MULTI-REGIONAL CLINICAL TRIALS

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

Advancing Pediatric Platform Trials:

Streamlining Development, Maximizing Impact

Washington, DC

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MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

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Introduction

On October 29 and 30th, 2024, the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) hosted a hybrid meeting to examine the potential benefits, challenges, and opportunities of platform trials for pediatric populations. In addition to general issues considered, three diseases – pediatric oncology, major depressive disorder (MDD), and multi-drug-resistant tuberculosis (MDR-TB) – were chosen as areas of focus, each of which represents a different condition, epidemiology, setting, therapeutic challenge, and patient population, chosen to illuminate different potential approaches and solutions. This report is a summary of the meeting proceedings.

Executive Summary

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 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

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

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*

Background

Children do not have the same access as adults to many of the medications used to treat serious and life-threatening conditions. Pediatric drug development has lagged behind that of adults and, as a result, many available therapies are inaccessible to children or can only be accessed off-label, with uncertainties regarding optimal dosage, toxicity, and efficacy. To increase children's access to safe and effective medication, the United States (US) and the European Union (EU) have instituted requirements for new drugs to be tested in children where appropriate (Box 1). Under the Pediatric Research Equity Act (PREA), the US Food and Drug Administration (FDA) can require new drugs to be tested in children after they have been licensed for use in adults. Under the Paediatric Regulation, the European Medicines Agency (EMA) requires drug manufacturers to ensure that studies will be performed in children. However, despite these regulations, conducting pediatric studies is expensive for drug manufacturers and is rarely a commercial priority.

Platform studies offer substantial efficiencies that could speed up the approval of safe and effective medicines for children, particularly when multiple companies collaborate on a single study. Use of a shared control arm lowers the percentage of participants in the placebo group, and statistical methods that borrow across test arms add inferential efficiencies. But platform trials have challenges of their own, some of which are specific to pediatric populations.

To explore how platform trials evaluating multiple assets from different pharmaceutical companies can speed the delivery of innovative therapies to pediatric patient populations, the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) hosted a two-day workshop in partnership with industry sponsors, clinical researchers, patient advocates, regulators, legal experts, non-profit foundations, government representatives, and statisticians. The goal of this effort was to identify knowledge gaps and practical challenges that impact clinical trial planning and execution of platform trials for children, and to recommend actionable approaches to address those issues.
Meeting participants formed three breakout groups to explore the potential applications of platform trials in major depressive disorder (MDD), multi-drug-resistant tuberculosis (MDR-TB), and pediatric oncology. These three indications were chosen to capture different challenges and opportunities related to pediatric drug development, and collectively, they inform other therapeutic areas. The Workshop Planning Committee, consisting of a multi-stakeholder group of experts, guided the development of the workshop across each priority disease area. The workshop agenda is in Appendix 1, and the list of participants is in Appendix 2.

Introduction and Charge to Participants

Despite decades of effort, said Lisa Koppelman (MRCT Center), it is still challenging to conduct pediatric clinical trials. The MRCT Center launched its pediatric program several years ago to support efforts to ensure children can access evidence-based medicines and treatments by promoting clinical research in children.[2] The MRCT Center convened this workshop as a logical next step in the overall pediatric-focused effort to bring together individuals with the necessary expertise to solve the problems that interfere with accomplishing this goal. "This group knows the pain points and challenges of platform trials," said Ms. Koppelman, and while many of these challenges are not unique to pediatrics, introducing children into the equation creates an extra layer of complication.

Platform trials have the potential to speed up the delivery of safe and effective medicines to children, said Ms. Koppelman. Their utility was highlighted during the Covid-19 epidemic, when platform trials enabled multiple products to be investigated simultaneously. Additional efficiencies may be derived from platform trials' shared infrastructure, pre-approved protocols, cost savings, and Bayesian borrowing (to improve statistical significance). Furthermore, platform trials can optimize risk exposure through a shared control arm, a centralized system of data capture and oversight, and the ability to provide earlier access to treatments. But platform trials also bring new challenges, she noted. These include maintaining congruency across multiple arms, attributing adverse events appropriately and commonly, sharing data, managing companies' confidential information, and the potential for overinterpretation of findings.

Each of the three disease areas selected for this workshop exemplifies a particular challenge. Research on Multi-Drug-Resistant Tuberculosis (MDR-TB) must contend with resource-limited environments and limited market incentives. Clinical trials for pediatric oncology take an inordinately long time to complete. Major Depressive Disorder (MDD) has been poorly studied in children and faces multiple study design challenges, including selection of participants, variable diagnostic considerations, and the placebo response.

> "Protecting children and adolescents means that we include them in research…Further, young people have a voice, and that voice must be considered, heard, and reflected throughout product development and the clinical research lifecycle, including platform trials." – *Lisa Koppelman*

[2] See https://mrctcenter.org/project/promoting-global-clinical-research-in-children/ (accessed on December 18, 2024).

Ms. Koppelman outlined the goals of this workshop, as follows:

- Develop the principles, ethical foundations, and operational considerations upon which platform trials can be pursued for studies of pediatric investigational products.
- Identify knowledge gaps and practical challenges that impact clinical trial planning and execution.
- Recommend actionable approaches to address these and other identified issues.

Three keynote speakers laid a foundation for the working group deliberations. After two days of meetings, these groups reconvened to report back on their efforts and to chart a course forward.

Laying the Foundation: The Keynote Presentations

Platform Trials for Children: History, Common Goals, and a Path Forward

A Brief History of Drug Development and Children

Dr. Danny Benjamin (Distinguished Professor of Pediatrics, Duke University Medical Center; Chair, Pediatric Trials Network of National Institute of Child Health and Human Development) opened his keynote address with a stark bit of history highlighting landmark steps in the regulation of drugs in the US that were driven by the deaths of children. The US FDA was established in 1906 in response to the deaths of 13 children who had been injected with horse serum containing diphtheria antitoxin. In 1937, 107 people, including many children, died after being administered sulfanilamide dissolved in ethylene glycol, prompting legislation that required drugs to be tested for safety in animals.[3] And in 1962, after thalidomide killed or maimed over 10,000 children, additional legislation required that drugs be tested for both safety and efficacy.[4] In the decades that followed, most drugs have only been clinically tested in adults. "Time and again children died, and we wrote legislation to protect adults, based on the deaths of children," said Dr. Benjamin. As a result, by the end of

[3] See https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-ii-1938-food-drug-cosmetic-act (accessed on December 31, 2024).
[4] See https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-iii-drugs-and-foods-under-1938-act-and-its-amendments (accessed on December 31, 2024).

the 20th century, most of the licensed drugs did not have data addressing dosing, safety, or efficacy for children; 90 percent of medicines were not studied in neonates.

Definition of a Pediatric Platform Trial

For the purpose of this meeting, Dr. Benjamin defined a platform trial as a clinical trial where multiple treatments or diseases are evaluated within the same protocol. This could include testing one therapy on multiple diseases (basket trial) or testing multiple therapies on a single disease (umbrella trial). A pediatric platform trial that is under an investigational new drug (IND) application must comply with FDA regulations regarding the maintenance of electronic records[5] in the US and/or with EMA regulations in the EU. For most products being tested, there is already a first indication in older humans, and the purpose of the trial is to evaluate that molecule in younger humans. The process of carrying out pediatric platform trials is still developing, said Dr. Benjamin. "We will eventually work towards…developing new drugs for children," but it will take several stages to get there, he said.

BPCA Exclusivity Program: An Incentive to Obtain Drug Data in Children

The Best Pharmaceuticals for Children Act (BPCA)[6] was passed in 2002 to encourage pediatric investigations aimed at informing the labeling of drugs for use in children. Under the BPCA, drug manufacturers can extend their period of exclusivity when they voluntarily conduct pediatric trials of a product. Prior to the passage of BPCA, said Dr. Benjamin, a drug as common as ampicillin had been given to hundreds of thousands of premature neonates, for whom there was a complete absence of data.

By 2006, at least 115 molecules had some data submitted to the FDA under BPCA, said Dr. Benjamin. Of these drugs, 100 had undergone labeling changes and 37 had substantially different dosing recommendations, with the most substantial changes in children under two years old (although few studies included neonates). Noting that all drugs are toxins, and that one-third had significant dosing changes, this work provided clear evidence "never to extrapolate dosing" based on adult data, he said. However, while children should not be treated as small adults, "it is also true that children are not Martians," said Dr. Benjamin.

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[5] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application (accessed on December 18, 2024).

[6] See https://www.nichd.nih.gov/research/supported/bpca/about (accessed on November 6, 2024).

Some types of drugs are easier to extrapolate than others, and the three topic areas covered in this workshop differ in their approaches to extrapolation.

The Pediatric Trials Network (PTN): Informing Dosing for Children

Dr. Benjamin recalled treating a baby with complicated meningitis early in his career and guessing the dose of medication. "Tired of guessing," he began a study of commonly used medicines in neonates, banking each baby's blood and analyzing it to determine the drug dose. He initially focused on antibiotics and antifungals that were being used to treat opportunistic infections in the Neonatal Intensive Care Unit (NICU). Consulted about a baby with a life-threatening fungal infection, Dr. Benjamin recommended increasing the antifungal dose ten-fold, citing data from his study. "This baby went out of the NICU in a car seat. Hearing intact, vision intact…this boy is in high school," he said. Based on this experience and dosing data from the first drugs under study, he concluded that "we're doing the right thing, and we need to do it for every molecule that's used as an anti-infective in the nursery."

> "The products were available, but because we didn't know the dosing, we were going to take her baby off life support." – *Dr. Danny Benjamin*

Since its launch in 2010, the Pediatric Trials Network (PTN)[7] has studied 150 molecules in babies and/or children, said Dr. Benjamin. Much of this work has been made possible by several large platform trials. PTN has 300 participating sites and is studying these drugs in emerging populations, including neonates, extracorporeal membrane oxygenation (ECMO), breastfeeding, and obesity. Other examples of PTN platform trials include a safety study of three different commonly used antibiotic regimens in premature infants;[8] the long-term safety of antipsychotics; and, in an international collaboration, the use of immunomodulators for treatment of Covid-19 pneumonia. PTN studies have led to two dozen labeling changes to date, said Dr. Benjamin.

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[7] See https://pediatrictrials.org (accessed on November 6, 2024).

[8] Smith MJ, Boutzoukas A, Autmizguine J, Hudak ML, Zinkhan E, Bloom BT, Heresi G, Lavery AP, Courtney SE, Sokol GM, Cotten CM, Bliss JM, Mendley S, Bendel C, Dammann CEL, Weitkamp JH, Saxonhouse MA, Mundakel GT, Debski J, Sharma G, Erinjeri J, Gao J, Benjamin DK Jr, Hornik CP, Smith PB, Cohen-Wolkowiez M; Best Pharmaceuticals for Children Act–Pediatric Trials Network Steering Committee. Antibiotic Safety and Effectiveness in Premature Infants with Complicated Intraabdominal Infections. Pediatr Infect Dis J. 2021 Jun 1;40(6):550-555.

Lessons Learned from the PTN

PTN studies offer numerous lessons regarding the successful conduct of platform trials in children, said Dr. Benjamin, who highlighted the following:

1. Cost-effectiveness is increased by testing multiple molecules at the same time. The Pediatric Opportunistic PK Study (POPS1) trial, begun in 2010, needed an extensive pediatric-specific site infrastructure. By platforming 20 products, Dr. Benjamin and colleagues obtained sufficient funding so that each site could support full-time staff.
2. Input is needed from key stakeholders to inform site selection, evaluation, activation, and training.
3. Exercise "flexibility, flexibility, flexibility" in bioanalytical procedures and methods, said Dr. Benjamin. For example, where drugs differ widely in PK, it may be necessary to employ a range of sampling schemes.
4. Platform studies can be designed as "choose your own adventure," enabling participants to select which treatment arm to enroll in.
5. Diversity in sites leads to diversity in participants, and this needs to be accounted for in study design. The goals of the study need to be aligned with the study setting (for example, inpatient vs. outpatient sites in an antipsychotic study).
6. Platform studies need the flexibility to pivot midstream.
7. In pediatric studies, a single "site" may consist of 20 sub-sites, each one needing training and coordination.
8. The current state of the Electronic Health Record is "not good," said Dr. Benjamin. Medication administration and timing are not rigorously recorded. Therefore, study sites require training to maintain high-quality data.

"The 3 well-known stages of research:

1) no one can do this,

2) someone should do this,

3) we have always done this.

My prayer for you is that five or ten years from now someone in the back will say, 'MDD, that's easy, we've always done that.'" - *Dr. Danny Benjamin*

Box 1.

US and EU regulations aimed at increasing children's access to safe and effective medication.

United States

Best Pharmaceuticals for Children Act (BPCA)[9] – 2002

BPCA grants an additional six months of patent exclusivity when drug manufacturers perform pediatric studies to improve labeling for patented drugs used in children. BPCA also authorizes the National Institutes of Health (NIH) to prioritize the testing of off-patent pediatric drugs and submit the data for labeling changes.

Pediatric Research Equity Act (PREA)[10] – 2003

PREA requires sponsors of new drug applications (NDAs) or biologics license applications (BLAs) to assess formulations of these drugs in pediatric patients. This requirement is waived for drugs with a non-pediatric-relevant indication or an orphan designation. Under a 2012 modification of PREA, sponsors planning to submit an application for a drug subject to PREA are required to identify needed pediatric studies and submit an initial pediatric study plan (iPSP)[11] early in development.

Research to Accelerate Cures and Equity (RACE)[12] Act – 2017

RACE requires all new adult oncology therapeutics with relevance to pediatric cancer to be studied in children. This act closed the "orphan drug loophole," which had exempted over 70 percent of new oncology drugs from the requirements of PREA due to an orphan designation.

European Union

EU Paediatric Regulation[13] – 2007

[9] See https://www.nichd.nih.gov/research/supported/bpca/about (accessed on November 12, 2024).
[10] See https://www.congress.gov/bill/108th-congress/senate-bill/650 (accessed on December 17, 2024).
[11] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended (accessed on December 31, 2024).
[12] See https://www.congress.gov/bill/115th-congress/house-bill/1231 (accessed on December 31, 2024).
[13] See https://www.ema.europa.eu/en/human-regulatory-overview/paediatric-medicines-overview

The Paediatric Regulation aims to ensure that medicines for children are of high quality and properly researched. It established the Paediatric Committee (PDCO), which authorizes companies to study drugs in children as part of a Paediatric Investigation Plan (PIP).[14]

Intellectual Property Considerations in Platform Trials

Two Types of Intellectual Property (IP): Patents and Know-how

Dr. Melissa Rones (Partner, Ropes & Gray LLC) described how platform trials impact companies' intellectual property considerations, focusing on two categories of intellectual property: patents and confidential information (also called "know-how"). A patent is a grant from the federal government conferring "limited exclusivity," i.e., the right of the patent owner to exclude third parties from practicing the patented invention for a limited period of time. Patents are registered intellectual property that can be licensed, bought, and sold. Importantly, a patent is "the quid pro quo for disclosure," said Dr. Rones; it confers a limited monopoly to the owner in exchange for revealing how to make and use the invention. The intent of patents is to encourage innovation by providing incentives for disclosure. However, patents only protect against activities within a particular jurisdiction for a particular time period; pursuing a patent is expensive and time-consuming and requires a willingness to disclose.

The "flip side of disclosure" is trade secrets, or know-how, said Dr. Rones. Know-how consists of confidential information that has economic value and is kept secret, like a "special sauce." Know-how can be kept secret for longer than patented information, and it does not require any registration. "The power of know-how is in controlling its confidentiality and dissemination," she said, and this control of information could be for a limited amount of time – say, long enough to provide a head start in the marketplace – or indefinitely. Know-how may be protected by state and federal trade secrets laws or by contractual agreements.

[14] See https://www.ema.europa.eu/en/human-regulatory-overview/research-development/paediatric-medicines-research-development/paediatric-investigation-plans (accessed on December 17, 2024).

Importance and Role of Intellectual Property in the Development of Drugs & Biologics

Companies that manufacture drugs and biologics employ teams of lawyers who monitor innovation on an incremental basis in order to maintain control over their patents and know-how, said Dr. Rones. The stakes are high, as IP barriers influence investment and impact the time when the company will lose its exclusive right to an invention; the high stakes favor a high level of risk aversion that may influence cooperation in platform trials. Patents may be filed to protect the compound itself, along with initial method(s) of use, preferred formulations, or new uses. Importantly for this workshop, she said, patents may protect specific dosing regimens, patient subpopulations, or strategies for reducing side effects. Where a company is in its patent filing strategy may influence how it manages IP risks.

IP Considerations in Pediatric Platform Trials

Typically, the primary market for a new drug is among adults, said Dr. Rones. Companies may pursue pediatric approval to satisfy regulatory requirements or to serve patients, but the pediatric market is unlikely to drive profitability. Added to this, platform trials may require a greater level of transparency between independent innovators than standard clinical trials, risking control of the resulting IP and disclosure of know-how. This creates a high-risk/low-reward scenario. Contracts can mitigate the IP risks, but "transaction costs are high, and uncertainty remains," feeding into risk aversion, she said.

Dr. Rones described some of the particular IP concerns that attend platform trials. For standard clinical trials, there are standardized confidentiality and non-use provisions that can lessen concerns about the risks to IP. Even in the case of combination therapy using drugs from multiple sources, "there is an alignment of interests" among the innovators: either all profit or none does. In contrast, platform clinical trials involve multiple innovators without offering a win-win outcome. Trial design may require a heightened level of transparency among innovators, which could impact ownership of new inventions that emerge as a result of the trial. IP issues are made even more complex if the various compounds are at different stages of development or commercialization in adults. Maintaining exclusive ownership of one's invention is critical, she said.

Nonetheless, pediatric platform trials create "enormous opportunity" for managing trial cost and access, achieving economies of scale and scope, and advancing patient care, said Dr. Rones; "so how can we balance the IP concerns…and still get it done?"

Defining a Solution Space: An IP Risk Matrix

On the one hand, platform clinical trials represent an effective tool for innovators to fulfill their regulatory obligations while advancing important pediatric studies. On the other hand, IP concerns create barriers to participation. Dr. Rones suggested defining a solution space to bridge this gap. This solution space could take the form of a matrix that treats each IP concern individually and identifies an individual risk continuum for each concern. For example, there is a continuum of risk that applies to different stages of a compound's development or commercialization in adults. Different risk levels are also inherent to different compound modalities, the degree of similarity of compounds being tested, features of clinical trial design, the necessary level of transparency, size of the in-house risk management team, stage of the compound's IP development portfolio, and company culture, among other considerations, said Dr. Rones. "I've counted 30 dimensions of the matrix," said one participant.

Dr. Rones suggested that her proposed risk continuum might identify scenarios where IP concerns would be least likely to create a barrier to participation in pediatric platform clinical trials. For example, less risk might adhere to compounds that are at a later stage of development or already commercialized in adults, to formulations with longer periods of regulatory exclusivity, or to trials involving compounds with differing targets and/or mechanisms of action. Risk might also be lowered by delegating the clinical trial design to an independent third party, by limiting the need to share confidential information, or by filing secondary patent applications relating to trial outcomes before commencing the trial. Each company could aim to identify scenarios where the level of IP risk is sufficiently mitigated to allow it to engage in platform trials with other innovators. Companies could use an IP risk matrix as a tool to facilitate participation in pediatric platform clinical trials, starting with lower-risk opportunities.

Panel Discussion: How Can Platform Trials be Sped Up and IP Risks Mitigated?

How Can PREA-Compliant Trials be Sped Up?

Researchers expressed frustration with the slow pace at which companies undertake pediatric trials to meet PREA requirements. The legal challenges remain long after the scientific methodology has been worked out, said Dr. Benjamin; "if you wait for the

lawyers…it will take an eternity." He recommended starting with a draft protocol and candidate molecules before engaging lawyers. Cost savings are the major incentive for doing a platform trial, he said, but "you won't know the cost savings until you have the design…[so] get the protocol in first." "That's where, from an organizational perspective, having a way to assess the risk…is going to be helpful," added Dr. Rones.

Dr. Rones advocated for starting with low-risk opportunities, when drugs have already been developed in adults and there is minimal IP risk combined with clear upsides, such as cost savings and advancing pediatric care. However, she discouraged the FDA from using PREA to incentivize companies to conduct platform trials earlier, calling it a "disincentive" to push trials before the IP is sufficiently mature and while internal know-how is at stake. "You get them done sooner by [gaining] experience with getting them done later…in settings where the risk is lower from an IP perspective," she said.

The FDA is interested in getting drugs approved for children who need them, in a timely way, and enabling patients to access the drugs, said one participant**.** For companies to develop an efficient pathway to get there once the timing is right seems reasonable, she said, but "once you've decided that the timing is right, don't take ten years to get the contracts negotiated and the trial up and running." An **industry representative** suggested assessing the IP risk earlier in order to maximize the reward of patent exclusivity, "so the timing [of the reward] doesn't fall off the scale."

Since the U.S. Research to Accelerate Cures and Equity (RACE) was passed to incentivize companies to perform pediatric oncology drug trials, "anecdotally, companies are talking to us earlier," said an academic investigator. However, he added, academic investigators end up taking on the risks when they develop concepts that "die for reasons that we can't control." He was hopeful that a risk matrix, coupled with a standard contract, might help speed up this process. Dr. Rones cautioned that the risk matrix concept does not lend itself to standardization because companies have different priorities. Some standardization is needed to reduce transaction costs and timelines, but it will only come from experience, she said.

"I'm not suggesting the wait needs to be out to the end of the patent term…we don't operate in a zero-risk environment. But how successful you were will only be evaluated in hindsight. The problem is uncertainty; some companies have to be first movers." – *Dr. Melissa Rones*

When the FDA first provided guidance for extrapolating drug efficacy, safety, and dosing to pediatric populations, it described three categories of similarity: full, partial, or none, said one participant. Only later was the level of similarity described as a continuum.[15] In the same way, she suggested, it might be preferable to build a framework for pediatric platform trials starting with three sample conditions – easy, medium, and impossible – rather than building a continuum from the start.

Do Pediatric Platform Trials Carry Risks for the Adult Market?

The economic value of IP is almost always linked to the adult market, said one participant, who suggested that increasing drug testing in children, which is the focus of this workshop, has the potential to reduce a drug's value if it is de-prioritized in adults due to a disappointing performance in a pediatric platform trial. An academic investigator countered that this scenario is entirely hypothetical. Among drugs studied since the establishment of the BPCA, "the number of times where we've actually seen a big difference [between adults and children] in survival or safety for molecules in the same class with the same disease is a slim fraction," he said, adding that this risk was unlikely to be any higher in a platform trial than in a standard clinical trial using the same study design. "That is probably true…but it will not prevent companies from worrying," said another researcher.

Platform Trials Present Different Considerations for Patients

Participants considered the various ways patient preference can play out in platform trials that differ from a single drug study. If patients don't get their drug of choice, or if their arm fails, "can they jump into another?" asked one. "At the end of the day, it's all about enrolling the trial…what is the benefit to the patient of this versus a single study?" In Dr. Benjamin's experience, platform trials offered cost savings and efficiency overall, but there was "potential for winners and losers across the platform." The site is the strongest predictor of enrollment in his studies. He doesn't typically see a difference in enrollment between arms. However, in rare cases, parents may select one arm, causing it to fill up before the other arms.

[15] See https://www.fda.gov/media/161190/download (accessed on November 12, 2024).

There are elements to platform trials that are more attractive to patients, such as the reduced likelihood of being in a control group, noted one participant. Preference for one arm over another can be dealt with in several ways - for example, by first enrolling patients in the trial and then randomizing and consenting to the arm to which they are assigned. As an incentive, patients who declined to participate after being assigned to an arm would have to wait a certain amount of time to be re-randomized.

