Position Paper: Platform-Adjacent Trials in PRACTICAL
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Platform trials can enhance trial efficiency to accelerate discovery

Platform trials offer distinct advantages over traditional clinical trials to facilitate collaboration and accelerate discovery. By employing a single shared control group for multiple interventional comparisons within one domain, the number of patients required to establish treatment effect for novel interventions is substantially reduced. Alternately, patients can be co-enrolled and co-randomized in multiple domains using a factorial design to estimate treatment effects of multiple non-conflicting/unrelated interventions. Synergistic effects can be evaluated by quantifying interactions between randomized treatment assignment in different domains. These strategies can accelerate discovery by significantly reducing the total number of patients needed to conduct the same number of trials and by allowing multiple trials to run concurrently.

Platform trials facilitate trial conduct through shared, standardized resources

Because specific biological, physiological, and clinical measurements and endpoints may of consistent relevance to a given disease state irrespective of the type of intervention under study (e.g., biomarkers of epithelial lung injury in acute hypoxemic respiratory failure) platforms standardized techniques and resources developed and standardized for one domain (e.g., biobanking) can be leveraged in other domains to facilitate data collection and endpoint ascertainment. The methods and techniques and logistics developed within the platform represent intellectual property of the platform applicable to the study of additional interventions and domains. Because these methods have been developed, there is no need to "reinvent the wheel" with new manuals of procedures etc. with each new trial.

Obstacles to platform trial participation

Despite these advantages, certain considerations may prevent platform trial participation.

Target population
Differences in target population may present an obstacle to platform participation, an issue that can be mitigated by employing broad and pragmatic eligibility criteria for platform trial enrolment in the platform master protocol.

Trial sponsorship and regulatory requirements
A more substantial challenge pertains to regulatory considerations. Investigators, in particular those in industry, may wish to retain direct sponsor oversight of the trial. This is especially the case when bringing a new drug or device to market, and the trial is subject to close regulatory scrutiny. Because interventions and domains in a platform are governed by a master protocol, sponsor oversight is stipulated to the sponsor of the master protocol, often preventing industry or primary investigator from serving as sponsor. For industry partners seeking regulatory

approval, the stakes are very high and the platform lead investigators may not be willing to assume the legal and scientific responsibility for such trials.

The concept of a platform-adjacent trial

Given these obstacles, we propose the concept of a "platform-adjacent" trial that constitutes a partnership between a new clinical trial and the existing platform, where the new clinical trial is not conducted under the platform master protocol, but varying degrees of platform collaboration and cooperation are implemented to accrue advantages for both platform and the independent trial.

A range of scenarios can be entertained, as outlined below. Under all scenarios, the establishment of a collaboration between the platform and a clinical trial partner would be subject to approval by the Executive Committee and Platform Steering Committees of the platform.

Platform-adjacent trial scenarios

PRACTICAL defines platform-adjacent trials as trials that operate apart from the PRACTICAL master protocol but with official endorsement of the Platform Steering Committee. This endorsement affirms PRACTICAL platform support for the trial and enables the collaborating trial to leverage PRACTICAL trial resources for the conduct of the trial.

A platform-adjacent trial can leverage PRACTICAL resources in a number of ways.

Shared document resources
The PRACTICAL platform team has developed a range of documents in support of trial conduct (case report forms, manual of operations, standard operating procedures, protocols).

A clinical trial accepted as a platform-adjacent trial might benefit from use of these documents to develop their clinical trial, leveraging the expertise and efforts of established investigators in the field.

Most of these documents will be made publicly available in any case, available for use by other investigators regardless of whether they request or obtain platform-adjacent trial status.

Shared trial network
The PRACTICAL platform has engaged a large multi-national network of centres. Many of these centres have experience in management of acute hypoxemic respiratory failure and in clinical trials and therefore represent ideal sites for clinical trial participation.

A clinical trial accepted as a platform-adjacent trial could utilize the PRACTICAL network. For example, the PRACTICAL platform could endorse or promote the trial across their network to help recruit sites for the new clinical trial.

Shared analytic resources

PRACTICAL has unique expertise and experience in designing and implementing Bayesian adaptive trials. A clinical trial accepted as a platform-adjacent trial might be able to leverage the PRACTICAL team's experience and expertise to operationalize a Bayesian adaptive trial of their intervention.

Shared trial management

PRACTICAL is operated by an experienced and effective clinical research organization, Ozmosis Research Inc.. Platform-adjacent trials operating on the PRACTICAL platform network could benefit from the established relationships between trial management and participating sites by utilizing Ozmosis Research Inc. as the clinical research organization for their trial.

Stipulations for platform-adjacent trials

1. Criteria for trials to be considered for platform-adjacent status
    i. Studying patients with acute hypoxemic respiratory failure
    ii. Platform Steering Committee generally supportive of clinical trial question and design (no formal assessment process but no areas of concern identified on review of protocol synopsis)
    iii. No anticipated issues with co-enrolment or any important conflicts or competition with active PRACTICAL domains

2. Process for obtaining platform-adjacent status
    i. The PI(s) for the trial seeking platform-adjacent status submits a request in writing to the Executive Committee. This request will outline the proposed collaboration scenario based on the options outlined above and provide the protocol synopsis for the planned trial.
    ii. The Executive Committee will screen the request to ensure that it meets eligibility criteria. And if the proposal is potentially suitable for endorsement, then the Platform Steering Committee will have an opportunity to review the proposal and identify any concerns or limitations preventing endorsement. The Executive Committee will integrate feedback from the Steering Committee to make final decisions about the platform-adjacent trial.