MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Executive Summary

Advancing Pediatric Platform Trials:

Streamlining Development, Maximizing Impact

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When children have serious or life-threatening conditions, they should receive the best treatment available. However, children do not have the same access as adults to many therapies for these conditions, because drug development for children has lagged behind that for adults. The pediatric market is small, and medicinal products are often tested in children after approval for adults. Therefore, the United States (US) and European Union (EU) have required new drugs to be tested in children, but it often takes a decade or more after a drug has been licensed for adults until it is approved for use in children. Platform studies could speed the approval of safe and effective medicines for children, particularly when multiple companies collaborate.

In its simplest form, a single-disease platform study might contain one shared control arm and multiple test arms, each of which tests a different treatment. Meeting similar eligibility requirements, enrolled participants are randomly assigned to each arm. Once a platform trial is established, it could run almost continuously at multiple sites, with new treatment arms being added as new drugs become available. Unlike single clinical trials, the shared infrastructure of a platform trial exists and need not be built anew for every new drug. Platform trials appear to offer improved efficiency, including faster recruitment, as fewer participants are assigned to the standard-of-care or placebo arm, which is an attractive feature to participants. They also offer increased flexibility, making it relatively easy to add or discontinue arms while continuing other arms of the platform. Platform trials with multiple test arms can achieve the same power with a smaller sample size than multiple individual trials. Within some constraints, each arm can be customizable, and the size of an arm can vary. The cost-effectiveness of a platform trial is increased by testing multiple molecules simultaneously.

Challenges to Pediatric Platform Trials

Despite their advantages, pediatric platform trials can be difficult to initiate and conduct for industry, regulators, and investigators. Intellectual property (IP) considerations impact companies' willingness to participate in platform trials, as multi-company platform trials require greater transparency than standard, single-company clinical trials. The IP and confidentiality concerns become even more complex if the tested compounds are at different stages of development in adults, as the economic value of these drugs is linked to the adult market. Indeed, confidentiality, IP, and other legal and operational concerns are often harder to surmount than the scientific ones.

There are risks related to the timing of a platform trial in the life cycle of a new compound. Initiating a pediatric trial before the adult trial is complete carries the risk that, years into the

study, results in adults will be negative. Starting too late risks patent expiration, a time when company financial incentives attenuate. This is specific to pediatric exclusivity and, of course, only arises in cases where attaining pediatric exclusivity is a possibility.

Regulatory review can be unpredictable, even when adding an arm to an existing platform study. While the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) representatives both may wish to smooth the path to platform trials, companies are reluctant to revise pre-approved protocols in order to join platform trials, which subjects them to additional regulatory review. The extended time required for regulatory review is a major impediment and risk factor for industry, which strives for efficient, predictable, and timely trial approval and initiation.

Finally, academic researchers do not participate in regulator-industry interactions, creating gaps in communication; the long-time course to publication can be a disincentive to academic researchers.

At the meeting, one patient advocate noted that patients and parents are willing to take greater risks than regulators, companies, or anyone, "for any chance of survival."

Pediatric Major Depressive Disorder (MDD)

Refractory Pediatric MDD presents challenges that are not specific to platform trials. Pediatric and adult depression have similar neurobiology and similar drug targets, but the disorders differ on a phenomenological level, and treatments that are approved in adults often fail to be effective in children. Teenagers with MDD tend not to judge their mental health based on the same parameters used by the raters, and younger children can have a very different presentation than adolescents. Additionally, there are differences between outpatient and inpatient MDD patients. Perhaps as a result, the standard rating scale for child depression does not do an optimal job of capturing the symptoms that may change secondary to a trial intervention.

The high placebo response in MDD in children is a particular concern, and is often the reason that single, stand-alone trials fail to reject the null hypothesis. While a biological understanding of the placebo response is still unclear, it needs to be at the lower end of the observed range to obtain an informative trial outcome. Trial inclusion and exclusion criteria, however, often skew the enrolled population towards those with less severe disease, increasing the placebo response. In short, current methodologies for studying MDD are not ideal. At the same time, sponsors are unwilling to invest in developing new validated methods, which stymies advancement in the field.

The MDD working group committed to three courses of action: (1) initiating a pre-competitive effort to improve trial design, including the development of better assessment tools and simulation studies using existing trial data; (2) engaging a neutral convener to organize stakeholders and establish a roadmap for translating pre-competitive work into a future platform trial; and (3) organizing a series of work packages (e.g., trial design recommendations, endpoints, etc.) for enabling future feasibility of a platform trial.

It was noted that at least 24 companies are working on therapies for MDD, all of which will need to be evaluated in children, so optimizing these studies should be an immediate priority. Regulatory agencies may need to offer a financial or other incentive for industry to participate in this effort, but once resolved, these drugs should be evaluated in a platform trial.

Pediatric Oncology

In the US and internationally, oncology has experience conducting pediatric platform trials; however, significant limitations have been identified in our current systems. For international trials, navigating the multi-layered approval process necessary to operationalize a global clinical trial of a new therapy early in development is a significant problem. In the US, there are cost and efficiency gains with using the infrastructure created by the National Cancer Institute (NCI, NIH) and specifically the Children's Oncology Group (COG). However, the NCI's policies and positions on data-sharing, trial design, and pharmacovigilance make many international and industry collaborations difficult.

Scientifically, researchers noted an increased move towards characterizing pediatric cancers based on molecular markers. As the identified biomarkers grow in number, the cancers become more narrowly defined, as do their treatments, making it harder to recruit sufficient trial participants for what are already rare diseases.[1] By requiring fewer participants than a series of standalone trials, platform trials would make it easier to test multiple treatments for a rare pediatric cancer.