Timing Presents Risks for both Academic Researchers and Drug Companies

Timing can seriously impact risk, not only for the company but for the academic researcher developing the compound, noted one participant. Starting a pediatric trial before the adult trial is completed carries the risk that, several years into the study, the result in adults will be negative. Waiting too long risks hitting the end of the patent, "and they [companies] are not interested." Academic researchers may spend years developing a drug, only to have the company choose someone else's molecule instead. "Our goal is to get access to these drugs as quickly as possible. But there's risk on the academic side," he said.

The timing of standard pediatric trials typically involves a long timeline, said one participant, with companies doing five separate studies 18 months apart – first testing adults, then 12-to-18-year-olds, then six-to-12-year-olds, then two-to-six-year-olds, then term infants, then preterm infants – which is "super not helpful." Instead, he recommended starting with school-age children and up, who can tell you how they feel, then opening an arm for ages two to six, "where you are likely to get a dosing surprise," then opening another arm for children under age two, at an age when the cytochrome P-450 system is still developing, so metabolism may be nonlinear. This quicker schedule offers a potential safety benefit by limiting the time during which neonatologists prescribe the drug off-label, "and all of a sudden you have gray baby syndrome," citing an adverse reaction to the antibiotic chloramphenicol in neonates that results from immaturity of the metabolic pathways required for a drug's detoxification.

The decision of whom to test should be based on which populations would benefit most from a given treatment, said one participant. For some drugs, such as antimicrobials, there may be a public health need for the entire community down to preterm infants to have access, but others may only test down to age six due to safety concerns. This is different than gene therapy for genetic disorders, she noted, where the benefit is often highest earliest in life.

Participants considered what types of disease and what types of outcomes are most amenable to being studied in a platform trial. The platform setting may be most beneficial

when studying efficacy, where sharing a common placebo group reduces the likelihood that any given patient will be randomly assigned to placebo, and this makes platform trials especially attractive to patients with diseases that have high morbidity and mortality, said one participant. Another suggested that platform-trials may be particularly attractive for pediatrics, where the majority of drugs being developed are for rare diseases, and "everyone is trying to get to the same population."

The Independent Broker: A Role for CROs?

Participants considered various avenues for mitigating the IP risks associated with platform trials. One suggested engaging contract research organizations (CROs), which provide "soup to nuts…manufacturing through clinical trials and commercialization, and everything in-between," without owning any IP. The CRO has confidentiality agreements with all sponsors and could be a good broker, she said, noting, however, that "the devil is in the details," and the needs of big pharma differ from those of small biotech companies.

CROs can be a mixed blessing, countered an industry representative who had used a CRO to run a platform trial involving assets from multiple companies. "The challenge became taking an innovative platform trial and sticking it into business-as-usual with a CRO," he said. All the potential cost savings disappeared because the CRO model was "the slower you go, the more money you make, and the worse job you do, the more you can bill us for doing a better job next time." CROs are "just now starting to get the hang of pediatric trials," replied a CRO representative, noting that contracts can specify penalties if the CRO fails at recruitment/retention or falls behind milestones. The industry representative acknowledged that his CRO arrangement, in which each company held a separate IND and worked separately with the CRO without a third-party broker, created "a lot of friction." It's important to know how these models impact cost efficiencies and economies of scale, "to set internal expectations," added another participant.

Pediatric Platform Trials are Evolving Towards Standard Practice

One researcher compared the evolution of pediatric platform trials to the stepwise process of child development. In a tongue-in-cheek analogy, this researcher described the progression of researchers working after hours, without compensation, in cobbled-together-spaces, and progressing "…to getting an IND…to Part 11-compliant and labeling change…in the off-patent space," he said. Current platform studies are testing molecules that have an indication

in adults, and the next step will be to include new innovator molecules. He foresees more routine application of PREA requirements, followed by more routine exclusivity, eventually leading to a state in which developing new innovator molecules for children through platform trials will become standard practice.

Platform trials offer several opportunities for cost savings, noted one participant. One source of savings is when masking is required, and innovators share a common pool of placebo patients. Another economy comes from testing multiple drugs: "Going from drug 20 to 30 is much cheaper than going from drug one to two. You gain efficiency as more drugs enter the platform." A third efficiency stems from the ability to hold just one IND across the platform. However, he cautioned, "if everyone holds their own IND and does their own regulatory filings…and we only study two drugs and don't share a common placebo, cost savings will be limited."

> "I was a parent of an infant with leukemia, and today there is still no option of medicine that would have kept her from dying. I only wish this discussion had happened 15 years ago. 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*

Platform Trials: Why and What

In his keynote speech, Professor Dr. Stefan M. Gold (Professor of Clinical Neuroscience and Immunology at Charité Universitätsmedizin, Berlin, Germany) summarized the design and structure of platform trials, drawing on the example of the EU Patient-Centric Clinical Trial Platforms (EU-PEARL) and the EU-PEARL Integrated Platform Trial for MDD, which was designed to test therapies for adult treatment-resistant depression.

EU-PEARL: An Integrated Research Platform (IRP)

The EU-PEARL consortium[16] consists of a public-private partnership of hospitals, universities, patient organizations, industry, regulatory authorities, and statisticians, said Dr. Gold, and its

[16] See https://eu-pearl.eu (accessed on December 31, 2024).

task is "to explore how platform trials…can help us to develop drugs, repurpose drugs, and maybe also generate data on comparative efficacy of certain treatments, in a more efficient, faster, and patient-centric way." The involvement of patient advocates was essential to this effort.

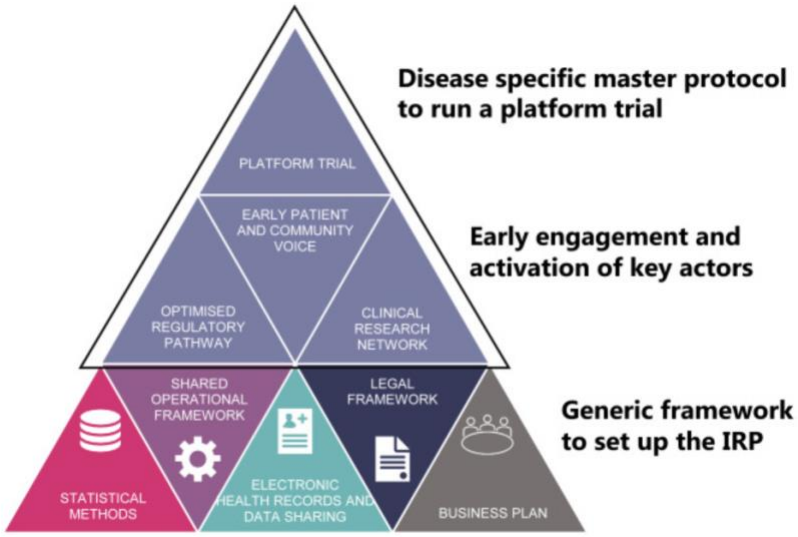
> "The foundational principle of all of this was that lived experience and patient representatives should be engaged from day one…they were a really central part of our consortium." – *Professor Dr. Stefan Gold*

EU-PEARL held its kickoff meeting in November 2019. All stakeholder groups were engaged throughout the process, which began as a design project focusing on simulation and tool development. The result was what Dr. Gold termed an "integrated research platform**"** (IRP), where a platform trial would be "embedded in a whole range of other activities that had to do with the scientific, legal, regulatory, and ethical aspects," including a strong focus on lived experience and patient representation. This design project generated useful tools that are available as open-access building blocks for platform trials on the EU-PEARL website,[17] said Dr. Gold, including a template master protocol, statistical tools, and guides for establishing a site network, constructing the legal framework, and dealing with issues of IP, security, and governance.

The EU-PEARL Integrated Research Platform model can be visualized as a pyramid, starting with the production of non-disease-specific tools for platform trials at its base, followed by early engagement of key actors in the next layer, finally leading to disease-specific master protocols for running platform trials (Figure 1). While platform trials can be more efficient than traditional clinical trials, they do not cure all problems, said Dr. Gold, and every element of a trial's design will have a price attached to it.

Figure 1. EU-PEARL Approach: Elements of an Integrated Research Platform[18]

[17] See https://eu-pearl.eu
[18] Koenig F, Spiertz C, Millar D, Rodríguez-Navarro S, Machín N, Van Dessel A, Genescà J, Pericàs JM, Posch M; EU-PEARL Consortium. Current state-of-the-art and gaps in platform trials: 10 things you should know, insights from EU-PEARL. EClinicalMedicine. 2023 Dec 26; 67:102384.



"Platform trials can be extremely efficient and overcome some of the problems that we have in clinical trials generally, but all of these choices and all of these features come at a certain price." – *Professor Dr. Stefan Gold*

Why Run Platform Trials for Treatment-Resistant Depression?

Psychiatry has lagged substantially behind other areas of medicine in new drug approvals, said Dr. Gold.[19] The field needs better and faster ways to generate robust evidence that can lead to new treatments. Even for existing treatments, the kind of solid comparative effectiveness evidence that could guide clinical decision-making is often lacking. "If we were to answer all these different questions…with our classical approach, one trial for each treatment or for each question, that will take a very long time," he said.

Mental health trials also suffer from widespread problems of statistical power, said Dr. Gold. A clinical trial should be able to detect an effect size down to around 0.4, he said, because 0.4 is in the range of average effect size of drugs currently used across both general medicine and psychiatry and, therefore, likely to be clinically relevant.[20] However, a recent

[19] See Mullard A. 2023 FDA approvals. Nat Rev Drug Discov. 2024 Feb;23(2):88-95.
[20] Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012 Feb;200(2):97-106.

metareview of tens of thousands of randomized controlled trials testing various therapies for a range of psychiatric disorders found that the mean power to detect this effect size was about 30 percent across all treatment modalities and disorders.[21] This is a "major, major issue," said Dr. Gold, who suggested that clinical trials be run "in a way that would enable us to actually detect these types of effects, because they're probably clinically meaningful."

"Platform trials have logistical, operational, and statistical efficiencies that have the potential to overcome some of these shortcomings," said Dr. Gold. These efficiencies are illustrated in Figure 2, which compares the size and structure of a hypothetical platform trial with five test arms to that of five separate two-arm randomized control trials (RCT). Dr. Gold cited several examples of successful platform trials. The I-SPY[22] and STAMPEDE[23] trials for breast and prostate cancer, respectively, tested numerous drugs and found several that succeeded, producing answers "faster and more efficiently" than individual trials. Most impressive, said Dr. Gold, the RECOVERY (Randomized Evaluation of Covid-19 Therapy)[24] trial obtained its first positive, guideline-changing results just 100 days after the protocol was submitted for review. Many treatments have since been tested on the RECOVERY platform, which is still active.

[21] de Vries YA, Schoevers RA, Higgins JPT, Munafò MR, Bastiaansen JA. Statistical power in clinical trials of interventions for mood, anxiety, and psychotic disorders. Psychol Med. 2023 Jul;53(10):4499-4506.
[22] See https://www.quantumleaphealth.org/for-patients/i-spy-trials (accessed on December 31, 2024).
[23] See https://www.stampedetrial.org (accessed on December 31, 2024).
[24] See https://www.recoverytrial.net/ (accessed on December 31, 2024).

Figure 2. Platform Trials Offer Improved Speed and Efficiency[25]

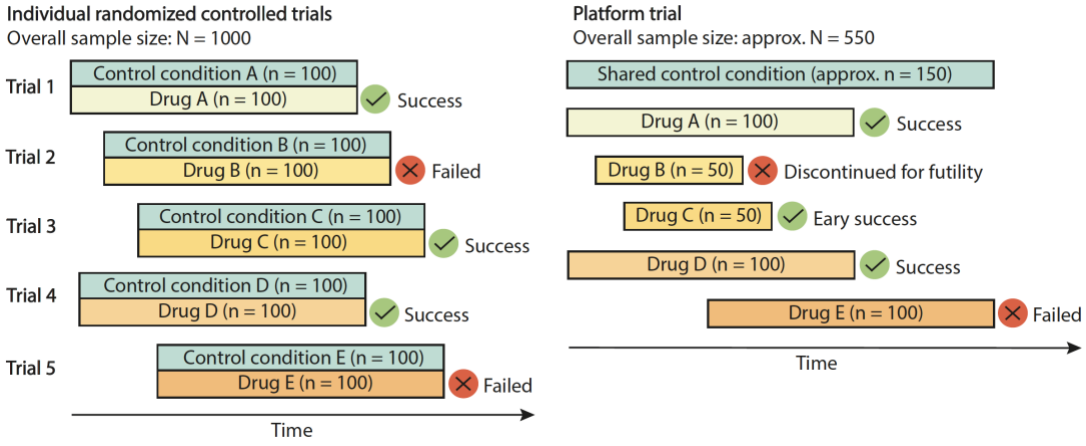


Figure 3. Platform Trials Offer Improved Speed and Efficiency (cont'd)

"One treatment, one trial"	**Platform Trial**
• Inefficient (infrastructure built from scratch for each trial) • Limited in the questions they address • Typically, 50 percent of participants assigned to control group • Limited power to detect smaller (but potentially relevant) clinical effects	• Shared infrastructure → faster recruitment • Comparative efficacy / effectiveness • Fewer participants on control / placebo • Shared controls → increased power • Increased flexibility (adding and dropping of arms) • Can accommodate different types of treatments

The Structure of a Platform Trial for Treatment-Resistant Depression

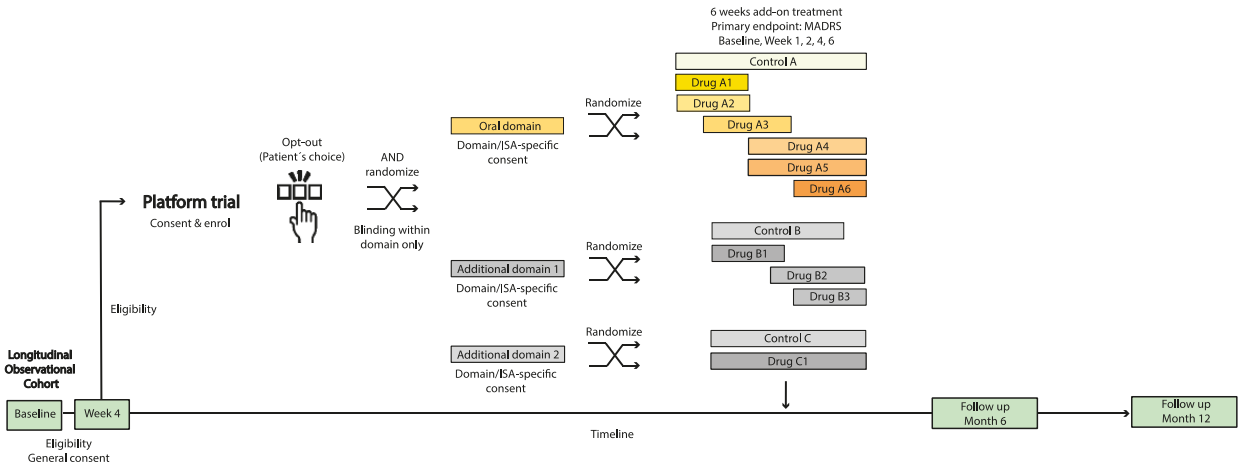
Dr. Gold discussed several considerations that went into developing the EU-PEARL Platform Trial for Treatment-Resistant Depression.[26] The score on a clinician-based rating scale[27] at six

[25] Gold, S.M., Bofill Roig, M., Miranda, J.J. *et al.* Platform trials and the future of evaluating therapeutic behavioural interventions. *Nat Rev Psychol* **1**, 7–8 (2022).
[26] See https://eu-pearl.eu/case-studies/mdd/ (accessed on December 31, 2024).
[27] See https://www.mdcalc.com/calc/4058/montgomery-asberg-depression-rating-scale-madrs (accessed on December 18, 2024).

weeks is the primary endpoint, but the design also allows for a choice of secondary outcomes among a menu of symptom burdens, as well as testing for fast-acting treatments within one to two weeks. It was particularly important to build a platform that would allow for different routes of administration, said Dr. Gold. Initial trial arms would evaluate oral drugs (as an add-on to an existing antidepressant), but the platform needed to allow for other routes of administration as well. The various routes, therefore, defined "domains," with each domain comprising drugs that are similar enough in their route and dosing regimen to share a blinded control.

Each arm of the platform is customizable, said Dr. Gold, and every compound owner can choose the size of their arm. Simulation models used sample sizes between 40 and 120 for illustration purposes, but the trial can accommodate a much wider range of sample sizes (up to 600). The researchers intend to use the platform to accelerate Phase II proof-of-concept testing, but it can - in principle - also accommodate Phase III and Phase IV trials.

Figure 4. An Integrated Platform Trial for MDD[28]



As shown in Figure 4, participants first enter the trial via a longitudinal observational or "readiness" cohort (green boxes). Once treatment-resistant depression has been established, they are offered participation in the platform trial ("eligibility" arrow). Participants can opt out of one domain in which case they will be randomized to one of the remaining domains.

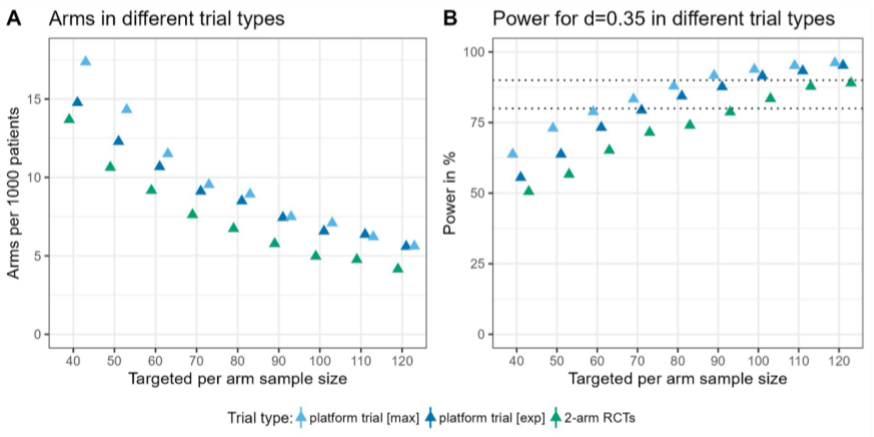
[28] From presentation by Stefan Gold on October 30, 2024.

Blinding only occurs within each domain. In the example shown in Figure 4, the first participants to enroll in the oral domain are randomized to the control group or drugs A1 or A2, but later enrollees may be randomized to control, A3, A4, or A5; the number of arms varies over time. At the end of the six-week treatment, participants return to the observational cohort, and long-term safety and outcome data are obtained at six and 12 months. Some people may remain in the observational cohort and never enter the platform.

To determine the statistical power of this platform, Dr. Gold and colleagues tested different permutations of assumptions (such as the number of drugs and recruitment speed for each domain) and performed a power analysis for each scenario. Under all conditions, platform trials, on average, enabled 20 to 30 percent more drugs to be tested than standard clinical trials for the same number of participants (Figure 5, left). Furthermore, the necessary power to reliably detect an effect size of 0.35 could be achieved with fewer people in the experimental arm of a platform trial, compared to a traditional two-arm RCT (Figure 5, right: compare sample sizes required to clear the 80 percent power threshold for detection of a 0.35 effect size for each trial type).

Figure 5. Results of one million simulated trials: platform trials vs two-arm RCTs[29]

- **Higher power** and **more arms read-out** per 1000 patients for a platform trial compared to the "classic" approach with individual 2-arm trials



- 10.000 simulation runs per combination of simulation parameters
- more than 1 million simulated trials overall
- 38 scenarios explored in detail

[29] Gold SM, Mäntylä F-L, Donoghue K, Brasanac J, Freitag MM, König F, Posch M, Ramos-Quiroga JA, Benedetti F, Köhler-Forsberg O, Grootendorst N, Hoogendijk W, Pariante CM, Katz ER, Webb S, Lennox B, Furukawa, TA, Otte C. Transforming the evidence landscape in mental health with platform trials. *Nature Mental Health* in press.

"We actually do find the statistical efficiency that, in theory, we should have… more answers, and higher power for moderate effect sizes." – *Professor Dr. Stefan Gold*

EU-PEARL spent three-and-a-half years developing a suite of disease-agnostic tools for designing platform trials as well as collaboratively drafting MDD-specific documents, including the master protocol, said Dr. Gold. Building on this tool set and preparatory work, the MDD working group was subsequently able to secure funding from the Wellcome Trust to launch the actual trial, PEARLDIVER. The team will test its first two oral drugs in the next years in a proof-of-platform trial, using repurposed drugs that are generic and off-patent. It will draw on a network of 30 sites in six European countries, with a major academic hospital in each country serving as the national coordinating center. The study includes a nonprofit European clinical research organization[30] and a team of statisticians.[31] "At the core of our consortium are people with lived experience, who co-designed this and who also will have seats on the steering bodies of the trial," added Dr. Gold.

Lessons from EU-PEARL and Applications to Pediatric Platform Trials

Every design choice and benefit of a platform trial comes at a cost, said Dr. Gold. Each stakeholder group has its particular concerns: regulators, ethics commissions, people with lived experience, industry, academics, and clinicians. Dr. Gold summarized some of the concerns that were mentioned during the extensive listening sessions that were conducted for the trial with these stakeholder groups, as well as ways these are being addressed in the context of the EU-PEARL treatment-resistant depression trial (Table 1).

Table 1. Challenges, Barriers, and Mitigation Strategies for the EU-PEARL MDD Platform Trial[32]

	Challenge	Mitigation strategy
Regulatory	Difficulties with obtaining regulatory approval due to novel trial design	Early engagement with regulatory authorities and ethics commissions during the planning stage

[30] See https://ecrin.org (accessed on January 3, 2025).
[31] See https://data-science.meduniwien.ac.at/institute/medizinische-statistik/ (accessed on February 19, 2025).
[32] From presentation by Stefan Gold on October 30, 2024.

		Continued communication throughout the life cycle of the platform trial
Trial design	Blinding can be challenging in platform trials that accommodate different types of treatments (routes of administration, etc.)	Split the platform trial into "domains" (e.g., drugs with same route of administration and dosing paradigm, etc.) that can be fully blinded and thus share a placebo arm
	Blinding issues could be exacerbated given the importance of expectancy effects in mental health and the subjective nature of many commonly used outcome measures. Lower probability to be assigned to placebo may increase responses in placebo groups.	Set a lower limit of placebo allocation Consider communicating range of allocation likelihood rather than exact numbers
	Time trends in treatment responses (incl placebo responses) are likely, e.g. when a particularly "attractive" treatment enters or leaves the trial	To avoid bias by time trends, restrict primary analyses to using only concurrent controls and/or keep the allocation ratio fixed / use stratified analyses
	Need for understanding the trial's operating characteristics under different scenarios prior to launch	In-depth pre-trial simulations to inform design choices
	Frequent interim analyses needed	Establish infrastructure for efficient dataflow and appropriately staffed / experienced statistics team
Acceptability	Potential participants may be reluctant to join because of the complexity of the trial	Involvement of lived experience (LE) experts from the very beginning of the design process Outreach campaigns co-designed
	Trial can contain vastly different treatment forms which may not all be equally attractive and participants may thus be reluctant to agree to be randomized	LE experts as collaborators in key roles (including choice of treatments to be tested) Consider opt-out or opt-in features for domains of the trial Consider adding the opportunity to re-randomize to subsequent cohort / domain, if participant does not benefit from initial treatment

Treatment Pipeline	Depth of the treatment / drug development pipeline to sustain a platform trial may not be known or potentially insufficient for certain indications	Build the platform trial so that it can also accommodate candidates for repurposing as well as comparative effectiveness These will be in addition to running newly developed treatments / drugs
	Industry / compound owners may be reluctant to run their drugs in a platform trial, where they have limited control over design and conduct	Establish "proof of platform" by launching, recruiting, and reading out arms of repurposed drugs to demonstrate feasibility "Neutral" ownership of infrastructure Initiate collaborative discussions with industry early and maintain throughout Consider offering incentives for early buy-in (discounted user fees / case payments, etc.)

