTION

Making Adaptive Platform Trials Fit to Host Registration Trials of New Drugs and Devices

BACKGROUND AND CONTEXT

The DCRI Think Tank is an interactive meeting that engages diverse perspectives and leadership expertise from across the clinical research ecosystem to address key issues in clinical research, policy, and practice to improve health. On January 29-30, 2025, the Duke Clinical Research Institute (DCRI) brought together experts to discuss the use of platform trials for registration. Despite successes within select therapeutic areas, such as subsets of oncology and COVID, adaptive platform trials have not been widely used as a mechanism for registration. Specifically for this meeting, the adaptive platform trial was defined as a master protocol under which multiple interventions are tested, in one or more indications, where such interventions are enabled to enter or leave the platform based on a pre-defined decision algorithm.

KEY TAKEAWAYS AND THEMES

- **Many of the operational and logistical challenges that are cited as challenges of adaptive platform trials (APTs) are not unique to APTs, but rather endemic to problems in randomized controlled trials (RCTs).** These challenges are more obvious in APTs either because the novelty of the APT is being scrutinized or because a particular challenge, though notably generic to trials, is exacerbated by some of the complexities associated with the launch of an APT.

- **True value proposition and efficiency gains through platform trials need to be quantified by therapeutic area of interest.** Certain areas within oncology and COVID have identified platform trials as a way to improve efficiency and quickly investigate more interventions than traditional RCTs. However, the efficiency gains are highly dependent on the therapeutic area of interest and are not well quantified across other diseases in the clinical research ecosystem. APTs are essentially an expansion of the toolset for evaluation of new drugs and devices but, as with any tool, do not address all problems equally. The value of APTs depends on the specific characteristics of the problem or question at hand and cannot be looked at as a one-size-fits-all.

- **Clear delineation of the benefits, risks, and ways to mitigate risk will promote stakeholders' confidence in using platform trials for registration.** Broadly, the benefits can include cost savings, accelerated decision-making for continued product development, reduced screen failure rates, reduction in sample size in the case of shared controls, and enhanced patient placement in investigational studies for which they are eligible. Each trial will have unique benefits as well as risks. While the risks often depend on the trial phase and design elements, risks for industry partners considering APTs are most prominently related to the loss of ownership or control on the design and data or impact of other arms within the APT by comparison.

- **Early and frequent engagement of key stakeholders when multiple groups are involved contributes to the success (or failure) of platform trials.** Given the complexity of platform trials investigating agents from different industry partners, the importance of engaging industry partners, patient groups, regulatory agencies, operational partners, and academic institutions from the beginning will allow for a more harmonized global vision and smoother, more efficient implementation.

- **Platform trials can be leveraged for registration beyond oncology and COVID.** APTs could be advantageous as part of registration pathways, particularly for interventions to be studied in rare diseases or diseases that are common but require precision approaches to treat each subset of the disease that requires different therapies. Furthermore, there is growing interest in conducting phase 2 studies within a platform trial framework. The uncertainty present at the time of a phase 2 trial may require the comparison of multiple arms, which an APT can handle effectively. Also, platform trials can aid in the creation of a seamless phase 2/3 design where the data from the phase 2 and phase 3 patients are efficiently incorporated into the registration package. This approach accelerates the decision-making process in early-phase drug development and maximizes resource efficiency.

- **Computer simulation needs to be carefully considered when designing a platform trial.** Computer simulations have the potential to de-risk platform trials, but they need to be clear and consistent to make APTs successful and acceptable to broad clinical research standards. In order to achieve this, there needs to be guidelines and standards established for APT simulation to ensure alpha error control and increase the comfort level of sponsors and regulatory bodies prior to running the trial. While there has been previous work done in this area, no standardized and widely accepted simulation guidelines exist for registration-enabling APT designs.

- **Ethical Considerations:** Like all research with human participants, APTs raise important ethical issues. These can be more difficult to address when APTs involve methodological complexities such as the use of simulation to determine study characteristics. However, these difficulties are not insurmountable and there are no reasons to think that APTs are, in principle, inconsistent with the interests of study participants. Additionally, many of the efficiencies sought through the use of APTs, such as the potential for faster development timelines or the involvement of fewer participants to answer the same study question, constitute ethical advantages if they can be achieved in practice.

- **Sponsor selection is an important consideration.** A third-party platform regulatory sponsor, such as a successful nonprofit research or patient advocacy organization, can help engage and balance the interests of potentially competing drug developers and setup infrastructure for the platform trial. Such organizations may serve as an integral foundation for collaborative APT strategy, facilitating regulatory and operational requirements through a carefully constructed framework involving academic, community hospital, and other study site locations, pharma/biotech partners, and regulatory agency input, yielding meaningful APTs and registration-ready data.

ACTIONABLE ITEMS

- **Develop metrics to evaluate value proposition and efficiency.** A set of components should be developed to understand the value proposition for each use case. The components can be developed through updating the CTTI Master Protocol Value Proposition Guide and the examination of specific use cases in order to provide a conceptual framework that companies can use to make a case for or against the platform approach.

- **Quantify economic efficiencies of platform designs.** Economic benefit across the life of APTs needs to be clearly defined. Some areas that are likely to be attractive to industry partners include increased ease in recruiting patients, reducing regulatory burden (particularly if a third party, such as nonprofit research or patient advocacy organization holds the IND), reduction in screen failure rates, and lower cost of getting an asset into the trial and to registration. However, this must be balanced with the increased upfront costs of establishing the platform trial infrastructure.

- **Develop standards for computer simulation.** Standardization of simulation plans will give confidence to industry partners and allow regulators a more informed, streamlined way to evaluate the potential of platform trials in early submission phases. This can be accomplished through the development and distribution of guidelines for trial computer simulation; including a straightforward checklist of elements that need to be included in the simulation plan, definition of base cases, and the range of assumptions underlying the simulations.

- **Create a space for the ongoing discussion of master protocols, including adaptive platform trials, successful and failed use cases, as well as operational best practices and infrastructure that can be leveraged.** During the development of a platform trial, stakeholders will benefit from the creation of a forum to exchange successful practices and lessons learned.

- **Continued education of the research community broadly on master protocols, including adaptive platform trials.** Education through publication of success stories and lessons learned, and continued quantification of efficiencies based on the experience of trialists and stakeholders will support acceptability across industry and the academic community. Furthermore, this may inform further regulatory guidance and encourage further uptake of APT designs by industry and other key stakeholders, ultimately aiding in the advancement of novel treatments in a variety of therapeutic areas.

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