The oncology working group committed to three courses of action: (1) establishing a forum and working group to continue this conversation, with all necessary stakeholders and decision makers; (2) engaging in process mapping for platform clinical trials in oncology, with a focus on addressing the core elements in contracts that cause problems; and (3) designing an example or model of a disease-specific or indication-specific platform trial that can support regulatory requirements (Paediatric Investigation Plan [PIP] / initial Pediatric Study Plan [iPSP]) and potential marketing authorization of assets derived from industry for pediatric oncology.

Pediatric Multi-Drug Resistant Tuberculosis (MDR-TB)

The current treatment for drug-resistant tuberculosis relies on roughly half a dozen drugs that are taken for up to two years. While newer regimens are shorter and have fewer side effects, they have only been evaluated for efficacy in adults. Pediatric drug trials for MDR-TB are hampered by long delays due to limited funding, lack of sufficient pediatric trial sites in settings with MDR-TB, and the operational inefficiencies of doing standalone trials, among other factors. The pipeline of drugs in development for TB has improved over the last

[1] Common molecular biomarkers open the way, however, to studies that group participants purely by molecular markers rather than histology, so-called "basket trials."

decade, but in comparison to cancer and MDD, and particularly given the burden of disease, it remains insufficient and insubstantial. Despite these challenges, the MDR-TB group concluded that an MDR-TB platform trial was worth pursuing because of the significant efficiencies it would bring.

MDR-TB has an advantage over the other two diseases, in that efficacy can be extrapolated from adults to children, with the exception of severe forms of extrapulmonary tuberculosis (EPTB) and TB meningitis. This should enable older children to be included in adult Phase III trials, and it places the emphasis of pediatric trials on Phase I/II pharmacokinetics (PK) and safety. However, there is an urgent need to increase the capacity to conduct pediatric MDR-TB trials. Currently, there are fewer than ten sites enrolling children with MDR-TB in clinical trials and fewer than 100 children enrolled in any calendar year. There are multiple efforts geared at increasing global capacity for pediatric drug-resistant (DR)-TB and MDR-TB trials.

MDR-TB is distinct in its dependence on an especially broad range of institutions. Funding for trials relies heavily on philanthropy and/or government funding, and every drug currently in development is the product of a consortium composed of academics, industry, non-profit organizations, and others. Research is global, necessitating the involvement of the regulatory agencies of multiple countries. In most of the world, TB is handled programmatically by public health agencies, so trial sites and their leadership need to connect with these programs to help them to direct patients to consider participation. Often, however, practical challenges prevent participation: the distances to a trial site, for instance, are far, and transportation is difficult. At the level of individual sites, practitioners require the expertise and capacity to engage in research, and there should be outreach to community members who can find patients and encourage them to participate. In order to keep trial sites active in research, expertise and connectivity must be maintained when a project ends.

The MDR-TB working group committed to three courses of action: (1) pursuing a global platform trial focused on Phase I/II PK and safety evaluations, taking advantage of the ability to extrapolate efficacy from adult trials; (2) engaging public and philanthropic funders to support long-term infrastructure and operational sustainability; and (3) expanding and strengthening global trial site capacity, including building partnerships with national TB programs and community-based referral networks to ensure consistent enrollment and retention.

Conclusion

There was strong support for pursuing pediatric platform trials in all three disease areas, albeit with very different aims. While oncology is conducting Phase III registrational trials, MDD is considering pre-competitive and non-competitive research aimed at improving the conduct of trials prior to developing a platform, and MDR-TB is discussing Phase I/II trials focused on PK and safety.

There is a need for capacity-building for both MDR-TB and MDD, albeit at different levels. Consistent across all disease areas is the need for a neutral convenor to maintain momentum and forward progress. Given the significant differences among the three disease areas, each therapeutic area or disease type should pursue their own goals in the next phase of the work.

Recommendations

This workshop is a first step. The next is to develop a process map, in which each element of the pediatric clinical trials process is analyzed separately, with the goal of optimizing these elements to speed up the trial process. Every stakeholder will need to examine their own processes and then be prepared to share them for constructive discussion. Regulators, academics, and representatives of industry who were present all agreed to participate in this activity. The planning committee and each disease subgroup will be reconvened. Although each disease area will need to complete its own process map, there are common challenges, strategies, and solutions, and the three disease groups will benefit from continuing this conversation together.

There also needs to be a more general conversation between the regulatory agencies and a broad set of companies to introduce efficiencies and more thoughtful, pragmatic approaches in the way companies engage with regulatory agencies, a challenge that is even more acute in the domain of platform trials. When industry representatives meet with regulators to negotiate a PIP or iPSP, there should be a way for academic representatives to participate in the scientific discussion.

For this effort to succeed, all stakeholders need to be engaged from the outset. This means expanding the square of academia, industry, regulators, and governmental and non-profit funders to a pentagon or hexagon that includes patient advocates and, in some cases, physicians/community providers. Regulators from international agencies beyond the FDA and EMA should be engaged early in the process.

"Time and again children died, and we wrote legislation to protect adults, based on the deaths of children. [As a result] most labels say, 'not safe for children.'" – *Academic Investigator*

"On the one hand, there are so many drugs and too few patients. But on the other hand…we need more drugs that we really think are going to work." – *Industry Representative*

"It's a spurious argument to say, we'll only give you the money if it's going to be used for filing. We're helping industry answer the question…the investment shouldn't depend on whether the outcome is positive or not." – *Academic Investigator*

"We need to think outside the box…We've boxed ourselves in on implementation so much that we've forgotten what the laws actually say." – *Industry Representative*

"Risks that we are willing to take may be different from those of the regulators and companies. Parents will move heaven and earth for any chance of survival." – *Patient Advocate*