Major Design Features are Driven by the Particular Disease

The decision to focus on Phase II rather than Phase III studies was based on concerns specific to depression, said Dr. Gold. These include fluctuations in the placebo response, the potential for functional unblinding, and "the fact that your placebo allocation is lower than 50 percent, and there's fairly good evidence that the smaller the likelihood of receiving placebo, the larger will be your placebo response." Dr. Gold noted that these concerns are field-specific and don't rule out using platforms for either seamless Phase II/III or Phase III trials in the future or for other subgroups or diseases. Dr. Gold also emphasized that there would be no placebo-only control group in the treatment-resistant depression trial; every participant would receive the experimental drug or placebo in addition to their current SSRI or SNRI.

Considerations for Trials Involving Multiple Companies

Platform trials that test drugs from multiple companies should be sponsored by a "neutral entity" (e.g., academic hospitals), said Dr. Gold, noting that the Treatment-Resistant

Depression trial is sponsored by Charité Universitätsmedizin Berlin, and that EU-PEARL offers detailed advice on handling the sponsorship role in such trials.[33]

Concerns regarding pharma hesitation influenced the choice to use generic drugs for the first two arms of the MDD platform, said Dr. Gold. These will be oral pills that have been shown in at least one small RCT to have some promise in major depression, and they will be selected from a short list of candidates in a transparent way, with input from the scientific community. Noting that other platforms have had difficulty convincing commercial companies to be the first to join, Dr. Gold said, "we wanted to show that it works in more of an academic approach, to lower the hesitation for commercial partners."

Domain Opt-Out: A Patient-Centric Approach with Implications for Pediatrics

Different routes of administration are "a huge problem in pediatrics," noted an industry representative who was concerned about the bias created when patients are allowed to opt out of a particular route. Dr. Gold acknowledged that this can lead to "different populations" in the various domains. However, the alternative, i.e., forcing people to get randomized to a domain that they don't want, can create a problem "at the tail end, because you get selective dropout...so you're just moving your problem from before randomization to after." He noted that the only way to fully blind platform trial arms across domains would be to give each trial participant several additional sham/placebo treatments, which is untenable.

Since the act of separating administration routes into domains automatically creates "a bias…that makes them not directly comparable," Dr. Gold and colleagues decided to go "fully patient-centric" and give participants the freedom to opt out of a domain, accepting the risk that the populations in different domains might be slightly different, but mitigating the risk of selective dropouts. This approach has the added advantage of mirroring the populations most likely to later use these drugs, "because if somebody's really averse to intravenous (IV) administration, in clinical practice, they will never choose an IV treatment," he said. "This was one of those scenarios where we had to find a compromise between what the statisticians wanted, the regulators wanted, the clinicians wanted, and the patient representatives wanted."

[33] See https://eu-pearl.eu/tools/ (accessed on December 31, 2024).

Meeting European Regulatory Requirements with a Platform Trial

The regulatory requirements implemented by the EU Clinical Trials Information System (CTIS)[34] were not designed for platform trials, particularly in terms of reviewing each new arm. With CTIS, "you have two choices," said Dr. Gold; "either a new arm is an amendment, or a new arm is a new trial." Amendments are problematic because CTIS can only process one amendment at a time, so if a platform trial is very active, then some arms may be blocked as they wait for other arms to be approved. To avoid this outcome, Dr. Gold and colleagues will apply for each arm as a new trial, with the hope that "the process will be more rapid because it's based on an already-approved master protocol."

Another concern is the possibility that individual countries will request specific changes to the protocol. To avoid this, Dr. Gold and colleagues held informal consultations with regulators from EMA, the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA), and FDA early in the design process. They are introducing the platform in stages, he said – first to five EU countries that are in regulatory alignment and then to the UK, "to see how easily you can expand such a trial across a new regulatory space…if you closely work with the regulators."

[34] See https://www.ema.europa.eu/en/human-regulatory-overview/research-development/clinical-trials-human-medicines/clinical-trials-information-system (accessed on December 18, 2024).

Breakout Session: MDD

Limitations of Clinical Trials for Pediatric MDD

Clinical trials for pediatric MDD have had limited success. Pervasive issues bedevil this field, and these issues need to be addressed either before or in conjunction with embarking on platform trials. Much of the group's discussion was focused on identifying the most significant obstacles and suggesting ways to overcome them.

Extrapolation from Adults to Children

Extrapolation is based on three general ideas, said one participant: similarity of disease, similarity of the treatment response, and the drug pharmacology.[35] Phenomenological differences between adolescent and adult depression suggest that the diseases may be different, he added; even for drugs that work in both populations, the optimal dose may differ. A researcher countered that, based on the literature, pediatric and adult depression have similar neurobiology.[36] Even if the adult and pediatric targets differ phenomenologically, both participants agreed that they are biologically similar. Nonetheless, citing differences in severity of illness assayed by the Children's Depression Rating Scale (CDRS) compared to the adult Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS), another researcher noted, "we're still not quite where we need to be to capture the symptoms that change in a trial."

When phenomenological differences appear between children and adults with depression, "is that a difference in the disease, or is it a mismatch between the knowledge you're trying to measure and the instruments you're using?" asked one participant. There are also differences between outpatient and inpatient children, but whether this constitutes a disease difference, or a sampling issue is unclear, added another. Children in the five-to-ten-year-old range may have a very different presentation, and a different disease, from adolescents, added a third. Participants also noted differences in internal versus external validity.

[35] See ICH guideline E11A on pediatric extrapolation https://www.ema.europa.eu/en/ich-guideline-e11a-pediatric-extrapolation-scientific-guideline#current-version-effective-from-25-january-2025-69539 (accessed on January 13, 2025).
[36] Singh MK, Gorelik AJ, Stave C, Gotlib IH. Genetics, epigenetics, and neurobiology of childhood-onset depression: an umbrella review. Mol Psychiatry. 2024 Mar;29(3):553-565.

Dosing

The dosing regimens studied in several pediatric MDD trials have not been adequately justified, said an academic researcher.[37] It remains unclear whether pediatric MDD patients require unique dosing considerations to achieve the same exposure as adults with MDD, or whether they require a higher exposure to achieve similar results. A dose-finding study of paroxetine found that children were being over-medicated, while the SSRI most often used for pediatric MDD, sertraline, has never had a positive study for this indication due to "mis-dosing" in the trials, he said. This researcher suggested that the failure of past pediatric MDD trials may reflect incorrect dosing, rather than a fundamental difference in the disease between adult and pediatric MDD patients.

The same researcher went on to explain that, for many agents, there does not appear to be a relationship between drug concentration and efficacy. Exposure parameters may be a predictor of efficacy, but these are not being measured in pediatrics. He then gave the example of aripiprazole, a partial dopamine agonist, which may vary in concentration over the life cycle, with PK parameter estimates showing no relationship between concentration and response. Dose will also differ for a maintenance versus an acute phase treatment paradigm.

The High Placebo Response Rate Complicates Clinical Trials

"Part of the problem we're dealing with is not that the drugs don't work, it's that the placebo rate is so high," said one academic researcher. Taking all pediatric trials together, she continued, the response rate to active drug is about 0.6, while the response to placebo can range anywhere from 0.3 to 0.55; a five percent difference between drug and placebo can't be distinguished in a clinical trial. Kids have a higher placebo response than adults, perhaps reflecting the greater resilience of kids in distress, said another researcher.

One participant suggested that trials would do better to accept the high placebo response and work around it, using strategies like randomized discontinuation. The high placebo response may be more of a problem for acute treatment, he added, noting that lamotrigine did not receive an acute indication in children or adults with bipolar disorder but only a

[37] Findling RL, McNamara NK, Stansbrey RJ, Feeny NC, Young CM, Peric FV, Youngstrom EA. The relevance of pharmacokinetic studies in designing efficacy trials in juvenile major depression. J Child Adolesc Psychopharmacol. 2006 Feb-Apr;16(1-2):131-45. doi: 10.1089/cap.2006.16.131. PMID: 16553534.

maintenance indication for relapse prevention in adults: "maybe we're going about this all wrong," and these drugs should be tested as maintenance treatments in children.

> **"Maybe in pediatric depression you need to pivot to a maintenance approach, because in that situation you can at least [validate] that these are kids that are not just acutely depressed, but persistently depressed…It is also necessary for us to avoid contaminating our acute trial with high placebo responders." – *Academic Investigator***

Why is the Placebo Response Rate So High?

Looking at drugs that were tested in both pediatric MDD and pediatric anxiety, the signal detection was higher in anxiety disorders than in depression, said one researcher. "There's something about pediatric depression that seems to be quite susceptible [to placebo]," she said, and it may relate to the severity of illness (i.e., enrolling patients who are not severe enough), to a measurement challenge, or to trying to capture an acute change in a more chronic condition. Citing a 2024 National Institute of Mental Health (NIMH) placebo response workshop,[38] one participant noted that the severity of MDD among clinical trial participants has declined in the last 20 years, and this could be enhancing the placebo effect.

As the number of sites and the number of raters increase, so does the placebo response, said one participant; this is exacerbated by the use of less-experienced individuals to do the ratings. That has implications for global studies, which would introduce more raters as well as more heterogeneity, said another. Nonetheless, the first participant cautioned that using centralized raters to standardize assessments has been "a disaster."

The Problem of Inadequate Disease Severity in Trial Populations

The EU-PEARL adult MDD platform was notable for giving the drug as an add-on to patients' existing treatment, which has not previously been discussed in the pediatric space. This is an important distinction, said one researcher, because trials with monotherapy might be more likely to engage patients who are not as sick and are therefore more susceptible to placebo.

[38] See https://www.nimh.nih.gov/news/events/2024/placebo-workshop-translational-research-domains-and-key-questions (accessed on January 14, 2025).

This has been a problem with prior pediatric MDD trials where the high placebo response was attributed to the fact that "the kids just weren't refractory enough." In children, she said, earlier onset disease is more severe, but nonetheless, "we still find, even with the higher severity, kids are very [susceptible] to placebo." In psychiatric drug development, adjunctive treatments are being explored for patients who partially respond to treatments but may benefit from co-treatment with another agent. This is also considered a de-risking strategy. "In pediatrics," she added, "we may similarly have to find a population of very sick kids to begin with." Studying combination therapies in pediatric MDD is new, she said, so obtaining regulatory approval may pose challenges.

The inclusion and exclusion criteria of clinical trials can have a tremendous effect on the placebo response rate, agreed another researcher. Based on the regulatory requirements in FDA trials of add-on therapy in adults, he said, "we get a very skewed population of treatment-refractory patients." Usually, the FDA requires these patients to be on either escitalopram or fluoxetine, although sometimes they can be on sertraline. Severely treatment-refractory patients are unlikely to be on one of the two FDA-approved drugs, so the patients who enroll tend to be "not really the most acute or the most refractory," he added. Additional inclusion/exclusion criteria, such as the degree of self-injury permitted, may also skew the placebo response rate.

Approaches to Addressing the High Placebo Response Rate

Starting everyone on a drug and then randomizing withdrawal (randomized discontinuation) is "an inferential way of getting at placebo," said one participant: "if you discontinue a drug and kids remain perfectly stable, then you know that you may have had a placebo response." Another way to approach this, he said, is by starting all participants on placebo: "You start by swallowing a pill. Maybe you're swallowing a pill with a placebo for one week, two, three…and the point of randomization is unknown to any of us."

One advantage of platform trials is their ability to reduce placebo exposure to a minimum, said another participant. This helps with recruitment, but it can be a double-edged sword. The more active arms in a trial, the lower the likelihood of receiving placebo, the higher the expectancy, which inflates the placebo response. A crossover study could encourage participation, she suggested, because all participants will have the opportunity to receive active drug. But an academic researcher = noted that the FDA prefers concurrent controls to sequential comparison.

Participants discussed the possibility of using old clinical trial data or longitudinal Patient Health Questionnaire [PHQ]-2 and PHQ-9 data to develop models that could then be interrogated with various hypotheses to see if they provide clues about how to avoid pitfalls such as the placebo effect. They also considered the feasibility of using electro-cephalography (EEG) or other techniques to screen out participants who may be highly sensitive to placebo.

Platform Trials for Pediatric MDD: Study Design Challenges and Opportunities

Treatment resistant depression in children is a complex condition that may require testing multiple different mechanisms of action. By enabling multiple treatments to be evaluated simultaneously, while offering greater efficiency and the ability to adapt based on emerging data, platform trials may accelerate the development of therapies. Some challenges of platform trials in general and as applied to pediatric MDD were outlined

General Platform Trial Design Challenges

Platform trials have complex designs, with the need to coordinate multiple interventions and manage logistics, and this requires both good oversight and a stable source of finances. The adaptive features of design must balance flexibility with scientific rigor. The greater complexity of platform trials raises statistical concerns, including a higher likelihood of a Type 1 error. Finally, platforms raise regulatory issues, with multiple stakeholders and concerns about the regulatory implications of adaptive design.

These general challenges can be overcome. Platform trials require clear and concise protocols; templates can add efficiency. Bayesian approaches or other advanced statistical methods can be used to handle multiple test arms, and there should be clear, predefined interim analysis plans and stopping rules. Regulators should be engaged early.

Challenges in MDD

A major challenge for MDD trials is the heterogeneity of the population (including symptom duration, type, and severity; treatment history; comorbidities; environment; and genetics): "depression is not depression is not depression…we have these nine symptoms, but you only

need five, what combinations do you have?" Another challenge is the role of psychosocial interventions and whether to discontinue them, hold them stable, or offer them first, "to maybe get the placebo effect out of the way." High placebo response rates can obscure the treatment effects. These treatment effects can be either delayed-onset or fast-onset, perhaps requiring different trial durations depending on how fast-acting the agents are. There is also the problem that the effectiveness of maintenance treatments is difficult to evaluate, likely because patients are not at sufficiently high risk of relapsing.

Challenges in Children and Adolescents with MDD

Children with MDD raise particular challenges. Ethical considerations include the need for a rigorous informed consent and assent process, as well as navigating parental concerns and questions of equipoise. Developmental variability may require different rating scales, different informants, or tailored interventions, depending on age and maturity. Environmental variability, in terms of psychosocial determinants, may affect MDD symptoms and outcomes before and during the trial. It may be necessary to stratify by childhood trauma. Recruitment and retention are challenging, and the high placebo response of children remains a significant challenge.

Several strategies to overcome these challenges were mentioned. Parents and caregivers should receive comprehensive education on the trial during consent, and patient advocates should be involved in the study design process. To aid retention, an academic researcher recommended using age-appropriate, child-friendly assessment tools with fun formats like games or apps. He suggested collaborating with schools, pediatricians, and community organizations on recruitment. Limiting the amount of psychosocial intervention during screening could reduce the Hawthorne effects[39] of being in the study.

Strategies for Addressing the High Placebo Response in Pediatric Trials for MDD

The high placebo response in pediatric MDD is not fully understood; while expectation of benefit is a factor, environmental forces also play a role. These can include the increased attention from parents and healthcare practitioners associated with trial participation. It may

[39] The Hawthorne effect is the phenomenon where individuals modify their behavior simply because they are aware of being observed or studied, often leading to temporary performance improvements.

also be a function of an insufficiently rigorous diagnostic process, leading to the enrollment of patients who do not actually have MDD.

Several strategies were suggested for overcoming the high placebo response. In any trial, these should include a rigorous screening process with clear severity cutoffs, controlled conditions that limit interactions to the minimum required for assessment and ensure the placebo group is not enhanced outside of the trial, and regular check-ins with families to reduce attrition.

Platform trials may offer additional opportunities for limiting the placebo response. The real-time data analysis afforded by adaptive design could help detect and mitigate an early placebo response, e.g., by adding new arms, changing assessment, or changing the control.Stratified randomization (randomizing on features like higher baseline or history) could enrich for groups with comparable placebo response rates. Innovative assessment tools that employ more objective measures, such as neurobiological markers or digital phenotyping, could be used alongside subjective measures of severity and treatment effects. It is also important to educate caregivers and patients about realistic expectations, he said. Noting a drop-off in treatment effect in Phase III studies following a positive Phase II trial, he suggested toning down, or not discussing, Phase II results when enrolling patients for Phase III studies.

> "Any platform that's erected should have a digital component to it, which can be shared across trials and across different agents." – *Academic Researcher*

Use of Adaptive Designs in Clinical Trials

A recent survey of clinical trials found a range of adaptive designs in use.[40] These include adaptive dose-finding or dose-ranging, continual reassessment, adaptive randomization, group sequential designs, and seamless Phase II-III design, as well as various statistical and other strategies. Platform trials can aid with these strategies, he noted, for example, by finding the right dose early and then closing other arms, or by continuing a trial seamlessly from Phase II to Phase III using existing sites.

[40] Ben-Eltriki M, Rafiq A, Paul A, Prabhu D, Afolabi MOS, Baslhaw R, Neilson CJ, Driedger M, Mahmud SM, Lacaze-Masmonteil T, Marlin S, Offringa M, Butcher N, Heath A, Kelly LE. Adaptive designs in clinical trials: a systematic review-part I. BMC Med Res Methodol. 2024 Oct 4;24(1):229.

Among pediatric clinical trials, adaptive designs are employed primarily in the older age groups and are rarely used in studies of children under two.[41] Adaptive dose-finding was a commonly used part of the adaptation. Most of these studies used a frequentist statistical approach, although some employed Bayesian analysis.

Ten Key Messages for Platform Trials (EU-PEARL)

Based on experience with EU-PEARL, ten recommendations for platform trials were proposed:

1. *Early stakeholder engagement*, involving regulatory agencies, patients, and healthcare professionals from the beginning.
2. *Integrated research platforms* (IRPs) that combine infrastructure, legal frameworks, and shared patient data to support continuous research.
3. *Master protocols* that streamline and standardize trial processes and can be reused across multiple sub-studies.
4. *Adaptive design* features that enhance flexibility and allow for real-time responses based on interim analysis.
5. *Shared control arms and data* across studies, reducing the number of required participants and ensuring that fewer receive placebo or standard treatment.
6. *Leveraging electronic health records* (EHRs) to assess trial feasibility and streamline the process of participant recruitment and site selection.
7. *Legal frameworks for collaboration*, which are particularly important when multiple companies are involved or when crossing national borders.
8. *Sustainable funding models and business plans* to maintain a platform trial over the long-term.
9. *Patient-centric approaches*, involving patients from the design stage to ensure that new therapies meet their needs and foster patient trust.
10. *Publication and data sharing,* including mechanisms to ensure the timely publication of results without compromising the integrity of ongoing sub-studies.

Specific Concerns Regarding Platform Trials for Pediatric MDD

Participants discussed their concerns regarding the use of platform trials for pediatric MDD.

[41] Ben-Eltriki M, et al. Research Square. DOI: https://doi.org/10.21203/rs.3.rs-3829888/v1 (accessed on January 15, 2025).

Patient-Centric Approaches: Adopting New Strategies

Noting that the most important priorities reported by patients in a recent Delphi study were in the domain of symptom severity scales (i.e., the Children's Depression Rating Scale [CDRS]) already in use, one participant wondered what other strategies could be used to make trials more patient-centric. A Patient-Centered Outcomes Research Institute (PCORI) funded study of antipsychotics was cited, where patients prioritized weight gain over quality of life. "Your primary [endpoint] might be sacred," he said, "but if you want to have fewer assessments, what are the ones that matter to the patients?"

"It's counterintuitive sometimes. You'd think [patients] would want to primarily rely on quality-of-life measures but…they have other ideas in mind, which you wouldn't necessarily suspect until you engage them." – *Funder*

"We don't have an adolescent patient in here," said one researcher. "It would be very interesting to ask teenagers *how do you know* when your depression's over…nobody says when I can get all my homework done…Sometimes I ask the question, what's still missing when somebody says they're 50 percent better?" Quality of life and functioning are "very whooshy symptoms," added another. People may define their quality of life differently, but it should be possible to account for this using patient-centric outcome measures, said an industry representative: "there's no reason why you couldn't use X for my measure and Y for your measure, it's still quality-of-life …we could design a metric."

It takes time for treatment to move the needle on quality-of-life, said one participant, and this creates a problem for detection in short trials. A second noted that pediatric medicine has been economized to short trials, made even shorter when testing rapidly acting drugs. "We're expecting to see treatment responses within 24 hours for a refractory depression," but depression in kids "tends to be chronic and persistent if it's real." Maintenance trials could last five months or a year, and "who's going to fund that?" asked the first.

An academic researcher noted that the NIH is focusing on biological markers of target engagement, with the expectation that drugs that more directly engage the target may be more successful. If patient-centric measures become the priority, then how might they impact signal detection? To get more input from patients, participants considered the

possibility of holding a patient-focused drug development (PFDD) meeting for pediatric MDD.[42]

The Placebo Effect Creates a Paradox for Trial Design

More time spent with patients means more placebo effect. There used to be instructions on how to give warm pharmacological management without being "too effusive, too supportive, too nice," but that practice seems to have "gone by the wayside," said one participant. Despite this association between time and placebo effect, he nonetheless noted that the first positive investigator-initiated fluoxetine study repeated the Kiddie Schedule for Affective Disorders and Schizophrenia [K-SADS] assessment multiple times prior to randomization, "to make sure that they really were depressed," and this "flies in the face of the other side…you spend tons of time doing a K-SADS repeatedly, but they still remain depressed." However, putting children through multiple K-SADS prior to randomization may not be feasible.

Overly rigorous attention to eligibility can adversely impact recruitment, but pressure to recruit and incentives for enrollment may impact quality control. In this environment, ratcheting up the baseline severity threshold creates a new worry that baseline scores will be inflated, noted a funder. Score inflation causes regression to the mean, and this runs the risk of enhancing the placebo response. "Greater severity is important, but how do you mitigate the risk of regression?" he asked. The way to do this is to blind the sites to the actual cutoff, said an academic investigator, for example, by enrolling people who score over 75 but only including those who score 80 or higher in the analysis. Trials with a placebo lead-in should keep supporting placebo responders for the duration of the study, said the funder, which would remove the financial incentive for the rating sites to inflate patients' scores in order to incentivize length of participation.

Reconsidering Methodologies

As treatments become more acute, the timeline for responsiveness of a symptom becomes increasingly important, noted an academic researcher, but the CDRS may not be valid for trials that look at rapid onset of action. This led to a discussion of methodologies. Participants noted that current methodologies are not ideal, but sponsors are unwilling to

[42] The Depresson and Bipolar Support Alliance (DBSA) sponsored a PFDD meeting on adult MDD in 2018. See https://www.dbsalliance.org/wp-content/uploads/2019/10/final-Externally-led-VOPR.pdf (accessed on January 15, 2025).

invest in developing new ones. "It's boring, it's old, it's phenomenological…We are left with methodologies that we really wish we could look at more rigorously. Yet the field doesn't advance."

> "We don't have the ideal methodologies. But who's going to sponsor development of those methodologies?" – *Industry Representative*

> "Right now, sponsors have been saying do this trial and do it this way. Well, doing this trial and doing it this way is not working very well." – *Industry Representative*

One researcher noted that only four or five items on the CDRS were needed to predict the drug vs. placebo response to escitalopram, and that certain aspects of depression in children, like boredom or no longer engaging in activities they enjoy, should be weighted more than others, like bad grades. "What are the most telling items on the CDRS?" she asked.

Pre-Competitive Studies Are Needed

There was general agreement that there is currently insufficient information to design a platform trial for pediatric MDD, and that this information should be obtained through cooperative, pre-competitive studies.

"We don't even know the normal fluctuation" of untreated pediatric depression, said one researcher, who suggested analyzing the results of PHQ-2 or PHQ-9 well-child screening tests for depression longitudinally and examining the trends in scores for children who were not treated.

Noting that the existing CDRS scale has worked for fluoxetine and escitalopram, while many other drugs have failed, an industry representative suggested that "maybe, in depression, we aren't trying enough doses," with failures resulting from incorrect duration or exposure to the drug. A platform design is ideally suited for testing multiple doses, noted an academic investigator.

In Baltimore and Richmond, VA, the most commonly used antidepressant for the treatment of major depression appears to be the SSRI sertraline, which can only be prescribed off-label, noted one participant. Sertraline failed in clinical trials and is not FDA-approved for this indication, but some people who do not respond to other agents do well on the drug. He suggested that sertraline's apparent efficacy may be due to a strong placebo response and that people keep using it "because it seems to work."

Regulatory Policies Need to Encourage Pre-Competitive Studies

The FDA is "sending signals…that unless the sponsors do something more than what they're required to do, they're not going to get exclusivity," noted an industry representative, "so why not start thinking about what has to be done?" The Reagan-Udall Foundation for the FDA[43] funds methods development in the pre-competitive space. Scale development for pediatrics will only be done by industry if there is a positive incentive, such as an extra six months of adult exclusivity. NIH cannot provide sufficient funds for this type of effort, which needs to be a collective effort, said an attendee.

Amid a mental health crisis in the US and rising suicide rates among youth, the Surgeon General has stated that one in five kids have mental illness, said one participant, who suggested that the Surgeon General might fund better measure development, "because right now there's no incentive to get a better measure...except for the two drugs that are approved, we're working blind."

"There is a clear societal need for us to organize around the critical needs," said an industry representative. "We need to be thinking about how we reorganize ourselves from a research standpoint to actually generate the necessary information that helps us better understand …what is critical about the disease, what is critical about the population, what are the critical milestones… so that we can actually get to this place of conducting these types of trials."

Efforts to Identify More Homogenous Test Populations

An attendee described recent efforts to identify populations that would respond better to specific treatments. Using pharmacogenomic analysis, Denovo Pharma identified a genomic variant that was tied to the response to treatment with their triple re-uptake inhibitor, which

[43] See https://reaganudall.org (accessed on January 15, 2025).

had failed in several earlier trials.[44] The FDA has granted them Fast Track designation for treatment-resistant depression. Alto Neuroscience[45] and Neumarker[46] are developing biomarkers, using EEG and machine learning, to identify individuals who will or will not respond to specific treatments, as well as studying the response of super placebo responders.

Biomarker development becomes more complicated as the number of sites increases, requiring standardization of equipment and centralized analysis. However, centralized, real-time analysis makes adaptive trials more feasible. If this leads to precision medicine for psychiatry, said an industry representative, it will require devices like an EEG and machine learning in every office: "I guess I'll hook it up to Google or Apple…and decide, do I start them on a drug or are they just expecting me to be nice?"

One participant suggested performing latent profile analysis (LPA), using categories of responses to the CDRS, for example, to define subgroups once people have been enrolled in the platform. Indeed, a post-hoc analysis of large groups that had previously been randomized might identify a latent profile that predicts a good responder to drug or a good responder to placebo. Going forward, this could inform a Bayesian approach with randomization to particular profiles.

Another participant suggested narrowing the population of patients in a platform trial to refractory or difficult-to-treat depression, rather than to broad or heterogeneous forms of depression.

Platforms versus Precision Medicine

There's a fundamental flaw in marrying platforms to precision medicine, said an industry representative. While platforms draw on commonalities of drugs, biomarker-driven interventions narrow both the target population and the relevant treatments. The benefit of platform designs stems from the ease of putting an asset in the platform and generating data on secondary endpoints that are important to patients, such as weight, he said. But MDD presents a big challenge due to the high placebo rate and dissatisfaction with the measurements. "There's a fundamental fix that's needed, and I'm not sure if the platform solves for that." Regarding precision approaches that define sub-populations for trial arms,

[44] See https://www.denovobiopharma.com/en/news_info.html?id=160 (accessed on January 15, 2025).
[45] See https://altoneuroscience.com/platform/publications/ (accessed on January 15, 2025).
[46] See https://neumarker.ai (accessed on January 15, 2025).

"oncology does it all the time," said another participant. Cancers are broken down by molecular markers, and neuropsychology could try a similar approach.

A platform trial that uses adaptive design and a standard control group can address many of the challenges that have been raised, said an academic researcher. The long-term investment offers an opportunity to sort out major problems like dosing and stopping rules. Platform studies can also be used to test combination therapies.

Strategies to Encourage Industry Participation in Pre-Competitive Trials

While there is a need and a scientific basis for pediatric trials, most companies do this work because they are required to do so, said one participant. "The hook for the companies is in their requirement, not the [financial] incentive." She noted that at least 24 companies are publicly engaged in work on MDD, and all these will have assets that need to be evaluated in children, so it is an opportune time to figure out the critical elements and objectives of a platform trial that could actually get to effective therapies in this population.

But "how do you motivate, incentivize, fund pre-competitive work, which is not required?" asked a second participant, versus plugging new treatments into the arms of a platform. BCPA and PREA exist because there is a societal need for information on drugs for children, said the first participant. So, if the societal need is for pre-competitive information, "there should be nothing preventing the FDA from agreeing to a pediatric plan," she said.

"We have to address the elephants in the room," said an industry representative, "clearly, it's been documented that a lot of [pediatric MDD trials] failed because of incentives for exclusivity: do it fast, do it fast, do it fast…Because you don't have to have a positive trial, you just have to get it done. I think that's part of the placebo response, the heterogeneity, all of that." To get better data she said, this work should be led by a consortium of stakeholders "who understand these issues and who can do the work."

BPCA provides a vehicle for studies that could fill knowledge gaps and go beyond what is required through PREA, said an attendee. This might require a financial reward, she added, noting that "we have used requests very creatively in the past…to get at some of the gaps in knowledge that we couldn't get a sponsor to do outside of that."

Actionable Ideas on Pediatric MDD

Based on a wide-ranging discussion, participants concluded that it would be premature to design a platform for pediatric MDD clinical trials before improving trial design. An industry representative co-facilitating this session summarized several aspects of trial design that need particular attention, as follows:

- Scale development: "Are we measuring the right thing?"
- Identification of appropriate populations: Can biomarkers (or other methods, like LPA) be used to develop a precision approach?
- Use of old clinical trial data, or longitudinal PHQ-2 and PHQ-9 data, to develop models that could then be interrogated with various hypotheses, to determine if they provide clues about how to avoid pitfalls such as the placebo effect.
- Convene a consortium, required for these pre-competitive activities, that could then segue into designing a platform.

"You don't want to build a platform out of bad trial design. You want to find a good trial design and build a platform based on that good trial." – *Industry Representative*

"Can you begin to model a trial design using existing data rather than just throwing a product into the wind and hoping?" – *Industry Representative*

"If you build it, they will come…if you can build a trial platform, perhaps the enthusiasm for platform trials will take…[and] if not a platform, then what?" – *Academic Investigator*

Implementing a Plan for Addressing the Problems and Paving the Way Towards Pediatric MDD Platform Trials

Participants considered strategies for overcoming the vast array of obstacles that they'd identified in the previous day's discussion.

Building a Consortium, Engaging Industry

Doing something "a little bit different" that involves pre-competitive work would need to engage all the same stakeholders that are needed for designing platforms, including the EMA, FDA, and MHRA, said an industry representative. These stakeholders would need to get together and decide what specific pre-competitive work is needed. To engage industry, he suggested that the FDA produce a written request that includes both PREA requirements and some pre-competitive work. "FDA has the current authority to do that, if they thought it was a good idea," he said, and industry should be willing to put up the money if it led to systemic improvements in trial outcomes. There would have to be a stipulation that allows the results to be generalizable knowledge that everyone can use, added another industry representative.

The best way to convince industry to invest in pre-competitive work on MDD, said a third industry representative, would be to reduce "things that produce huge burdens for us for conducting trials that can add substantially to our costs." These include the long amount of time it can take to conduct trials, which is often attributable to slow recruitment or to overly complex designs. If the pre-competitive work helped make trials more efficient and streamlined and made it easier for people to participate, that could help incentivize industry, he said. Offering incentives for participation (e.g., some free sessions with a therapist) would help with recruitment, he added, but due to the generally poor access to mental health care, ethics committees reject these efforts as being overly incentivizing.

This same industry representative mentioned another challenge, which is that participants are excluded for many reasons, not all of which are valid. In the case of pediatric studies, this may involve "some obscure inclusion/exclusion criteria that…may apply to adults but not to children," such as requiring that participants have already had a certain number of past treatments.

> "If you were going to go in and ask for funding for pre-competitive work, there would need to be a clear line of sight between that pre-competitive work and…more efficient and effective pediatric trials." – *Industry Representative*

Industry won't just take your word that a pre-competitive investment will reduce their costs, cautioned one participant from industry. Proving this will require multiple stakeholders and a work package that clearly lays out the time savings. A second industry representative agreed, adding that "some of the ROI is actually creating a framework, from an assessment

tool perspective and better understanding of the disease," that will facilitate future studies. This needs to be developed and led by a public/private partnership, she said, and support from the regulatory authorities is critical. There will always be individual company trials, and these also need to benefit from the pre-competitive investment, she added, with decisions made on an asset-by-asset basis.

Non-platform trials can be put into trial platforms, noted one industry representative. Regarding risk, she argued that putting an innovative product in a pediatric trial designed to meet regulatory requirements is a very different level of risk than putting an adult Phase III asset into a platform.

Participants were not aware of any evidence that failed pediatric trials under PREA had a negative impact on economic projections for the adult market.

Patient advocates could drive this effort to improve the quality of clinical trials through pre-competitive research, suggested one participant, noting that the Children's Tumor Foundation (Neurofibromatosis research) co-led the development of the pediatric platform for that program.[47] A second participant envisioned a set of protocols that would cover the landscape of issues that need to be explored. Clinicians who are part of the pre-competitive platform network would receive a portfolio with the various protocols. "These aren't huge studies," he noted.

This discussion is describing two different spaces, said another participant: a pre-competitive space, with a consortium of all stakeholders working together to address issues fundamental to doing pediatric MDD trials; and an implementation space, where a CRO could manage multiple industry partners and a site network. She suggested that industry players could move forward via a Critical Path Innovation Meeting (CPIM).

Engaging Participants, Reducing Stigma

Many people with major depression refuse medication "because taking a pill means I'm crazy," said one academic researcher. On top of that, participation in clinical trials is seen as

[47] See https://www.ctf.org/news/ctf-gcar-announce-strategic-alliance-nf-platform-clinical-trial/ (Accessed on April 9, 2025)

being in an experiment, which carries stigma of its own. The researcher contrasted this to cancer, where "you're going to go be in the best, newest treatment to cure your cancer; we don't have the same approach to the treatment of depression." Getting patients to enroll in clinical trials for depression requires fighting multiple stigmas.

One obstacle to getting children into trials is that patients are given treatments "without understanding that there really isn't good data in kids," said another researcher; everyone assumes that drugs that were approved in adults also work in kids, whereas "the data seems to suggest the opposite a lot of the time." Patients are hearing that there are not a lot of approved treatments, and yet they are receiving medications with high side effects, added an attendee; "what's the value of receiving these products when they don't know if they truly work?" Given this conflicting narrative, she said, it's crucial to figure out the right messaging so that families understand the importance of enrolling children in clinical trials to get treatments that work.

With the Surgeon General's advisory on youth mental health,[48] this is a good time to engage the public, to address both the stigma and the general aversion to being experimented on, said one participant. Citing the successes of platforms for COVID and breast cancer, a second participant noted that MDD can be as harmful to individuals as a life-threatening global pandemic. "Patient advocacy and how this is communicated out is super important…that's a key driver," he said. A third concurred, noting that MDD is the number one cause of disability in kids, both in the US and worldwide.

Some individuals might be more willing to participate if they can keep their partially effective existing drug and add an additional medication to their treatment, suggested one researcher.

Comparative Effectiveness

Participants considered the incentives for sponsors to participate in comparative effectiveness trials using approved products. A platform does not need to compare the active arms to each other, said an industry representative. Nonetheless, this is valuable information, and academic researchers in the EU-PEARL MDD trial chose to interrogate comparative effectiveness, even though the companies just wanted Phase II results. Once the

[48] See https://www.hhs.gov/sites/default/files/surgeon-general-youth-mental-health-advisory.pdf (accessed on January 16, 2025).

results from individual arms have been published, he said, it is possible to reverse-engineer the Bayesian borrowing and compare treatment effects between arms.

Matching the Drugs to the Patients

MDD is unusual, in that treatments approved in adults fail to work in children, said one participant from industry. He suggested that perhaps the drugs do indeed work in children, but studies have failed to capture that benefit. "Even if the disease has some presentation differences, the drug should work," he said. This may be an issue of matching drugs to the right sub-populations of patients, suggested a researcher.

Given the "tons and tons of failures" trying to precision match treatments to children, the researcher suggested analyzing existing phase IV data, with the goal of better matching children to treatments. This has the potential to produce better adherence and better outcomes, she said, and can be done even in the absence of funding for new trials.

> **"We have tons of off-label treatments being used in very erratic, unregulated, and I would say irresponsible ways, because there's no guidance. That's standard of care."** – *Academic Investigator*

With more rigorous study design, it may be worthwhile to rerun agents that failed previously but are being used off-label because they benefit some children with MDD, said one participant. Studies could be refined through methods that have been discussed at this workshop, said a second participant, including latent class analysis, biomarker discovery, and stratification based on sociodemographic factors. Super-placebo responders could be screened out with psychotherapy, she suggested, although it is not sufficient just to screen out these individuals, there needs to be further refinement of the target population. A third participant suggested including fluoxetine as a positive control, "because if it fails, then it's probably a problem with the platform."

Improving both efficiency and quality of these trials goes far beyond pediatrics, said one participant from industry, noting select pharmaceutical companies are trying to develop more precise approaches for testing mood disorders in general. It's important to de-risk these trials up front, he said, for example, by not requiring a 600-patient trial for a drug that already has proof-of-concept in adults and seems to work in children. Companies have left

neuroscience because the risks are too high, he said. It may appear that the treatment milieu for depression is saturated, he added, but for two-thirds of people, these drugs do not work the first time, and this becomes "much, much more complicated" for pediatrics.

> "Improving our scientific accuracy and our ability to be more efficient scientifically will improve our outcome." – *Industry Representative*

Support for a Pediatric MDD Platform

A platform trial design has huge opportunities and should be developed, said one researcher. In addition to increased efficiency and reduced exposure to placebo, a platform introduces training and standards that elevate the quality of the member sites, he said, increasing the precision and quality of the data.

There are questions about what trials to run on a platform. Given that children are less responsive than adults, he suggested starting with an augmentation design, which may be easier to bring to Europe, and selecting for patients with earlier onset disease, which is less responsive to placebo. This researcher cited the EU-PEARL MDD trial as an example of starting with later-stage drugs to validate the system before embarking on industry-funded trials, perhaps rerunning some medications that failed to separate from placebo in earlier trials and using fluoxetine as a standard.

Participants expressed an urgency to move forward rapidly, to address the huge public health problem that is pediatric MDD. This will require a pre-competitive effort to optimize the accuracy and efficiency of clinical trials. They encouraged the establishment of a consortium of all stakeholders immediately.

Summary

One of the session facilitators summarized the next steps:

- Establish a consortium that brings together all stakeholders.
- Identify convenors for pre-competitive work (FNIH, Critical Path, or another third-party convenor)
    - Structure this work with an aim to improve the efficiency and the quality of the studies that are done in pediatrics, and to meet regulatory requirements with greater speed and efficiency, reducing costs.

    - Realize the goal of better scale development.
    - Model trial simulations using existing data, with the aim of identifying strategies that reduce the impact of the placebo response.
- Include the patient voice, which is essential; patient advocates may co-lead this process.
- The consortium should identify work packages; EU-PEARL provides a good playbook.
- The consortium needs to identify funding sources.

Breakout Session: Pediatric Oncology

Among the three medical indications that form the focus of this meeting, cancer is the only one that has, to date, been addressed through platform trials in children. Certain features of childhood cancers, including the relatively small patient pool and the multitude of drugs that have been approved for adults, seem to favor the use of platform trials. Nonetheless, only a handful of platform studies have been done, and they have taken an inordinately long time to initiate. "How can we get to a place where platform trials are fulfilling a need, efficient, and helping all the stakeholders, especially patients?" asked an industry representative.

Lessons from Pediatric Oncology Platform Trials

Panelists reviewed their experiences with past or current pediatric platform trials in order to help inform the design of future trials.

Glo-BNHL: A Platform Trial for Pediatric Relapsed and Refractory B-cell non-Hodgkins Lymphoma (B-NHL)

Although survival for B-NHL has improved, a significant fraction of these cancers is refractory to therapy or relapse after treatment. Little progress has been made for children and young adults with relapsed disease, whose long-term cure rates remain lower than 30%. There are potentially promising agents in development for adults with B-NHL, and these should be assessed in children, but the limited number of pediatric patients has been a challenge to drug development.

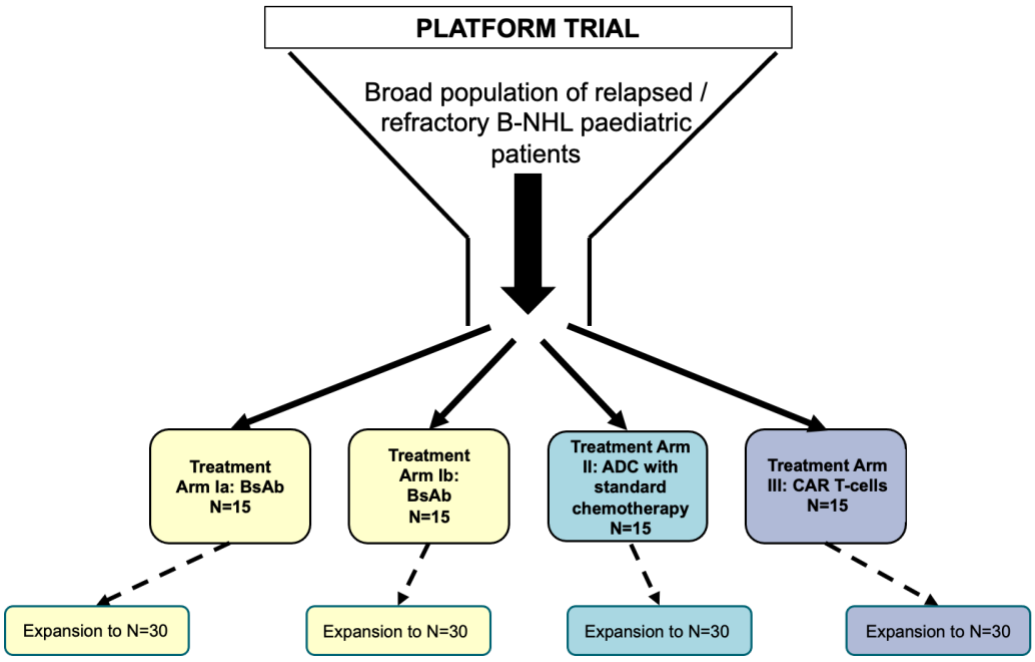
The Glo-BNHL Platform Trial was built on two concepts developed through the ACCELERATE[49] multistakeholder collaboration, said Dr. Pamela Kearns (Emeritus Professor of Clinical Paediatric Oncology at the University of Birmingham) in her presentation to the oncology breakout session participants. This 2019 pediatric strategy forum[50] recommended using an academic platform trial to study this rare disease, and an investigation into how academic-sponsored clinical trials might be conducted at a level sufficient to support

[49] See https://www.accelerate-platform.org (accessed on February 21, 2025).

[50] Pearson ADJ, de Rojas T, Karres D, Reaman G, Scobie N, Fox E, Lesa G, Ligas F, Norga K, Nysom K, Pappo A, Weigel B, Weiner SL, Vassal G. Impact of ACCELERATE Paediatric Strategy Forums: a review of the value of multi-stakeholder meetings in oncology drug development. J Natl Cancer Inst. 2024 Feb 8;116(2):200-207. doi: 10.1093/jnci/djad239. PMID: 37975877; PMCID: PMC10852613.

regulatory approval of a drug.[51] The resulting design included the following key elements: (1) the Glo-BNHL platform was open to all children with relapsed or refractory BNHL; (2) the classes of drugs to be tested were those most likely to be beneficial in the pediatric population; (3) patients entered different arms based on where they were in the disease pathway; and (4) a Bayesian approach was used to handle the small patient population, reviewing outcomes every three patients (Figure 6).

Figure 6. Design of the Glo-BNHL Pediatric Platform Study[52]



On the regulatory side, the EMA provided qualification advice and a letter of support,[53] stating that the Glo-BNHL trial design was consistent with its PIP requirements, which was "absolutely critical" for the trial's success, said Dr. Kearns. The academic sponsor held the IND, and the regulator approved the platform before all the particular drugs were even

[51] De Wilde B, Barry E, Fox E, Karres D, Kieran M, Manlay J, Ludwinski D, Reaman G, Kearns P. The Critical Role of Academic Clinical Trials in Pediatric Cancer Drug Approvals: Design, Conduct, and Fit for Purpose Data for Positive Regulatory Decisions. J Clin Oncol. 2022 Oct 10;40(29):3456. doi: 10.1200/JCO.22.00033. Epub 2022 Aug 10. PMID: 35947814.
[52] From presentation by Pamela Kearns on October 29, 2024.
[53] See https://www.ema.europa.eu/en/documents/other/letter-support-global-platform-study-novel-medicines-paediatric-and-adolescent-relapsed-and-refractory-b-cell-non-hodgkin-lymphoma-glo-bnhl-platform_en.pdf (accessed on December 20, 2024).

selected. Glo-BNHL differed from most platform trials in its focus on obtaining data that industry could use to fulfill regulatory development requirements (such as a PIP) and file for a pediatric indication, rather than on drug discovery, noted an industry representative.

Glo-BNHL provided these lessons for future pediatric oncology platform trials, said Dr. Kearns:

- Start with a multi-stakeholder strategy forum to identify an evidence-driven unmet need and to select the classes of drugs to be tested.
- Employ a multistakeholder approach throughout, including patient advocate input.
- Include a large and experienced clinical trials unit, including statisticians with expertise in rare diseases and Bayesian methods.
- Engage early with regulators to approve the design, along with EMA qualification advice that helps maintain adherence to the design.
- Establish an independently chaired trial steering committee that uses a formalized scoring system to evaluate assets from companies that want to join the trial.
- Use a transparent fit-for-filing funding model, consisting of a publicly funded core infrastructure and pharma funding per arm.
- Collaborate with pharma partners to ensure that the standards and data meet their needs.

The Leukemia & Lymphoma Society (LLS) Pediatric Acute Leukemia (PedAL) Initiative

Survival in children with acute myeloid leukemia (AML) remains poor, despite maximally intensive therapy. AML is a disease of increasing incidence with age, and there is a growing market incentive for the development of novel therapies for adults with AML. Regulatory incentives and requirements have worked to bring companies to the table early in drug development. However, two major issues have resulted: 1) oncogenic and treatment differences between children and adults with AML may lead industry to evaluate therapies or combination regimens in children that are not a high priority or impact; and 2) the development of higher priority agents may be delayed or discontinued for financial reasons despite potential for benefit in children.

LLS PedAL is an international collaboration designed to address long-standing challenges to drug development for pediatric leukemia, with a focus on AML, said an academic

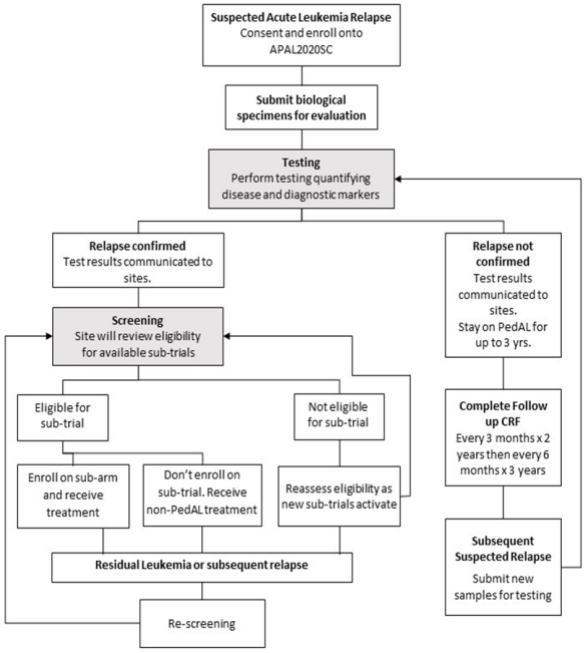
investigator.[54] In North America, LLS PedAL includes a longitudinal screening trial that follows patients from diagnosis to relapse to response to the relapse therapies, providing data needed to support targeted trials of drugs for children with relapsed acute leukemia (Figure 7).

In North America, the screening platform has been a "huge success," said this same investigator. As of March 2025, there were 181 pending or approved sites, with a total of 439 patients enrolled and 341 confirmed as having either myeloid or lymphoid leukemia diagnoses. All patients are enrolled in the screening trial, which forms the basis of the platform. Individual patients may then be selected for participation in the clinical trials, each of which tests a distinct mechanism and therapeutic strategy. One therapeutic trial is currently enrolling patients internationally, and a second should open soon.

[54] Ceolin V, Ishimaru S, Karol SE, Bautista F, Goemans BF, Gueguen G, Willemse M, Di Laurenzio L, Lukin J, van Tinteren H, Locatelli F, Petit A, Tomizawa D, Norton A, Kaspers G, Reinhardt D, Tasian SK, Nichols G, Kolb EA, Zwaan CM, Cooper TM. The PedAL/EuPAL Project: A Global Initiative to Address the Unmet Medical Needs of Pediatric Patients with Relapsed or Refractory Acute Myeloid Leukemia. Cancers (Basel). 2023 Dec 22;16(1):78. doi: 10.3390/cancers16010078. PMID: 38201506; PMCID: PMC10778551.

Figure 7. PedAL Screening Trial: Study Schema[55]

- **Initial Screening**
  - Clinical data
  - Target screening:
    - Immunophenotyping
    - Centralized DNA/RNA sequencing
  - Banking (bone marrow and blood)
- **If Relapse is Confirmed**
  - Follow-up data x 5 yr
  - Serial response evaluation by Hematologics, Inc
- **IF Relapse is NOT Confirmed**
  - Follow-up data x 3 yr
  - Rescreening anytime



Inadequate support by the existing regulatory approval system for clinical trials is a challenge, said the investigator. There is inadequate support to efficiently navigate the multi-layered approval process necessary for a global clinical trial of a new therapy early in development. Partly as a consequence, trials have been discontinued after consuming substantial time and resources. In some cases, this was due to de-prioritization by the industry partner because of data in adults with AML or expected financial returns across their portfolio. In other instances, trial development is abandoned when there is a failure to align stakeholders on intellectual property and data-sharing agreements. In a proposed international trial of a menin inhibitor, for example, the trial was abandoned after three years of development, in part because of complex and evolving expectations for data ownership among international cooperative groups. Others were discontinued when a company replaced a drug with a next-generation asset in its portfolio or when the company was purchased by a larger entity. On the positive side, two combination trials with Venetoclax and Ziftomenib, respectively, for relapsed AML are actively accruing; neither trial is using the NCI/COG clinical trial development mechanism. LLS-PedAL was established with the expectation that NCI/COG collaboration could facilitate enrollment in North America, but

[55] From a presentation by an academic investigator on October 29, 2024.

barriers to international collaborations with NCI/COG remain, said the same academic investigator.

Suggestion:

- Hold a public forum at an annual pediatric oncology meeting to elicit input from multiple stakeholders on the prioritization of same-in-class drugs.

"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*

Pediatric MATCH

NCI-COG Pediatric MATCH[56] Precision Medicine Clinical Trial is a Phase II platform study that followed the Adult MATCH study and was sponsored by NCI, said another academic investigator. Pediatric MATCH had 13 treatment arms, all with single drugs aimed at the most common genetic mutations in pediatric solid tumors and lymphoma, and involved 11 different companies.

Results to Date and Lessons Learned

Pediatric MATCH has enrolled approximately 1400 patients since its inception in 2017, said the above investigator. Thirty-one percent could be matched to one of the drug targets, and 13 percent were enrolled in a sub-protocol. However, of the six subprotocols with data published to date, none met their response criteria. Six other subprotocols closed due to poor accrual and one is still enrolling. Approximately 40 percent of patients contributed both diagnostic and relapse biological specimens that have gone through whole genome DNA and RNA sequencing, said this same investigator; these data should enable studies of tumor evolution and shed light on why the drugs were ineffective.

Pediatric MATCH was "a success with an asterisk," continued the above academic investigator: "We can do it on scale, we can answer questions, but at the end of the day, we

[56] Parsons DW, Janeway KA, Patton DR, Winter CL, Coffey B, Williams PM, et al. Actionable Tumor Alterations and Treatment Protocol Enrollment of Pediatric and Young Adult Patients with Refractory Cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. J Clin Oncol. 2022;40(20):2224-34.

didn't find any home runs…if we had to do it again, we might have built-in rational combinations [of treatments]." The design of Pediatric MATCH made it easy for industry to be involved, and the results were "very, very informative," offered an industry representative. The data were extremely valuable from a scientific perspective, added another participant, but at the end of an era when most key driver events have been defined and have led to major successes using targeted single agents, "the complexity of cancer is the issue, particularly in the proof-of-concept trials."

> "These well-run, well-designed platform trials make it very easy for industry to take part, and Pediatric MATCH was a really good example of that." – *Industry Representative*

The Regulatory Perspective

Addressing the Conflicting Aims of Industry and Academia

Platform trials have the potential to break down development silos by building an infrastructure that essentially is a "one-stop shop," said an international regulator. The efficiencies obtained from platform trials can provide earlier go/no-go decision points, letting the most promising products move forward and giving patients timely access to new innovative treatments. However, "you bring the lawyers in, and boom, it gets difficult, because then there's a risk for the company." IP issues are a surrogate for "needing to generate economic value," and this need is contradictory to the nature of pediatric oncology.

The EMA's letter of support for the Glo-BNHL platform trial[53] lists the following key issues that must be addressed in order for platform trials to succeed, said the same international regulator:

- The trial's sponsor should be an independent organization, such as an academic institution, particularly if multiple companies' assets are involved.
- There must be a strong scientific rationale for choosing to conduct a platform trial and for considering alternative approaches, such as novel statistical methods.
- There should be a strategy for prioritizing particular innovations or questions.
- Importantly, all parties need to work collaboratively, to prevent commercial interests from interfering with their ability to accomplish the joint goal.

The good news, said an attendee, is that regulatory agencies have decades of experience with platform trials in adults, and the FDA has mechanisms to provide advice.[57,58] The regulatory issues are relatively minor, she added, and the FDA doesn't have any specific concerns regarding platform trials. The pediatric space adds the extra complexity of rarity, but this problem can be addressed.

Regulatory Review can be Unpredictable, even for an Existing Platform Study

When a company proposes to add an arm to Glo-BNHL, will their study get an expedited or at least more understanding review by the EMA and FDA, asked an industry representative. "Sometimes you don't know what reviewer you're going to get." Variability in reviewers' familiarity and experience with the platform and/or the disease could lead to delays and the re-adjudication of settled issues, although this remains to be tested for Glo-BNHL.

If a proposal comes from an established platform trial or one that obtained scientific advice from the EMA, "we go into the review with much more confidence in what we're reading," said the international regulator, and the attendee concurred. Both recognized that details of study design may need to be changed over time based on evidence obtained during the trial, and they encouraged participants to approach the regulators to make changes as needed. The FDA and EMA "work together …to smooth the path to platform trials," said the attendee, inviting participants to connect directly "if there are obstacles that [are being put] in the way."

> **"Industry should understand that a lot of risks have been vetted in advance, so there will potentially be less back-and-forth and less use of resources in getting regulatory approval." – Industry Representative**

Suggestion:

[57] See https://www.federalregister.gov/documents/2018/08/13/2018-17273/expansion-cohorts-use-in-first-in-human-clinical-trials-to-expedite-development-of-oncology-drugs (accessed on December 23, 2024).
[58] See https://www.fda.gov/media/120721/download (accessed on December 23, 2024).

- Develop a strategy for pharma to approach the FDA or EMA with a question and get an answer, with reduced risk that this will adversely impact approval of the iPSP or PIP.

The Industry Perspective

There are roadblocks to industry participation at multiple levels, including internally, during regulatory review, in discussions with academics, and in discussions with the NCI Cancer Therapy Evaluation Group (CTEP) and the NCI, said an industry representative. "The goal is to help the kids and get the drugs into them faster," she said, but each roadblock lengthens the timeline, and "by the time you're done, you haven't even begun the trial, and it's years." She enumerated the following specific concerns from the industry perspective: enrolling enough patients, particularly for very rare diseases; choosing which diseases to focus on; juggling the multiple regulatory bodies and agreements associated with global trials; and negotiating the complexity of combination studies, especially when the combination involves another company.

Concerns about Regulation / Communication is an Issue

In most cases, companies' reluctance to participate in Glo-BNHL stemmed from the need for a standardized backbone design that would be acceptable to the EMA, said an academic investigator who played a prominent role in the discussion. The problems were twofold: some products were in earlier stages of development and needed first-in-child and safety data that were difficult to incorporate into the trial; and some companies had an existing EMA-approved PIP that they were hesitant to return to the regulators to amend. Companies worry that regulatory authorities' re-review might open up new conversations about the drug that would be extended to the adult indication, said an industry representative. Regulators need to be supportive and streamline the approval process "so we can predict regulatory success," said another industry representative

Given the complexity of the biology, a strength of platform trials is that they enable researchers to identify negative results (e.g., failure to reject the null hypothesis) early through interim analysis and move on to other drugs, said an international regulator. However, the platform protocol for interim analysis may conflict with a company's own SOPs, noted an industry representative. It is important to de-risk the regulatory environment and facilitate communication early, she said, to get agreement on these plans.

Representatives of the FDA and EMA often talk about flexibility and engagement, but "our pharma partners don't…feel or trust that flexibility," said a different academic investigator. This "consistent theme" of industry reluctance to revise pre-approved iPSPs or PIPs in order to join platform trials, while the international regulator and another attendee advocate for these trials, is "definitely a gap," said one participant, who blamed it on the need for regulators to communicate with representatives of industry in the absence of the academic researchers. The attendee concurred, noting that "many times I feel like I am…getting indirect information." The international regulator would like to "close the triangle and allow us as regulators to talk to the academics" in those cases where regulatory product discussions are currently conducted only with the sponsor.

For the Glo-BNHL study, the regulator approved the study design before any companies were involved, which was "unbelievably useful," said an academic investigator. Companies were willing to concede some design features because regulators had already approved them; once the first company signed on, others became less hesitant.

"This is a big fear that we need to address, because it's very hard for a company to relinquish control. Who owns the data, and if we want to do an interim analysis more frequently, why would you stop us?... these little things become very big." – *Industry Representative*

Suggestion:

- Invite external stakeholders (academics and other experts) to participate in conversations between companies and regulators and get everyone aligned from the start.

IP is Not the Only Risk; Time is Crucial

Two important additional points differentiate pediatric from adult medicine and compound the risk to industry, said an industry representative. First, there may be minimal science to advance the pediatric indication beyond what was observed in adults, and second, some pediatric drug development is done to "check a box" based on a regulatory mandate. "We don't want to be a vehicle for meeting a company's obligation, because that is the wrong

incentive for consent," countered one participant. FDA only requires a pediatric study if they think there is potential for efficacy, added the attendee.

Companies will follow the science, answered the industry representative. But to convince them "that the obligation is a starting point and not an endpoint, and that platform studies offer a de-risking of that investment," he said, "it's not just the dollars…there has to be that benefit of time." A second industry representative concurred. The "fundamental question," added a third, "is this a mechanism that will get us to an answer faster, and what is the evidence of that being yes." "Fine, let's talk about that," said the international regulator: "let's agree on a PIP in 60 days [instead of 120], with certain prerequisites." Furthermore, he added, although the iterative nature of a platform trial requires researchers to engage more often with regulators; there is flexibility within the system that could potentially shorten the time required for reviewing a modification from 60 days to 30.

It is easy to engage industry in platform trials when products are post-approval and the goal is purely to benefit the community, with no other expectations or IP risk, said the first industry representative. But "when you layer in an obligation," such as a timeline by which the study must be completed, then it becomes harder to persuade companies to join platforms. "That's a challenge, to make sure that our platforms are ready to go at the time you need them," replied an academic investigator.

Alignment with the NCI is a Problem

The National Cancer Institute (NCI) is "the elephant not in the room," said one participant.[59] As the primary source of funding and access for pediatric cancer research in North America, NCI dictates the scientific review process and priorities, but working within the NCI-COG network involves a long timeline. "When we get alignment from the consortium or platform, then we go to health authorities and get alignment across the pond, and then CTEP[60] says no; it's just really hard and inefficient," said in industry representative. This lack of alignment serves as a disincentive to industry participation with academics, who are beholden to the NCI and its standards. A parallel challenge exists in Europe, said an academic investigator, where protocols approved by the EMA then need to be approved by each individual EU's country's competent authority for clinical trial approval.

[59] Note that representatives from NCI had been invited to participate in the workshop but were unable to attend due to preexisting commitments.
[60] See https://ctep.cancer.gov (accessed on December 30, 2024).

"There are too many folks with veto power…sometimes quibbling over things that are not that important." – *Industry Representative*

Pediatric Platform Trials Offer Multiple Benefits for Industry

Regulatory agreement between EMA and FDA is a "huge" de-risking factor for pharma, said an industry representative. Pediatric platform trials can be attractive if they save time and other resources, said a second. For companies that join a platform, the protocol can be "much more plug-and-play," offering time and other resource efficiencies, said an academic investigator. Given the rarity of cancers in children, one researcher noted the efficiencies of preserving patients and limiting the numbers in the control group. The efficiency of the design goes beyond numbers, added another researcher, noting that the academics who design them "make sure these trials are deliverable because…we work with these patients, we collaborate with patient advocates, and we understand the patient pathway."

"It's academic intelligence…we know our patient populations, we have brilliant statisticians, they bring a lot to the table that could benefit companies, but because we're early in this journey, there's no track record." – *Academic Investigator*

"Prediction [of regulatory success] is such a key point." – *Industry Representative*

"It's all about [pharma's] perception of risk and their interpretation of the rules, rather than actual risk or actual feedback that they might get." – *Academic Investigator*

A Biostatistician's Perspective

In a short presentation, one participant reviewed the pros and cons of pediatric platform trials from the perspective of a biostatistician. Within the context of rare pediatric diseases, she said, barriers to platform trials include: the possibility of a low accrual rate; the lack of a good early surrogate endpoint; the difficulty of obtaining real-time data needed to support adaptive design; opposition by the biostatisticians in CTEP[60] to "anything novel," including

platform trials in COG; IP concerns, particularly companies' objections to head-to-head drug comparisons; and a shortage of drugs to test. She suggested various approaches to addressing these barriers, such as: a willingness to accept a lower accrual and to wait longer for a more reliable endpoint; investment in staffing and training at the study sites; and engaging in early dialogue with CTEP, perhaps conducting pilot studies to alleviate concerns regarding feasibility.

The biostatistician enumerated various statistical considerations regarding platform trials.[61] Some of these are standard, such as Type 1 error (i.e., rejecting the null hypothesis when it is actually true, or a false positive) and power. Platform trials should use pre-specified methods to compare arms, and each arm should be compared to a contemporaneous cohort from the control group. For making multiple comparisons among groups that are not independent, such as different doses of the same drug, statistical methods may need to be adjusted, she said. While concerns about Type 1 error should not be allowed to terminate the study, "we still have to protect ourselves from making a really bad decision." Randomization is another concern, and she argued that pediatric oncology platform trials should be randomized and open label. The larger the control arm, the less of a problem with correlations among the test groups. Lastly, the biostatistician said, adaptive design should enable inefficacious arms to be dropped while gradually increasing accrual to "better" arms.

The Problem of Randomization and Controls for Pediatric Cancer Trials

As the pediatric trial population is broken down into increasingly small target-defined subsets of disease, randomization becomes infeasible, said an academic investigator. Additionally, parents are understandably reluctant to enter a randomized study when their child has already relapsed, given that the chance of survival - for example, after relapsed AML in children - hovers around 20 percent. Commercially available therapeutic options are similar to those at initial treatment, and, when the test drug has been successful in adults, parents want something new. However, industry will only join a platform trial if they are confident that the design will be approved, and regulatory authorities often view the lack of randomization as problematic. Patient advocacy has a role here, said an attendee, noting a "drumbeat" against randomization of pediatric trials.

[61] Roustit M, Demarcq O, Laporte S, Barthélémy P, Chassany O, Cucherat M, Demotes J, Diebolt V, Espérou H, Fouret C, Galaup A, Gambotti L, Gourio C, Guérin A, Labruyère C, Paoletti X, Porcher R, Simon T, Varoqueaux N. Platform trials. Therapies. 2023 Jan-Feb;78(1):29-38.

In the rare disease world, particularly in the relapse setting, control arms have become largely unfeasible and difficult to justify both scientifically and ethically, agreed an academic researcher. Some trial designs have no control arm, noted the biostatistician, with historical data on standard-of-care outcomes substituting for control data. The researcher suggested using artificial intelligence (AI) to create synthetic controls based on patients' age, disease state, and other characteristics when they first enter the study. Regulators want to know how these comparisons will be made prospectively, however, which requires developing methods that enable comparisons with little or no control arm. An industry representative cited the Children's Brain Tumor Network (CBTN),[62] a brain tumor real-world "evidence platform" with data that could be incorporated into clinical trials to provide a synthetic control arm.

Obstacles to International Collaboration on Platform Trials

Barriers to trans-Atlantic cooperation range from different definitions of terms to different regulatory systems. One of the biggest challenges has been pharmacovigilance, where the US and EU have conflicting expectations regarding the reporting of adverse events, said one participant. Drug distribution is another challenge, as is data privacy, with US privacy standards termed "inadequate" under the requirement of the EU general data protection regulations, said another participant.

Using Platforms for Phase I Studies

An academic researcher asked whether industry would consider testing safety and PK in children for drugs that had not been tested for that indication in adults. Many drugs show promise in animal models but have not yet been tested in humans, answered an industry representative, and this has created a need for first-in-child Phase I studies, but companies are reluctant to risk millions of dollars testing each drug. If platform studies could generate the data "faster and cheaper" and enable comparison among similar drugs at an early stage of development, there would be "a lot of enthusiasm," he said.

Suggestions:

- In a follow-up discussion, consider how to best generate the preclinical data needed to feed into the registration process for cancer drugs in children.

[62] See https://cbtn.org/ (accessed on November 26, 2024).

- Map out how platform trials might add value to this process and feed into the next decision point.
- Discuss how regulators can facilitate the industry's participation in platform trials and speed up the approval process of their respective development requirements (e.g., PIP or iPSP).
- Bring all regulatory requirements together in a "one-stop shop."

Overcoming the Roadblocks to Moving Pediatric Platform Trials Forward

The keynote speakers praised platform trials for their reduced cost, efficiency, relatively low business risk, and early endpoints, but "none of those apply in this room" because "cancer is the problem," said an academic investigator. Different obstacles exist: researchers want to get preliminary efficacy, not just PK; patients tend to be very sick with rare diseases; and the number of patients available for testing any particular treatment keeps getting smaller as a consequence of improved molecular definitions. Participants brainstormed a process for surmounting the obstacles to conducting platform trials for pediatric cancers.

Early Alignment: Coordinate Timelines for Approving Protocols Across Agencies

"The thing we all struggle with," said one participant, is retrofitting the study design within an already approved industry drug development plan (PIP or iPSP) to a platform or adapting the platform to fit the protocol. If approval could be aligned between FDA and EMA regulators "in the same timeline, that could give industry the confidence to come to us [academic investigators] …at the beginning," she said. This requires enhancing communication between the two agencies, said a regulator. In the meantime, sponsors should inform their project managers at the EMA and FDA when they submit a protocol to both agencies. The regulator recommended meeting with FDA regulators early in the development process. There is a growing number of examples of how this can work for all stakeholders. Nevertheless, for proof-of-concept trials that aim to address cancer's complexity, with multiple variables still open, it is crucial to anticipate flexibility and adaptation in order to allow for innovation and discovery.

Regarding troubles navigating the regulatory approval process, the regulator asked sponsors to "let us know…what your pain points are. Don't wait for a meeting like this to tell us." Given the rarity of most childhood cancers, said an academic investigator, "you're probably only going to do one trial…which is why the regulatory side of it is so crucial." If platform trials

were formally recommended for certain indications, then companies trying to develop a drug for one of those indications could work directly with the platform developers to write a protocol and seek regulatory approval, noted another participant.

Suggestions:

- Enhance communication between the EMA and FDA, to align their reviews of the same protocol.
- Make it easier for FDA and EMA regulators to participate in formal meetings together.

Model a Platform PIP/iPSP, or Model the Process

Noting that the FDA has developed a standard format for biosimilar iPSPs, an attendee suggested writing a standard platform iPSP or PIP for pediatric oncology. This could help recruit industry into platform trials, agreed an academic investigator. The EMA has disease-area-specific model PIPs, noted an industry representative.

Suggestion:

- Develop a model platform iPSP/PIP for pediatric oncology or for specific pediatric cancers.

Starting with a model PIP "puts the cart before the horse," countered an international regulator, who instead suggested mapping a path for aligning all the stakeholders. The priority should be to focus on an unmet need area and build an approach to address it, agreed an industry representative. This approach would have multiple components, including meetings, interactions among companies, and a platform-style PIP/iPSP.

Although everyone is after the same outcome, there are intricacies specific to industry, regulators, academia, and patient advocates, said another industry representative. The process needs to be mapped out so that everyone understands "what we have to abide by, what the legislation is, what the quality is, what our regulatory requirements are with monitoring, industry perspective…so that we can see the whole picture and achieve the ultimate goal."

Despite general agreement about the benefit of platform trials, the system in which they operate is not efficient, flexible, or agile enough to meet the needs of all stakeholders.

Therefore, a new process is needed, said a patient advocate. One participant suggested establishing a working group to extend the discussion beyond this meeting, into the process mapping stage. This discussion will need to be global, added another participant, noting that some indications lack sufficient patients to support a US-only platform trial.

Suggestions:

- Map a process for engaging stakeholders in discussions on how to use platform trials as an efficient solution for addressing unmet needs.
- Establish a working group to develop this process map.
- EMA and FDA should issue platform-specific scientific advice, offering feedback on trial design, agreeing to specific terms, and making an effort to uphold their commitments in a reviewer-independent manner.

> **"We don't want the PIP or iPSP to be the thing you're working towards; we want you to study the drugs." – *Attendee***

How to De-risk the Process so Pharma Will Participate?

"The recurrent theme is, 'we can't do it because the drug companies won't give us the drugs,'" and regulatory approval isn't the entire reason, said an academic researcher prominent throughout this breakout discussion. "What do we need to make pharma interested in coming on board into an academic platform trial?" she asked. An important feature of Glo-BNHL was the ability of the academic sponsor to discuss the study design with EMA regulators and gain their support without naming specific drugs, said a second researcher. This was possible because "there were a plethora of B-cell products in the pipeline," which would be much more difficult for a very rare condition, such as a molecularly defined, target-specific brain tumor, said a third researcher. "Start in a drug-agnostic way, but you also need to make sure that you have a pipeline," otherwise the study will be reliant on generic drugs and bespoke funding streams, he warned.

Suggestions:

- Hold a workshop with researchers and regulatory authorities to talk about general concepts of platform trial designs that would or would not be acceptable, in an asset-agnostic manner, to de-risk the process for pharma.

- Enable a way to get early feedback from the FDA on feasibility, to avoid "a creep in definitions" at the regulatory review stage.

The way to convince industry to provide drugs for platform trials is to get the companies involved earlier in the design process, said an industry representative. He offered the example of Pediatric MATCH: "We bought into the design, and then it was just a question of agreeing which drugs went into that platform study." Bringing companies in too early can have a downside, countered an academic investigator, who suggested, "somewhere in the middle when you've ironed out…core details."

> **"The challenge is that when we've identified the target, and drug companies have drugs that we're really interested in, that we can't bring them to the table…because what worries us is…the drugs don't get evaluated in this patient population at all." – *Academic Investigator***

> **"It's about involving us in that discussion as early as possible." – Industry Representative**

Data Monitoring is Expensive and Crucial

The real issue for industry is pharmacovigilance and trust in the data, said an industry representative. If industry is not comfortable with the way the data are being monitored, then "you have a very hard time regardless of who the partners are," he said, noting that academia and industry have different definitions of what it means to monitor data. Academia cannot fund every study at the highest level, countered two academic participants. Indeed, most of the COG studies "are designed with the explicit statement that we are not collecting data with an intention to file" for reasons of cost, said another investigator, but if the results are good, then "you're really dependent on the quality of the data collection systems [to] retrofit it."

Academia needs to ensure that its trials generate data with the extra audit trail needed for regulatory filing, countered an academic investigator, and industry needs to trust that

academia can work to this standard and be prepared to pay for it. An international regulator concurred, arguing that proof-of-concept evidence must be robust enough to indicate whether something works or doesn't, and that negative results should be published in order to move the science forward.

> **"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***

What Platform Trials Should Be Conducted for Pediatric Cancer?

"What's next…which tumor types have the highest unmet need in pediatrics that could really benefit from a platform trial?" asked an industry representative. Most unique drivers of cancer have been discovered and "we are still struggling to find the first signal on combinations that potentially can be registered," said an academic investigator.

The unmet need does not necessarily drive discovery in pharma, cautioned a second industry representative. He suggested that academic researchers might approach the problem from a different angle by looking at the industry pipeline and starting a two-way dialogue that balances this pipeline against the unmet need, focused on working together to shape future platform studies based on unmet need. LifeArc[63] is doing that through its Pediatric Bespoke Therapeutic Development workshops, which aim to identify both drug targets and clinically available compounds for roughly a dozen childhood cancers and select two diseases for international platform trials, said a funder. Taken together, pharma portfolios contain at least a few products that could potentially address unmet need, added an industry representative, who argued that the main issue is to inspire sufficient confidence in the platform so that industry will participate. Obtaining candidate therapies to test in a platform could be part of the process map, said an international regulator, and regulators could help by offering incentives to developers to test a promising asset for a specific disease in a platform trial.

[63] See https://www.lifearc.org

Summary

In summary, the oncology working group committed to three courses of action:

1. Establish a forum and working group to continue this conversation.
2. Engage in process mapping for platform clinical trials in oncology, looking at regulatory steps, disease mapping, partner consortia, and sponsors.
    - Derive lessons from the work done for pediatric AML and relapse B-NHL; start with process mapping for brain tumors et al.
    - Address the core elements in contracts that cause problems, "why it's an issue and what we can do to write contracts that eventually we all agree on."
    - Get "all the right people in the room at the same time…while the document is being written."
3. Design an example or model of a disease-specific or indication-specific platform PIP/iPSP.

Breakout Session: Multidrug Resistant Tuberculosis (MDR-TB)

Current capacity, opportunities, and challenges with pediatric trials in MDR-TB

Until recently, the treatment for drug-resistant tuberculosis included roughly half a dozen drugs for up to 18-24 months. Newer regimens containing recently developed novel agents are more effective, have fewer side effects, and have enabled the shortening of treatment durations down to six months in adults. However, access for children to these much-needed treatment innovations has been impeded due to long and avoidable delays in the pediatric trials of these new drugs.

The Burden of MDR-TB

Tuberculosis (TB) constitutes a massive burden throughout South Asia, sub-Saharan Africa, and parts of South America, said Dr. Anthony Garcia-Prats (University of Wisconsin-Madison and Stellenbosch University) who opened the session with a brief presentation. In 2022,

there were an estimated 10.6 million new cases and 1.32 million deaths from TB[64] This included 1.25 million new cases and 214,000 deaths in children under 15 years of age. The overall burden of MDR- and rifampicin-resistant (RR)-TB in 2022 was estimated at 410,000 incident cases and 160,000 deaths, with 30,000 of these cases occurring in children. Only 10-15% of these children received second-line drug treatment.

The majority of pulmonary TB in children is paucibacillary, with many patients having insufficient mycobacteria in their sputum to be detected with most currently available tests, said Garcia-Prats. A high proportion of children with TB are expected to have a clinical diagnosis without microbiological confirmation, which impacts trial eligibility and outcome assessment. Because the course of the disease and response to treatment in children with pulmonary TB is similar to that in adults, it is reasonable to extrapolate efficacy from adults to children for most forms of TB, with the exception of severe forms of extrapulmonary tuberculosis (EPTB) and TB meningitis.

Current Treatment Approaches to MDR/RR-TB

The current treatment regimen for MDR/RR-TB uses roughly half a dozen second-line drugs from a period of six-to-nine months up to two years, said Garcia-Prats. While the newest of these drugs are more effective, have fewer side effects, and enable shorter treatment durations, many children do not have access to them because of delays in studying them in children. A recent communication[65] from the WHO recommends a new six-month regimen for MDR-TB, but delays in pediatric evaluations of one of the drugs in the regimen make this treatment effectively inaccessible to many children with MDR-TB or RR-TB.

The Challenges of Evaluating New MDR-TB Drugs in Children

For the purpose of registration, trials of TB drugs in children are designed to evaluate pharmacokinetics (PK), dose, and safety (Phase I and Phase II), said Garcia-Prats. The fundamental clinical trial design is conserved across compounds, which lends itself to a platform trial, he said. It has been considered acceptable to extrapolate efficacy of treatments for most forms of TB from adults to children of all ages down to newborns,

[64] See https://www.cidrap.umn.edu/tuberculosis/who-report-shows-global-tuberculosis-cases-are-rising (accessed on January 24, 2025).
[65] See https://www.who.int/publications/i/item/B09123 (accessed on February 3, 2025).

relieving the need for efficacy trials in children. This includes children across the age spectrum, except for those with severe EPTB. Extrapolation is based on exposure matching to the optimal dose determined in adults, taking age and weight effects into account.

Pediatric TB trials have followed protracted timelines; they are starting too late and taking too long, said Garcia-Prats who gave the example of three relatively new TB drugs: delamanid, bedaquiline, and rifapentine. Following their approval for use in adults, it has taken anywhere from eight to 13 years for these drugs to be approved for use in children. Indeed, pediatric trials of bedaquiline have yet to be completed, even as medical providers are seeing clinically significant rates of bedaquiline-resistant TB. Meanwhile, pediatric trials of pretomanid, a first-line recommended drug for adults and older adolescents with MDR-TB, only started last year. This is a systemic problem not confined to TB, said Garcia-Prats, and it "has very concrete implications for children."

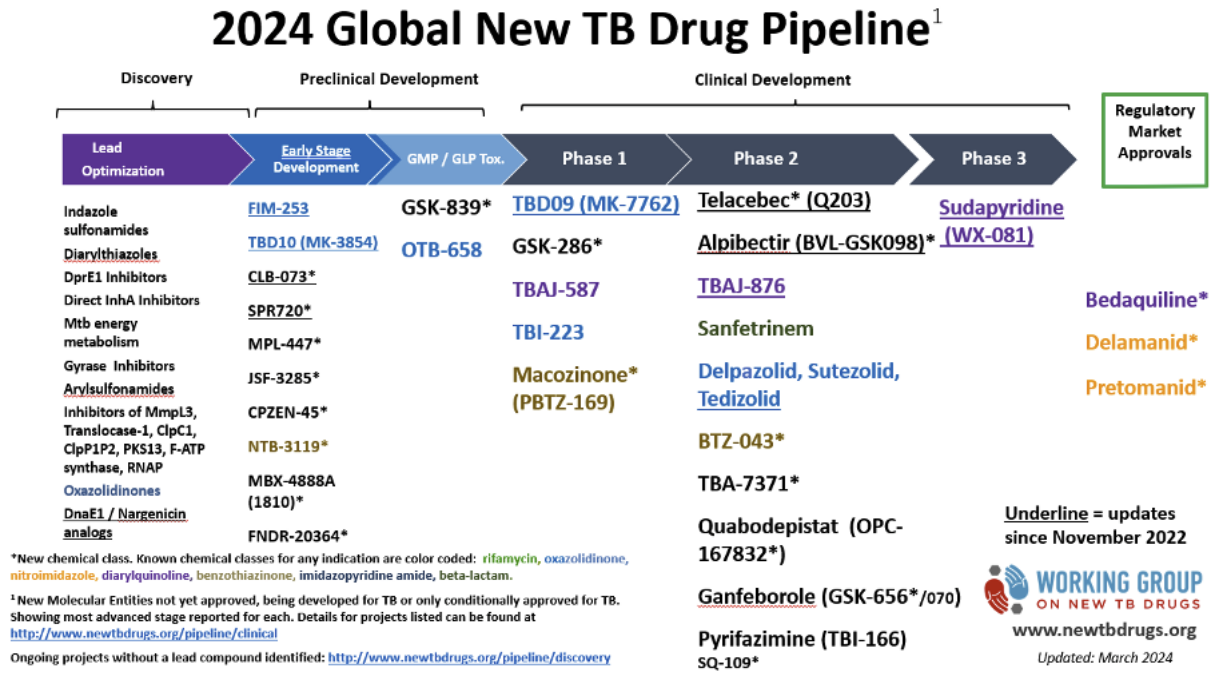
Sources of Delay in Trialing MDR-TB Drugs in Children

According to Garcia-Prats, the main sources of delay for pediatric MDR-TB trials include: limited funding and low priority for these studies; delayed formulation development for the youngest children; lack of clarity regarding optimal trial design and required data; inefficient trial design, including "very constricted eligibility criteria;" lack of sufficient pediatric trial sites in settings with MDR-TB; and operational inefficiencies of doing standalone studies, which lack coordination and require capacity-building.

New drugs are needed for treating MDR-TB because resistance is increasing to some of the drugs currently in use, said Garcia-Prats. He showed a "quite robust" pipeline of drugs currently in development (Figure 8), some of which may be safer and more effective than current first-line TB drugs. However, he said, "we really need some innovative thinking and investment in research" to bring these promising new drugs to children with MDR-TB.

Figure 8. 2024 Global New TB Drug Pipeline[66]

[66] Working Group on New TB Drugs. See https://docs.google.com/presentation/d/0B3BR7L--n_1AQ0c1ZjY5bzF3VnM/edit?resourcekey=0-2_9AtXD5aeK9t_lpHwllcA&slide=id.p1#slide=id.p1 (accessed on March 31, 2025).



Platform Trial for Pediatric Evaluation of New TB Drugs for Registration

General Aim and Advantages of a Platform Trial for Pediatric MDR-TB

The focus of this breakout group is to envision a platform trial aimed at registering new TB drugs for children, said Garcia-Prats. The platform trial would have a master protocol that outlines fundamental design elements, along with compound-specific protocols, each of which would consist of a single-arm Phase I/II trial focused on PK, safety, and tolerability. There would be no comparison between study arms.

A platform trial could address some of the sources of delay in pediatric TB trials, said Garcia-Prats. A master protocol would provide clarity regarding trial design, and necessary investment in more pediatric trial sites would improve coordination and lead to operational efficiencies. A multidisciplinary group of experts,[67] led by Garcia-Prats and a civil society

[67] CHEETA: Chasing Expedited and Equitable Treatment Access for Children with TB. See https://www.pediatrics.wisc.edu/tony-garcia-prats-awarded-grant-to-assess-new-pediatric-antituberculosis-developments/ (accessed on January 28, 2025).

representative, has been working to systematically identify sources of delays in pediatric TB drug evaluations and identify potential solutions and could help move forward some of the results of this meeting, he added.

Project to Accelerate New Treatments for TuBerculosis (PAN-TB)

An industry representative described the PAN-TB Collaboration, a partnership of six organizations coordinated by the Bill & Melinda Gates Medical Research Institute (Gates MRI).[68] PAN-TB will evaluate new regimens for treatment of active TB in adults in order to achieve a Target Regimen Profile[69] (TRP), said the industry representative. PAN-TB is developing Phase IIb/IIc treatment-shortening trials and testing drug combinations in animal models. It currently has one active clinical trial, which is not a platform trial. PAN-TB is just one of many such collaborations, he noted.[70]

PAN-TB is focused on Phase II, and once a regimen is selected to move to Phase III, that work will be conducted by Gates MRI, said the industry representative. The first two drugs tested in PAN-TB failed to meet the TRP criteria in Phase II.

Lessons from PAN-TB to Inform Pediatric TB Platform Trials (Figure 9)

No single company has sufficient assets to bring a completely novel TB drug regimen through the entire clinical trial process, said the industry representative, so partnerships are essential. PAN-TB is not entirely funded by the Gates Foundation, and it works because all the partners have combined forces and made significant contributions, both financially and in the form of drugs, protocol development, and governance. There was a collective approach to trial design and conduct of the trial is governed by all the partners, all of whom meet regularly.

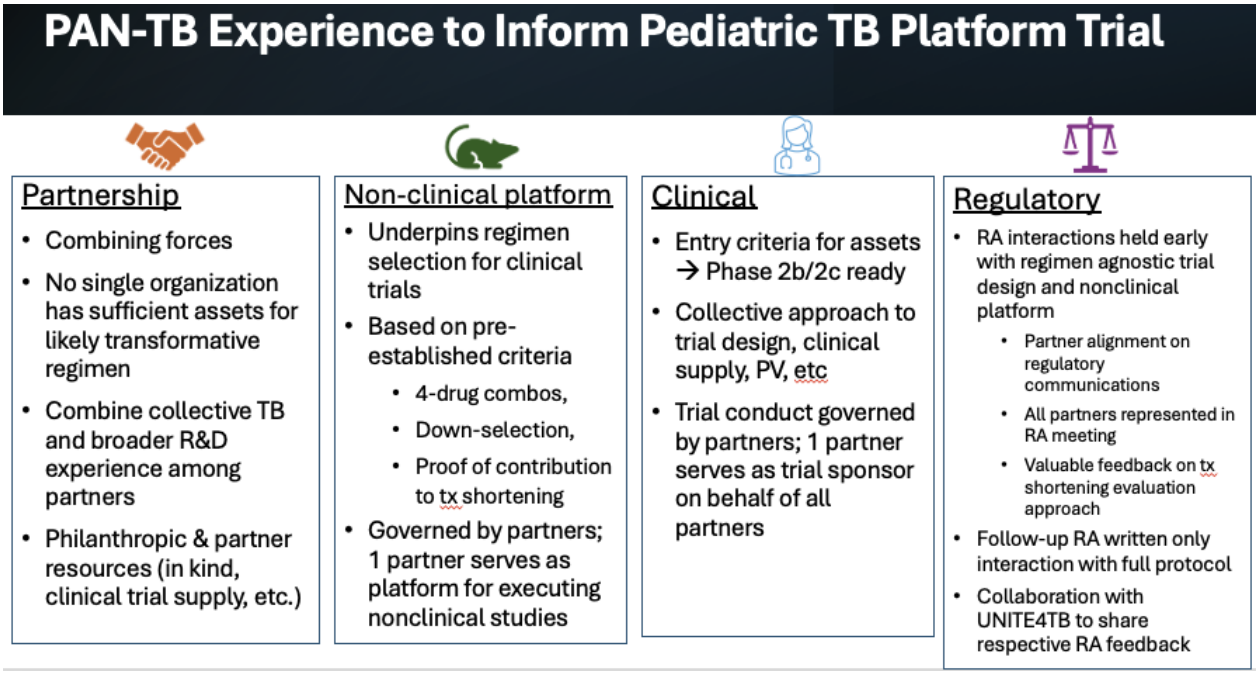
The non-clinical platform is essential for prioritizing which drugs and in which combinations to move forward for clinical testing, said the industry representative. Four-drug combinations are tested in a relapsing mouse model, which enables regimens to be evaluated far less expensively than in clinical trials. For a drug to be moved forward into clinical testing, there

[68] See https://www.pan-tb.org (accessed on January 28, 2025).
[69] According to the industry representative, the PAN-TB TRP looks very similar to the WHO TRP on PAN-TB. See https://www.who.int/publications/i/item/9789240081512 (accessed on January 28, 2025).
[70] The industry representative cited UNITE4TB, TBTC, ACTG, SmartTB, and PanACEA.

must be proof of its contribution to treatment shortening in mice. Decisions are made based on pre-established criteria and governed by the partners. Entry into the clinical trial requires that drugs be Phase IIb ready.

Regulatory interactions began early in the life of the PAN-TB collaboration, said the industry representative. The partners approached the FDA with a preliminary, regimen-agnostic trial design and received valuable feedback on their protocol. Design elements like randomizing the duration of treatment, collecting Phase III endpoints, or stopping some patients after two months to test for relapse, were "pressure-tested" with regulators. PAN-TB also communicates frequently with Unite4TB,[71] a collaboration with a similar trial design.

Figure 9. PAN-TB Experience to Inform Pediatric TB Platform Trials[72]



The industry representative highlighted the following key points for collaboration on a novel TB regimen development program: well-defined goals; mutual understanding among the partners regarding governance, execution, and managing issues; and clear and consistent communication among the partners at all levels. Organizations differ in terms of their

[71] See https://www.unite4tb.org (accessed on February 3, 2025).
[72] From a presentation by an industry representative on October 29, 2024.

structures and priorities, he noted, so their project-related goals (roles, budgets, timing, etc.) need to be explicitly aligned.

It Takes a Consortium to Develop a TB Treatment

"We wouldn't be here today without the Gates Foundation," said a civil society representative, noting that all the compounds currently in development for TB are the products of collaborations within consortia of academic, industry, TB Alliance, and other organizations. That said, every entity has its own strategic agenda, and a lot of resources go into aligning them; it took 20 months of lawyer negotiations just to finalize a data-sharing agreement for PAN-TB, said an industry representative.

Can Development of MDR-TB Drugs be Accelerated by Testing in Drug-Sensitive (DSTB) Populations?

The Proposal: Test MDR-TB Drugs in DSTB Populations

Participants debated the utility of incorporating new drugs for MDR-TB into a standard, drug-sensitive pediatric TB trial, in order to get the necessary PK data more quickly than can be done by recruiting children with MDR-TB, who constitute a "super hard-to-enroll population." An academic researcher suggested giving these drugs to patients with drug-sensitive TB for the number of weeks needed to get PK data and then transferring the patients to standard-of-care treatment. This might generate short-term PK data but not long-term safety data, another researcher noted. As long as some fraction of patients in each age bracket had MDR-TB (and would therefore remain on the test regimen), that could potentially save years of recruiting and still generate both the necessary amount of PK data and sufficient long-term safety data in each key age bracket, countered the first researcher. Safe doses can almost always be extrapolated using allometric scaling from adults down to age two years (but not lower), noted a third researcher.

Concerns: Regulatory, Ethical, Scientific

Participants discussed the regulatory and ethical implications of the researcher's proposal to test new drugs for MDR-TB in children with DSTB. "I don't think if I were a parent, I would

sign that," said one participant, "the individual risk-benefit argument would be a challenge." The MDR-TB drugs bedaquiline and clofazimine have such long half-lives that it would take several months just to reach steady state and get to the point where PK sampling could be done in an optimal way. Furthermore, some of these drugs have "quite disturbing adverse events," and therefore should not be given to children who could otherwise receive drug-sensitive TB treatment. This participant noted a "principle of drug development, which is, don't test your drug in a population [where you don't intend to use it]."

Testing drugs on individuals with exposure to or latent TB offers more opportunity for enrollment but is "far worse" from a risk-benefit standpoint, added an academic investigator. "You have to have a whistle-clean compound" for treating people with latent TB, he said, noting the example of pretomanid, which is only approved for study in girls because it had testicular toxicity in rats, despite having demonstrated no toxicity in primate or human studies. Another participant noted that an infant exposed to TB in the first year of life has a 30 to 40 percent chance of acquiring active TB, which is "a huge risk" that may affect the risk/benefit calculation.

Not everyone was convinced that, even after getting PK information more quickly by testing drugs on DSTB populations, the number of patients needed for long-term safety data would be reduced. In the case of MDR-TB, the primary justification for sample size is PK, so there might be justification for testing PK in a DSTB population and then testing long-term safety in a smaller MDR-TB population, said an academic investigator.

Support for Trials of MDR-TB Drugs in DSTB Populations

The researcher's suggestion to test new drugs for MDR-TB in children with DSTB has an analogue in HIV clinical trials, noted one participant. People with HIV exposures are considered high-risk despite the fact that their actual infection status is unknown, "and the need to generate that safety [data] and information makes for an acceptable risk" when it comes to testing treatments, he said. Indeed, the early bactericidal activity (EBA) studies in adults follow a similar approach to one proposed above, starting with monotherapy to demonstrate PK, safety, and efficacy, and then switching to the standard course of treatment, said an industry representative. One participant noted that bedaquiline and delamanid were initially tested only in patients with MDR-TB due to safety concerns, but newer TB drugs like TBAJ-876,[73] as well as the PBOS (pretomanid, bedaquiline, OPC-167832, and sutezolid) and

[73] See https://www.newtbdrugs.org/pipeline/compound/tbaj-876 (accessed on February 3, 2025).

DBOS (delamanid, bedaquiline, OPC-167832, and sutezolid) trials,[74] are being tested in adults with DSTB, which accelerates enrollment. These drugs are, however, are intended for people with DSTB, unlike many of the drugs currently in development for MDR-TB.

Scientific and Trial Design Considerations

Participants addressed a set of questions regarding TB trial design, responding to position statements that had been prepared in advance for each question.

Question 1: Consensus on the case for extrapolation and prioritization of Phase I/II trials using a master protocol.

> **Position:** A phase I/II platform trial focused on PK, dose-finding, safety, and acceptability of new TB drugs in children 1) is appropriate to generate the required data on new TB compounds in children, and 2) will accelerate the required pediatric evaluations substantially.

Participants expressed agreement with extrapolating efficacy from adults to children. One academic investigator noted that children could probably benefit with a shorter duration of treatment than adults, based on the Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children (SHINE)[75] trial and other studies. Indeed, the TB burden tends to be higher in adults, so it should be harder to find an effective regimen in adults than in children. These differences between adults and children demonstrate the importance of continuing to conduct Phase III trials in children to identify less-intense, shorter regimens with already-approved drugs that could work in this population, she added, even while Phase II platform trials remain essential for dosing and PK.

Regulatory Agencies are Not Aligned

[74] See https://www.prnewswire.com/news-releases/pan-tb-collaboration-to-advance-investigational-tuberculosis-drug-regimens-to-phase-2-clinical-trials-301607557.html (accessed on February 3, 2025).
[75] Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, Hissar S, Choo L, Musoke P, Mulenga V, Mave V, Joseph B, LeBeau K, Thomason MJ, Mboizi RB, Kapasa M, van der Zalm MM, Raichur P, Bhavani PK, McIlleron H, Demers AM, Aarnoutse R, Love-Koh J, Seddon JA, Welch SB, Graham SM, Hesseling AC, Gibb DM, Crook AM; SHINE Trial Team. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med. 2022 Mar 10;386(10):911-922. doi: 10.1056/NEJMoa2104535. PMID: 35263517; PMCID: PMC7612496.

The FDA and EMA have different views on what constitutes acceptable extrapolation, with disagreement regarding children under five years old, said an industry representative. This is due in part to differences in the pathogenesis of the disease, with a higher risk of extrapulmonary TB in young children and FDA's concern about extrapolating from pulmonary TB to extrapulmonary TB. However, noting that patients under five years of age are not served by a complete absence of dosing information, she suggested that the two agencies seek alignment to enable labeling for this population.

The EMA guidance allows extrapolation of drugs for pulmonary TB from 0-18 years, while the FDA guidance considers it acceptable for most pediatric populations, with the exception of children less than five years of age, said an academic investigator. In this instance, he said, there are three choices: for the FDA to put no information in the label, which is "not a good plan;" to tightly define dosing for children under five as "pulmonary only;" or to note on the label that efficacy is not extrapolated, "but doses of X, Y, and Z have been studied," which would be "an unusual decision." It was noted that everything is subject to regulations in the countries with the affected populations including India, China, Peru, et al.; international Guideline Development Groups use a "very different process than the FDA or the EMA."

Support for Extrapolating to Any Age

From a scientific perspective, it should be possible to extrapolate from adult pulmonary TB trials to children of any age with pulmonary TB, said an industry representative. Children with TB meningitis are easy to spot and could be excluded from trials. Even if kids with extrapulmonary TB were included in trials, they could remain on a completely optimized background regimen that should be sufficient for treatment, regardless of the efficacy of the investigational drug, said an academic investigator. Furthermore, given their higher risk of morbidity and mortality, "the benefit-risk ratio is actually in favor of enrolling children under two."

In the case of TB meningitis, children have been receiving a higher dose than adults for the shorter regimen, said another academic investigator, so "that's actually a case where we don't have an adult target to extrapolate from." The real concern is whether their TB is disseminated, replied an industry representative. It was noted that companies should not be required to study these drugs in children with TB meningitis unless they were trying to obtain an indication in TB meningitis.

Question 2: What are the relevant ages for inclusion in a trial and is there a need for an age de-escalation approach?

> **Position:** Children 0 to <18 years of age would be relevant to be included, depending on inclusion of older adolescents in adult trials. There are no outright barriers to parallel enrollment of pediatric age groups, and there are potential benefits to doing so. This would need to be considered on a compound-specific basis, considering PK and safety characteristics. If there is high variability in a compound's PK or substantial uncertainty in its metabolic pathway and maturation characteristics, then a staggered approach might be preferred.

Allometric scaling works well down to age two, and it's under two that the models really need testing, said an industry representative. Age de-escalation (testing progressively lower age groups in sequence) should not be a standard requirement; parallel enrollment across the age groups should be allowable, added an academic investigator.

Definition of age groups is somewhat fluid. Most adult trials go down to age 14, though some have gone down to age 12 or even age 10. Several participants supported moving rapidly from adult trials to age 12 and under, but age-appropriate formulations need to be ready and juvenile animal studies must be complete before studies can begin in children.

One participant proposed pushing the timing on pediatric trials by including children from ages, for example, 12 to 18 in the adult Phase III trials, and then obtaining PK data in children ages two to 12. For children of lower body weight, inclusion in adult trials might require weight-based dosing to achieve comparable exposures. This raises an ethical concern, noted a second participant, because a weight cutoff can effectively keep young adolescents out of trials that they are meant to be part of. To address this, the trial design could allow for dosing based on weight instead of imposing a weight cutoff.

HIV offers an important precedent for this conversation, said a UN agency representative. Regulators are strongly aligned in allowing for simultaneous enrollment of different age groups in HIV trials based on weight, down to age two. TB raises concerns of safety, PK, and ethics - essentially the same as HIV - and should therefore be amenable to a similar approach.

The only way to determine drug PK in children under two is to do the experiment, said an academic researcher, and the only way to make a drug available to all children is to conduct trials in all children. "If we feel that the safety issue is completely unmanageable in the smallest kids, then perhaps we shouldn't be using this drug in small kids at all." However,

linezolid has "absolutely massive" benefits, and mothers can detect the neuropsychiatric side effects of delamanid, "so there is a lot of space for looking at safety even in the absolute youngest ones," she said. For drugs with a good safety profile in adults, the question becomes whether to start at a likely effective dose based on extrapolation from adult data or to start at a lower dose and proceed gradually in order to minimize potential toxicity, said a second researcher. This field would benefit from platform studies to look at multiple drugs, including older ones for which there are still a lot of unanswered questions, said a third.

Question 3: Should new TB drugs be evaluated in the novel regimen being studied in adults, OR may they be evaluated as added to an optimized background regimen (OBR)?

> **Position:** Barring a concern about a drug-drug interaction or safety signal related to the combined use of drugs, evaluating each TB drug separately (added to an OBR) would provide sufficient data to ultimately combine the drug in regimens with other new and existing TB drugs. The key consideration is that the data to be generated must support extrapolation of the candidate drug's PK and safety to its expected indication.

According to the position statement, it would not be necessary to study the exact novel regimen in children that is going to be approved for use in adults, said an industry representative.

Support for Evaluating Drug Safety and PK of New Compounds Separately on Top of an OBR

New compounds for treating TB are being trialed for different indications: DSTB, DRTB, and MDR-TB, without certainty of their ultimate target, said one participant. There is value in understanding how to dose these drugs in children, irrespective of the regimens they will ultimately be used in, because they will have to be demonstrated to be safe in children in order to be used at all.

Concern About Evaluating a New Drug with an OBR

Pretomanid was not developed as a new drug on top of an OBR, cautioned a civil society representative. "Learn as much as you can in adults, learn the translational bits, and then get it in kids as quickly as possible" using the same regimen that was studied in adults, he said. "When you say pretomanid and OBR, I don't know what that is. That's never been done

before." An academic investigator concurred, adding that pediatrics should not be the place to identify new drug-drug interactions. Rather, the primary aim for pediatrics should be to describe each individual drug's PK. "The risk is still there, even with a well-described optimized background regimen…you're adding a new drug and there could be unexpected drug-drug interactions…That's why I'm favoring testing it in that current regimen," she said. "Then going forward, we can mimic what's been done in adults or change the regimens based on what's seen in adults."

The neuropsychiatric symptoms that emerged from the delamanid TB preventive treatment trial would have been much more difficult to discern if the drug had been given on top of an OBR, added an industry representative. "You want to understand the drug in a way that it's intended to be used," he said.

But How Else Can One Get PK Data in Children?

Getting PK data for a new drug on top of the OBR is not the same as defining a different drug regimen, argued an academic investigator. The new regimen is defined in adults, and efficacy is extrapolated to children. However, in order to get the PK data that defines the dose that matches adult exposures and safety, each compound in the regimen needs to be individually administered to children. If it makes sense to do this on top of an OBR, he said, it would be acceptable, barring any drug-drug interactions.

Can Efficacy be Extrapolated before Phase III Adult Trials are Completed?

If the PK study in children is done early, before having the results of the Phase III trial in adults, then it won't be possible to extrapolate efficacy, noted one participant. In this case, she argued, "we really have to carefully look at efficacy in kids," because they are taking on the risk of an unproven drug and should have the possibility of benefit. Efficacy is a continuum, not a binary, countered a second participant, and "you're going to have an idea about efficacy long before Phase III," so it's possible to do a study in children before the Phase III adult study is complete, knowing something about a drug's efficacy. "I'm curious how regulators would view that," said a third.

Platform Trials Can Speed Up the Process

It is essential to determine PK in children in order to use the adult regimen, said an industry representative. Getting all the individual PK data first provides the essential information needed to administer the entire regimen optimally in children, and this can speed up the process far better than trying to work out the entire multi-drug regimen in a platform trial design. Right now, everyone over age 14 with RR-TB can receive BPaL (bedaquiline + pretomanid + linezolid) and BPaLM (BPaL + moxifloxacin) regimens, she noted, but children cannot use it because there are no data on the appropriate dose and safety of pretomanid in younger children. A platform trial will allow this information to be obtained much faster.

"I'm happy to leave the regimen work to the adult clinicians and for us to answer the PK and dosing questions, because that's always what leaves the children in the dust…The real benefits where we're going to get our wins would be in really quickly moving forward with PK and safety work." – *Academic Investigator*

Trial Site Capacity and Operational Issues

Trial sites bring together multiple issues: regulatory, pharmacy, laboratory, and community. Participants considered which were most critical for the success of pediatric platform trials.

Question 1: What are critical characteristics/capacities required for trial sites to participate in a pediatric platform trial? What opportunities are there to tap into existing trial sites or build new site capacity?

What do Pediatric Platform Trial Sites Require?

An academic researcher questioned whether any characteristics would differ for platform versus investigational pediatric trials. About 90 percent of investigational trial sites can handle platform trials, said another researcher. What makes some sites unsuitable for platform trials is usually not that they lack the capability to do the basic blood draws and imaging, but rather that the pediatric staff is under-resourced, especially in public clinics. They might be able to test one drug but keeping up with ten different molecules can be overwhelming. For most international sites, "the barrier to doing multiple compounds simultaneously is actually doing pediatric trials at all," added a third.

In South Africa, most of the sites engaged in pediatric trials are doing multiple pediatric trials simultaneously, continued the third researcher, so "the platform model would save an enormous amount of time from a regulatory perspective, from a cost-saving perspective, and from a complexity perspective."

Where are the Sites?

Trial sites must be located in high disease burden areas. Outside of South Africa, not many sites are doing registrational level trials in TB, said one participant. However, there is untapped capacity in sites that are working in other areas, such as HIV, Covid-19, or malaria. HIV-focused sites are just coming online in countries with high DRTB disease burdens, including India, the Philippines, Pakistan, Bangladesh, China, and Peru. DRTB is a "massive burden" in Eastern Europe and Central Asia, said another participant, and the SMART4TB (Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination) Consortium[76] is trying to include sites in this region, but it can be challenging to enroll

[76] See https://tbcenter.jhu.edu/smart4tb/ (accessed on March 31, 2025).

children in clinical research in some Eastern European countries..

Trial Capacity is Low, but Efforts are Underway to Increase It

Of an estimated 30,000 children with MDR-TB, perhaps 3,200 to 5,500 are undergoing treatment, so this is a small population base to begin with, said an attendee. Fewer than ten sites worldwide are enrolling children with MDR-TB in clinical trials. Taking all sites together, the total number of children who could be enrolled in a calendar year is less than 100, which is a "major, major problem," said an academic investigator.

The countries with the highest burden of DRTB also tend to have more issues with logistics and infrastructure, said an industry representative, citing her experience with the (Innovative Health Initiative, Innovative Medicines Initiative) IHI IMI project Connect4Children,[77] a pan-European network that aims to improve the process of conducting clinical trials for children. Investigators who have access to the patients need help to be able to do registration trials, she said.

TB is handled programmatically around the world (outside the US), said another industry representative, with the bulk of patients seen in public clinics that are not academic or nonprofit. Some of these sites are very well-developed, as in South Africa, but there needs to be greater diversity among the trial population, he said. New sites should be developed where the public system can be aligned with a clinical trial, and this needs to be done strategically, to keep sites active and avoid gaps that result in loss of institutional knowledge.

Recognizing and Overcoming the Barriers to Capacity

Participants listed the main barriers to pediatric MDR-TB trial capacity as lack of expertise, inadequate administrative and regulatory oversight, and poor access to the affected population.

Approaches to these barriers could include simplifying protocols, said an industry representative: "you can't overburden them, because that's when quality starts to fall apart." Because pediatric capacity can be drained by the demands of caring for patients, program sites need the capacity to handle their clinical care before they can be considered for a trial, said an academic researcher. This would require investment. "The most productive sites are

[77] See https://conect4children.org (accessed on February 3, 2025).

ones where people are invested primarily in doing the research and doing it well," said a second researcher.

SMART4TB[76] is trying to build capacity for pediatric DRTB trials, added a third researcher, who described several different strategies being employed. In one, children are enrolled from the entire country and travel to the capital to participate in the clinical trial. In another, SMART4TB is trying to build trial capacity *de novo* at a clinical site that sees 120 children a year. In a third location, capacity for pediatric trials is being built at a site with existing capacity to run clinical trials in adults.

The trial in which a fourth researcher conducts her clinical studies is a large collaboration, and all participating trial sites have been able to maintain funding throughout, she said. This is crucial because the research staff has stayed and grown over time. "The biggest thing is having contingency, so that if a project ends, you don't lose the people that built up the expertise," she said.

> **"There are people who can do this. There are patients who are getting diagnosed in these settings, but they're not just going to show up at our doorstep and ask to be part of the trials. We're going to have to invest some resources." – *Academic Investigator***

Question 2: Are there anticipated regulatory or other practical challenges with implementing Candidate Specific Protocols (CSPs) as protocol amendments?

Anticipate Your Compounds, and Use the Manual of Procedures (MOP) to Make Changes

The hardest thing to change is the trial protocol, said an academic researcher. It is easier to add a molecule or details to the appendix, and the easiest thing to change is the manual of procedures (MOP). Therefore, when it comes to collecting PK data for ten different drugs, rather than describing the timing for each set of blood draws in the protocol itself, he moves these details to the appendix and the MOP. "You commit to [describing] PK parameters," and when a new molecule becomes available a year later, "you can just add it without having a whole series of changes to your protocol."

When starting a new trial platform, the academic investigator plans out sampling schemes for all molecules that might enter the trial at a later date, in a compound-agnostic fashion. "The key is to take all of the drugs that you see yourself studying for the next five or ten years…and map out optimal sampling windows for each of those molecules and how much blood you're

going to need," this same researcher said. Regulators will need to see all the dosing, but that level of detail should be pushed down to the CSP and not be written in the master protocol. This researcher's sampling studies, looking at drugs that are given as part of standard clinical care, are different from studies that introduce new drugs into patients who need therapy for DRTB, noted one participant. A more analogous regulatory situation might be the experience of pediatric oncology when it introduces new drugs into platform protocols, where these drugs are being evaluated for registration.

In a platform trial designed for another disease state, the master protocol had the basic elements of the clinical trial design, while the individual CSPs were longer and went into specific details, said an industry representative. This was a more cumbersome design initially, but the institutional review board/ethics committee and regulatory reviews went faster by the third or fourth arm. "It's hard to see all the benefits at the beginning," she said.

In South Africa, a protocol undergoes a full review by a large panel, with amendments reviewed by a small group on a rolling basis, said an academic investigator. He wondered how they would manage an amendment that includes "a full protocol for a new compound."

Industry & TB Drug Developer Perspectives

The platform trial being considered is not a standard comparative approach assessing efficacy, noted one participant, but more likely a set of multiple single-arm PK and safety studies designed to test dosing and preliminary safety. Compounds would not be compared to one another but would potentially benefit from a platform with a standard protocol and a structure that is ready to go when a new drug for MDR-TB is ready to be tested in children. Representatives of industry and drug developers shared their reflections.

Understanding and Reaching Patients with the Right Formulation

Industry's concerns vary depending on whether the drug is new or already available, said an industry representative. There will also be chemistry, manufacturing, and controls (CMC) concerns related to the formulation of the drug, as drugs for children may require flavoring, alternative excipients, or different routes of administration. All these concerns need to be resolved up front, during the trial design stage. The formulation also needs to be stable in hot, humid environments, said a second industry representative. A platform approach might help drug developers better visualize the target profile for their formulations and illuminate key principles regarding how the formulation could be developed, suggested another participant.

For drug developers in the US, said the first industry representative, the necessary cultural insight to get the right formulation at the right time for people living in other parts of the world is often lacking. The second concurred. "Brazil, Kenya, Uganda, everybody has their own way of doing things," and this includes regulation, she said. Furthermore, individual industry partners differ in their priorities and commitments to global health. Trials need to be more decentralized, going to the patient where possible, in order to facilitate recruitment. "That's especially true with pediatrics," she said, "because if a mom's got one sick kid, she probably has a couple more kids."

> "Do we all have the same commitment to this population? It's a worthy and a noble struggle, but it is a struggle nonetheless." – *Industry Representative*

There are Many Tradeoffs in Comparing Platforms to Standalone Trials

Comparing the relative benefits of a platform trial vs. a standalone study involves many considerations, said an industry representative, including speed, cost, upfront investment, and the resources needed. "Small decisions are not so small," including who is responsible for what parts, which quality systems will be used, dispute resolution, governance structure, and terms for ending the trial; "it's a long list of things, [and] the more that you do upfront, the more comfortable sponsors will feel in joining the platform trial." Another problem is attributing safety events to individual drugs when they are combined, said a second industry representative, noting that pediatric trials often combine investigational drugs with the OBR.

Data Standardization is a Significant Issue

Data intended for registration must hold up to intense scrutiny, noted an industry representative. Issues of data standardization can create a risk for industry partners in the context of a platform trial, he said, as can different companies' approaches to data collection. Indeed, harmonizing data in a platform trial and "managing that harmonization," particularly when it comes to the interpretation of evidence by different regulatory agencies, can be "an almost insurmountable task," said a second industry representative. To address this, he suggested conceiving of a platform trial as "a modular construction," where modules specific to particular drugs or industry partners could be added or removed.

Data standardization constitutes a practical challenge that, along with other issues described above, requires proactive engagement by all parties up front. At least with a platform trial, regulators only need to be approached once and not for each stakeholder separately, and this can aid harmonization, suggested the first industry representative.

The pediatric MDR-TB field might benefit from the experience of other disease areas to enable platform studies to be done at scale and more efficiently than individual trials, said one participant. Governance, IP, and decision-making structures associated with platform trials may be quite similar across disease areas. Participants noted that guidance documents exist to help develop master protocols and CSPs for platform trials. EU-PEARL offers tools and templates for platform trial operations,[78] and ICH M11[79] is being rewritten and will be available in electronic form.

[78] See https://eu-pearl.eu/tools-and-templates-for-pt-operations/ (accessed on February 3, 2025).
[79] See https://www.ema.europa.eu/en/ich-m11-guideline-clinical-study-protocol-template-and-technical-specifications-scientific-guideline (accessed on February 3, 2025).

"You have to answer whether the platform is sufficiently generic and yet customizable in a way that meets everybody's needs, and [the choices between generic and customizable] are very, very different." – *Civil Society Representative*

Platform Trials Require a Robust Drug Pipeline and Funding

Platforms would have to generate a robust pipeline that could support ten or fifteen years of activity in order to justify the upfront investment and long lead time, said an attendee, noting that the lead time could be reduced by engaging stakeholders now, discussing what a master protocol would look like, and moving the conversation forward. An industry representative concurred, saying that regulators should be approached now for agreement on pursuing a Phase I/Phase II platform design for children with parallel enrollment, to speed up the approval process.

How robust would the pipeline need to be to justify the extra work that goes into developing a platform? It's not until the fifth or sixth molecule that you start to really gain from the platform, said an academic investigator. The challenge is to get the first two or three companies in; this requires setting up the funding to justify this initial investment. The investigator accomplished this using a funds flow model,[80] as was used for the ACTIV-1 phase III clinical trial for treatment of COVID-19. Provided there is more than one molecule ready to test, the decision of whether or not to set up a platform should be based on the likelihood of a continued burden of disease and need for experimentation, not on the current number of available drugs, countered a civil society representative. An industry representative cautioned that industry pipelines for TB drugs have "dried up," with only GSK and Otsuka still in the game, along with the TB Alliance and Gates Foundation.

The Common Denominator is Funding

The TB drug pipeline is analogous to public transit, said a second civil society representative. The system will not work unless there are enough riders and it takes them places they want to go. This gets at the question of scale: "is there enough volume to fuel this?" The MDR-TB pipeline is larger than it was 20 years ago but still small compared to other therapeutic areas,

[80] See https://medschool.ucsf.edu/sites/medschool.ucsf.edu/files/inline-files/AAMC-next-generation-funds-flow-models%20-%20manatt%5B94%5D.pdf (accessed on February 3, 2025).

he said. Furthermore, "every vehicle needs fuel." Oncology has a waiting list of companies trying to enter the platform, whereas MDR-TB has three or four assets in Phase I and Phase II, with pediatric trials years away. "It's an existential question," he said.

> "A fundamental issue for everything we're talking about in advancing pediatric drug development is a resource issue." – *Civil Society Representative*

Platform Trials May Help, But the Devil is in the Details

Platform trials are a possible solution, said an academic investigator, but they require a public-private partnership for the first few molecules. "That deleverages a lot of the funding…stability…[and] site infrastructure problems," he said, noting that even if drugs for TB run out, those sites could be repurposed for other public health problems. There are parallel conversations going on in the larger TB community, said an industry representative, with PAN-TB,[81] Unite4TB,[82] and RAD-TB[83] building new regimens among multiple novel agents, using EU funding and public-private partnerships.

Given the challenges of harmonizing systems and identifying the right governance and SOP, the effort to establish and support a platform will require resources and ongoing collaboration, particularly with the first few products, said a UN agency representative. However, for a disease like pediatric MDR-TB, where obtaining sufficient enrollment in single studies remains a struggle, "being able to tap into a platform that already has the capacity and the reach…that will allow you to enroll your study and meet your regulatory requirement, seems pretty compelling," she said. "There is much more to gain than to lose on the platform approach," she said, but there are complicated aspects, and the details need to be worked out now.

Community Engagement and Country Engagement

The TB Trials Consortium (TBTC)[84] is a US Centers for Disease Control and Prevention (CDC)-funded clinical trial network with a community advisory board (CAB) that includes individuals

[81] See https://www.pan-tb.org (accessed on March 17, 2025).
[82] See https://www.unite4tb.org (accessed on March 17, 2025).
[83] See https://actgnetwork.org/clinical-trial/a5409-a-phase-2-randomized-adaptive-dose-ranging-open-label-trial-of-novel-regimens-for-the-treatment-of-pulmonary-tuberculosis-rad-tb/ (accessed on March 17, 2025).
[84] See https://www.cdc.gov/tb/research/tbtc.html (accessed on March 17, 2025).

affiliated with TBTC sites around the world, said a civil society representative. CAB members have seats on the core science protocol teams, and they provide input during protocol development and throughout the trial. CAB input is important, said an academic investigator, noting that "shorter does not always mean better," and when it comes to regimen development, the TB community is focused on patient choice. The community's goal is to optimize regimens "to meet patients where they are, what they can tolerate, and what their family wants." As platform trials are developed, "there will be a lot of work to bring communities along," said the civil society representative, and the CAB provides a good model for doing this.

To aid enrollment in platform trials, the academic investigator recommended the TBTC approach of having a community member who is associated with each site; "the South African sites are very engaged with their communities and know where to find patients." Connection with individual sites is important for overcoming cultural barriers as well, she added, noting that "every community's stigma and perception of TB is different, and it's very hard to have those conversations unless you understand." She also encouraged a programmatic and decentralized approach that enables people to be treated where they are, rather than having to go to a site. As a student, the academic investigator had been treated for MDR-TB by the CDC, which came to her, "and that made things a lot easier…in the US. I can't imagine having to go to a site to get the treatment," she said.

Summary

Despite multiple challenges, the MDR-TB group concluded that an MDR-TB platform trial was worth pursuing because of the significant efficiencies it would bring.

- The ability to extrapolate efficacy from adults to children should enable older children to be included in adult Phase III trials, and it places the emphasis of pediatric trials on Phase I/II PK and safety.
- There is an urgent need to increase the global capacity to conduct pediatric MDR-TB trials.
- The development of treatments for MDR-TB is heavily reliant on a broad range of stakeholders working together. This work will require continued philanthropic and/or government funding.
- Regulatory agencies and public health agencies from multiple countries will need to be actively engaged.
- Practical challenges will need to be overcome to facilitate participation of patients, while practitioners will need support to engage in this research. To keep the platform alive, expertise and connectivity must be maintained when individual projects end.

Report-Backs from Breakout Groups

Pediatric MDD

How Might Pediatric MDD Trials be Improved?

There have been many failures in pediatric MDD trials, said an academic investigator, and the MDD breakout group shared ideas for increasing the likelihood of success. These include enrolling a more homogenous cohort, clarifying incentives for all participants, doing more work to understand the nature and impact of the placebo response, and employing a variety of approaches to reduce the placebo response.

Participants were critical of the current standards for measuring endpoints and outcomes, which do not seem congruent with the actual effect of treatment on the patient's quality of life. Biomarkers, if and when developed, could be leveraged to enrich the population that has MDD and to screen out high placebo responders. Dosing was another concern. There was a strong interest in trials focusing on maintenance (i.e., persistent depression) rather than acute MDD, but these are longer-term and harder to fund. There is a "huge horizon of new assets" currently being tested for adult depression that will likely be candidates for pediatric trials, and platform trials offer a promising approach, said the academic investigator, but there is much work to do to address these issues.

> "It made no sense to put together a platform trial that just recapitulated all the failures of pediatric MDD trials in the past, in which case every product going into it would then fail." – *Industry Representative*

Operationally, What Would it Take to Execute a Platform Trial for Pediatric MDD?

It's too early to say what a platform trial for pediatric MDD ought to look like, said an industry representative. As they discussed ways to optimize the likelihood of success, participants noted that some drugs, like fluoxetine, succeed while many others fail, and it is not clear why. The focus turned to pre-competitive activities aimed at solving some of these persistent problems. These activities could include improving the measures to optimize treatment

effect or figuring out how to design trials so as to minimize the placebo effect. One suggestion was to use existing data from many products that have already been through pediatric trials (with no IP issues) to do clinical trial simulations of new models to optimize the possibility of separating the drug from the placebo response.

This pre-competitive work needs to be completed before designing the platform itself. Otherwise, said the industry representative, "there's 24 companies at least in this space on the adult side, and we'd put all those products in a platform and they'd all fail, unless we come up with a new way of doing business." Advocacy organizations could be helpful here, suggested an academic investigator.

Operationally, designing a platform trial for pediatric MDD would, "to some extent, recapitulate the ontogeny of EU-PEARL," said the industry representative. A neutral third-party convener, such as FNIH or Critical Path Institute, would bring together the multiple stakeholders; Critical Path Institute might be more appropriate for leading a global effort. A global study adds complications from both cultural and regulatory perspectives, noted an academic investigator. Patient voices are crucial, and the clear public health need with respect to pediatric mental health is an important motivator.

Summarizing the industry perspective, the industry representative said, "there needs to be a line of sight from some of these pre-competitive or non-competitive activities to where you could see how those would transition into a meaningful platform, and that could then increase the efficiency and the effectiveness of the pediatric program, to where ultimately you could see the return on investment."

The MDD breakout group's action plan is to engage with a convener and all the necessary stakeholders, organize internally, and be ready to start on the pre-competitive or non-competitive work in the next six to twelve months, said the industry representative. He envisioned a series of work packages, including: one for assessment; one for trial design; one for study simulation based on existing real-world data; and perhaps others as well.

> **"I think MDD was picked because it was the hardest one. There is absolutely nothing that exists around current collaborative efforts, zero, with a lot of failed trials." –** ***Industry Representative***

Understanding and Minimizing the Placebo Effect is Critical to Success

Keeping the placebo effect low is crucial for the success of any trial. The placebo effect for pediatric MDD is 30 to 55 percent, and the treatment effect is 60 percent, said an industry representative: "if you get a placebo of 30 percent, you're good; if you get a placebo of 55 percent, you're not so good." Many single-trial efforts have been designed to reduce the placebo effect and failed. Of course, it is possible that many drugs that work in adults with MDD do not work in children. While the biological targets are the same in both populations, there are differences in how adults and adolescents manifest depression at the phenomenological level. On the other hand, clinicians prescribe numerous products to children off-label because they believe that they work. For this reason, "the assumption is that it's the trial, not the drug," he said. Once a platform is designed, it would need to be validated with a drug that works well, like fluoxetine.

In discussing the placebo effect, participants emphasized the relatively modest effect sizes of most psychiatric drugs. It was noted that psychostimulants, which are the most effective, are also highly regulated because of their addictive potential. Perhaps the reason for the low effect size of MDD drugs is that the outcome measure is poor, suggested an academic investigator. When she treats a patient successfully for depression there is usually a dramatic improvement, but QOL measures and CDRS don't adequately capture this return to normal function, she said. "If you can figure out what that is, the 'I feel better' score, that's what's going to be the gold," agreed an attendee.

Pediatric Oncology

The Issue with Oncology is Complexity

Platform trials are effective when there are low business risks (e.g., drugs are commercially available), short-term endpoints like PK or biomarkers of efficacy, and sufficient patients and money to support the trial, said an industry representative; these conditions often do not apply in pediatric oncology. There have been successful platforms, but these have yet to yield data resulting in product approvals in pediatrics, which reflects the complexity of cancer. Nonetheless, in contrast to the two other groups, the pediatric oncologists, patient advocates, and other stakeholders have multiple foundational elements in place, having already worked together on platform trials.

Pediatric oncology comprises over 100 different diseases, said the industry representative, and these can be broken down further into molecularly defined buckets. "The disappointment is measured by which bucket you're sitting in…it's very much disease- and

target-specific." For example, in acute myeloid leukemia (AML), "we hit these kids upside the head with a bunch of different sledgehammers and…it doesn't feel like we are making rapid progress."

As an illustration of the difficulty of treating these cancers, the industry representative noted that target expression is not always predictive of response. The Pediatric MATCH study, which studied 13 drugs based on molecular profiling, had many arms close due to either lack of enrollment or lack of efficacy, despite the fact that all the children's cancers in each test arm expressed the molecular target. To clarify this issue, an academic researcher explained that the five to seven percent of relapsing pediatric cancer patients who do respond to targeted therapies are the ones who carry single oncogenic drivers. The rest have multiple oncogenic events as well as immune and metabolic drivers, and these require combination therapies, which are currently lacking.

Furthermore, the researcher added, the mutations driving recurrent tumors are often organ-independent. Resistance mechanisms appear across multiple tumor types, suggesting that it may be time to move from histology-driven to more molecularly-driven studies, as done in the AcSé-ESMART trial.[85] While this whittling and sorting of tumor subtypes has been happening in adult oncology for a very long time, there are 100 times more adults with cancer, noted the industry representative, and in pediatrics, subtyping – which is essential for therapeutic progress – makes rare cancers even rarer. A more tissue-agnostic, molecularly-driven platform would be more difficult to design but is certainly possible, said an attendee.

Platform Trials Could Help with This

"We need a mechanism in place where we can rapidly assess targeted therapies with various combinations in a specific disease," said one participant, and "platform trials are uniquely able to do this." An academic investigator agreed, noting, however, that testing combinations on children with non-survivable diseases complicates toxicity and efficacy assessments. "Though the chance of survival may be small, you're still swinging for the fences," he said. This approach requires early discussions with regulators and companies, "so they…trust in what we're doing."

[85] Geoerger B, Paoletti X, Bautista F, Gatz SA, Marshall LV, André N, Berlanga P, Ducassou S, Pasqualini C, Casanova M, Zwaan CM, Nysom K, Rubino J, Vuillier-Le Goff D, Archambaud B, Aboou S, Schleiermacher G, Dufour C, Blanc P, Hoog-Labouret N, Buzyn A, Vassal G. AcSé-ESMART, a European precision cancer medicine proof-of-concept platform trial. *Nat Med*. 2023;29(12):2985-2987. doi:10.1038/s41591-023-02580-5

Platform trials could be seen as one piece of the entire evidence-generation life-cycle in the pediatric oncology development space, noted another participant. They can be used to reach early go/no-go decisions, "failing fast while facilitating development efforts forward towards an indication." The evidence from these early trials could help in providing predictability to developers, selling the research to industry, and supporting regulatory flexibility.

Which Elements of a Platform are Generalizable, and Which are Tumor-Specific?

Participants noted that many processes for pediatric cancer platforms can be modeled after the platforms currently in existence, particularly when it comes to handling governance or regulatory issues. Operational aspects, including interactions of the academic sponsor with industry and regulators, were painstakingly worked out for Glo-BNHL, and these could be shared through a "how-to-do-a-platform trial-in-oncology document," said one researcher. Indeed, she added, one objective is "not a template for a trial, but a template for how to do the trial."

In terms of the scientific protocols, each type of pediatric cancer will likely require its own platform design, said one participant. Cancer is histology-specific, with different combinations of drugs, different toxicities, and different response metrics. A second participant reiterated, however, that some of the rarer cancers with different histological origins and few recurrent patients could potentially be studied together, focusing on their molecular features rather than their histology.

Although individual trials must be disease-specific, one overarching issue is the need is to work with the CTEP of the NCI. The most efficient way to get enough sample size in the US is to conduct national trials, but national trials need to go through the NCI-COG review mechanism, and CTEP statisticians often have non-negotiable concerns regarding the statistical methods used in platform trials. It will be important to include CTEP in future discussions, to better understand their concerns regarding platform trial designs.

Oncology Action Items

The breakout session focused on identifying some of the barriers and challenges to platforms and on finding value statements shared by all the stakeholders in the room, said an industry representative. The group's action items are as follows:

- Continue to engage in the work; there is a commitment to continuing this conversation.
- Develop process maps; draw lessons from the existing trials to map key processes from multiple perspectives (regulatory, pipeline, contracting, etc.); involve patient advocates and apply these to current and future platforms.
- Utilize the opportunity to create disease-specific advice in the form of a platform-specific PIP and iPSP; this could enable early buy-in from regulators and a sponsor, making it easier to engage industry and getting everyone on the same page.
- Develop a broader discussion among stakeholders not represented at the meeting, including members of CTEP and others, in order to understand the types of platform trial designs they might consider acceptable.

There are several potential sponsors, said the industry representative, including LLS,[86] COG,[87] and Innovative Therapies for Children with Cancer (ITCC).[88] There is a commitment to continuing discussions with partners in Europe and the US, including the EMA and FDA. TransCelerate Biopharma[89] is a nonprofit organization that is developing procedures for operationalizing platform trials with a focus on pediatrics, said another industry representative, and this workshop aligns well with the goals of that project. The industry representative suggested that all participants consider discussing a potential collaboration with them.

MDR-TB

Capacity Building is the Main Concern

Given the geographic locations where TB is prevalent, efforts to study MDR-TB operate against a background of limited funding and lack of significant commitment from industry, with a heavy reliance on non-profits and/or donors, said an industry representative. The

[86] https://www.lls.org (accessed on March 17, 2025).
[87] See https://www.childrensoncologygroup.org (accessed on March 17, 2025).
[88] See https://itccp4.com/our-platform (accessed on March 17, 2025).
[89] See https://www.transceleratebiopharmainc.com (accessed on February 12, 2025).

discussion kept returning to capacity-building and "all the issues that arise when you work in a resource-limited setting."

> "We had to always come back to the fact that we just don't have enough resources to study products for TB disease, and more so for TB disease in children." – *Industry Representative*

"A massive bottleneck to doing these trials right now is having sites in places that can access the patient population and have the capacity to do this level of registrational trials," said an academic investigator. There are a small number of international sites doing pediatric TB therapeutics trials, and 75 percent are in South Africa. Adult MDR-TB sites may not have the capacity, expertise, or interest to do pediatric trials. There needs to be investment in identifying and recruiting sites, building capacity, and engaging them in the work. "That takes resources and investment and time, but it's not impossible," he said, as there are excellent investigators and hardworking sites in all of these countries.

Very few sites can conduct pediatric MDR-TB trials, added the industry representative. The DS-TB population is much larger and easier to study, so it is possible that some questions may be answered by including that population. It was also noted that the clinical management of TB in high disease-burden settings is usually conducted programmatically through public health settings, so clinical trials need to be integrated into the existing public health infrastructure in those settings.

Extrapolating Efficacy: At What Ages?

Infectious diseases are at an advantage, said an industry representative, because for most infections, efficacy can be extrapolated from adults to children. However, because of certain differences in the pathophysiology and disease manifestations in younger children, the trial population in the younger age groups will have to exclude those with certain severe forms of TB, such as TB meningitis. Also, there is not regulatory alignment on extrapolation down to the youngest patient population, as noted and discussed throughout the breakout and reporting back sessions. If a platform trial is designed, it will be important to agree on this alignment.

There was general agreement that adolescents should be enrolled in adult trials, so the pediatric platform trial should focus on children ages 0 to 12-14 (depending on the lower limit for enrollment in adult trials).

What is the Pediatric MDR-TB Platform Trial About?

Noting that TB trials in adults are more focused on developing novel regimens than simply focusing on a single novel compound, an industry representative said, the aim of a platform trial in children needs to be worked out. Would it be geared towards evaluating novel regimens or towards evaluating the safety and PK of individual compounds? Because efficacy can be extrapolated, the pediatric platform would be used to conduct Phase I/II trials focused on PK and safety, answered an academic investigator, with each arm testing an individual compound independently of the others. Many of the benefits would, therefore, be operational, hopefully speeding up the process.

Specific Challenges to Doing a Platform Trial for Pediatric MDR-TB

These trials have to be implemented in high DR-TB-burden settings, which can be found in India, South Africa, the Philippines, Indonesia, Bangladesh, and Pakistan, said one researcher. Country engagement is "critical," and this includes engagement with regulatory authorities, national TB programs, researchers, and communities. It's also important to engage the perspectives of community members and TB survivors early in the process. This is another reason why trials must be embedded in the public health system, "because essentially you have to get to the last mile in places where getting to the last mile is very challenging," said a second researcher.

Another concern is the relatively anemic pipeline of compounds for TB, which is much weaker than for depression and cancer, though much better than it was two decades ago. This led the group to consider how many drugs in the pipeline would be sufficient to justify setting up a platform.

Many of the challenges raised in the workshop applied to pediatric trials of TB drugs in general and were not specific to implementing a platform trial. There were no "showstoppers," which was "reassuring," said one researcher, who sees "huge opportunities for efficiencies and to move forward pediatric TB drug evaluations through a platform trial approach." Furthermore, he noted that the experience from existing platform trials in the adult TB space can be leveraged to help bring partners and stakeholders together. Noting that current TB trials are "really slow," another researcher saw the major advantages of a platform as being to accelerate the regulatory and other steps that precede the actual clinical trial.

> **"I see this as a tool to speed things up…where we already have everything set up and we can just go from there…I'm very excited about the potential for drug-resistant TB." – *Academic Investigator***

Integrating MDR-TB Within a Larger Ecosystem of Infectious Diseases

A UN agency representative envisioned an integrated network with the capacity to run trials on multiple infectious diseases. This would benefit from current efforts to create a more enabling clinical trial ecosystem for pediatrics, she said, encouraging everyone to work

together to build on existing sites and develop "a more integrated approach that can serve the needs of multiple disease areas across the globe."

An academic investigator expressed skepticism at a multi-disease approach, noting that even in high-income academic centers, not all disease areas have investigators who can do clinical trials research. First you need to find the patients, then you need expertise in managing trials, she said. While shared infrastructure is valuable, much of this requires "supporting the career path of investigators around the world, which is challenging." An integrated approach could help maintain this expertise, countered the UN agency representative, by providing the opportunity to enroll patients and participate in new studies on a continual basis.

One participant has been working with colleagues to identify candidate sites in high DR-TB burden settings. Some of these sites study adults with TB, while some study children with different diseases. Trial sites are not reaching out to find patients with TB, he noted. Rather, TB is first diagnosed by national TB programs in public health settings, and then patients need to be plugged into trials. This requires establishing relationships with TB programs and research sites. The IMPAACT Network,[90] which is focused on pediatric HIV trials, has done this, and TB trials could potentially tap into the same referral pathway in locations with MDR-TB. It may also be possible to leverage pediatric Covid-19 study sites for MDR-TB trials.

It also works in the other direction. Infrastructure created for platform trials in pediatric MDR-TB, including regulatory coordination and some sites themselves, could also serve DSTB and other infectious disease trials. DR-TB is the "smaller circle," noted the academic investigator, so any site established to study it would have an easier time recruiting patients with DSTB.

Next Steps for MDR-TB

While the small drug pipeline is "a bit of a dampener," the overall assessment of the MDR-TB group was that a platform trial was worth pursuing because of the significant efficiencies it would bring, despite the challenges, said an industry representative. There are a few scientific issues to address, but these can be worked through.

Funding is "a major barrier, and it's not just a platform trial-related issue," said an academic researcher; public-private partnerships are essential. With engagement from the Gates Foundation, TB Alliance, and other nonprofits, "there are enough committed people in this space that I think we should be able to continue this discussion and find a way forward," said

[90] See https://www.impaactnetwork.org (accessed on February 12, 2025).

an industry representative. Adult compounds for MDR-TB are moving into Phase III trials and will need pediatric evaluations, and the researcher's group plans to use that opportunity to "move this forward very concretely."

> "We're not in this business of developing drugs for TB to make money, but I think there is a real unmet need. We have to serve the world's population, and pediatric patients are unfairly affected with TB, drug-sensitive or MDR." – *Industry Representative*

Comparing Clinical Trial Needs across the Three Diseases

The structure of a platform trial is "more palatable and more likely to succeed" than a clinical trials network, because it has a pre-existing protocol and sites, and "takes you from beginning to end," said one participant. Building a trial platform has the potential to improve the quality and precision of the data obtained at the sites, added another. This work will impact even standalone trials, said a third, by improving the capacity of clinical trial network sites, dealing with regulatory concerns, and enhancing collaboration and communication among the sites.

Nonetheless, the types of trials differ considerably among all three disease groups represented at this workshop, as does their purpose. While oncology is discussing Phase III trials, MDD is considering pre-competitive and non-competitive research prior to starting platform trials, and MDR-TB is discussing Phase I/II trials focused on PK and safety.

MDR-TB differs the most from the other groups. One distinction is the need for regulatory involvement of low-and middle-income countries, said an academic researcher; this work will rely not only on FDA and EMA engagement but should also benefit from the African Medicines Agency (AMA) and groups like International Coalition of Medicines Regulatory Authorities (ICMRA)[91] that are working to support global regulators. Another difference for MDR-TB trials is their dependence on public-private partnerships, with considerable financial support coming from private foundations.

[91] https://icmra.info/drupal/en (accessed on March 17, 2025)

MDR-TB does have the distinct advantage that researchers can rely on extrapolation, added the researcher, "such that there's a real effort to bring adult trials to an adolescent group at the get-go." This puts the burden of pediatric testing on PK and safety rather than efficacy, "so our challenges are a little different, as in how to do these trials," said an industry representative.

There is a need for capacity-building not only for MDR-TB but also for MDD, said one participant, albeit at a different order of magnitude. The existing pediatric networks are not set up for MDD trials, he said, and their sites are not the optimal places to find children with depression.

Consistent across all reports was the need for a neutral convenor to keep these conversations going, added an attendee, and that cannot be the FDA, a single company, or a single academic institution.

Given the significant differences among the three diseases, participants agreed that this work will likely need to be subdivided based on therapeutic area or disease type. It might be possible to develop platforms that could serve MDD and mood disorders, or MDR-TB, PAN-TB, and HIV TB, but this also depends on how similar the sites are and where the expertise is. Clearly, MDR-TB and oncology will need very different sites.

Moving Forward: Next Steps

These three diseases were chosen because none offers an easy answer or a single, disease-specific problem, said Dr. Bierer, who facilitated the final reporting out discussion. Rather, they illuminate different kinds of challenges specific to doing platform pediatric trials. "How do we create the infrastructure and enthusiasm to be in a different place several years from now?" she asked.

Process Mapping for Pediatric Platform Trials

Process Mapping

Process mapping--i.e., breaking down the entire pediatric clinical trials process into individual steps and determining the facilitators and barriers for each, with the goal of optimizing these to speed up the trials process – could enhance the approach to pediatric platform trials in general, said Dr. Bierer. The processes that emerge could then be used to build a variety of different platforms, depending on what in particular is being studied. Whether this process map should be a single product, or whether each disease group should design its own map, was left up to the participants, whose task it was to figure out "what else we need and who we need at the table for the next steps," she said.

This process map should start where there is experience, and that is in oncology, said an industry representative. Other disease areas can then decide which parts are replicable and where they diverge, but she cautioned against starting too generically and then having to fill in the details later. The groups should not work totally in isolation, said another participant. Not only do diseases like cancer and depression overlap, but "when we're in our own echo chambers, we don't see the pitfalls and challenges and vulnerabilities that we're facing," and these become clear when different groups talk to one another.

Patient advocates are keenly aware of the passage of time, said a patient advocate, and a key element of process mapping is to better understand how to improve efficiencies. "Everyone has their individual process, and we don't have a sightline into these" to understand where the inefficiencies lie and address them, which is essential to shorten the timeline for getting kids access to these drugs, she said.

Participation in the Mapping Process

Process mapping would require every stakeholder to "go back and examine their own processes and bring that to the table…academia, industry, and regulators," said an international regulator, but "I haven't heard anyone committing to…sharing their internal process to make that possible." He added that the EMA was "very willing and happy to contribute and participate in that exercise." The FDA is committed to working with the EMA to help create a process that satisfies both regulatory authorities, said an attendee, with hopefully other countries' regulatory authorities added over time.

An academic investigator with deep experience in pediatric oncology platform trials offered assistance from the ITCC consortium in writing the academic process map. This process map should have two elements, she said: methodological, which includes a role for statisticians, and operational, which "is the hardest…because we all reinvent the wheel." The ITCC has four academic institutions based in four different countries that have run (international) platform trials and can offer their expertise, she said, "where we've gone wrong and what's worked…so that if somebody else wants to run a platform trial, they don't fall into the same pitfalls." Academics are very comfortable with this level of disclosure, said another academic investigator, but "it's getting a peek at some of the internal pharma SOPs and processes that makes it so difficult."

"We're in on this, absolutely," said an industry representative. "I'm definitely available, interested, and hope to be involved in the future," said another. Industry probably can't share their actual SOPs, he added, but they could share "commonalities of general processes that will facilitate efficiency." "Our policy team is very happy to engage on the policy topics discussed, in particular on introducing pragmatic and efficient processes to agree/converge [on] pediatric plans," offered a third industry representative. Other industry representatives also voiced interest in engaging in these platform discussions as well.

Using Process Mapping to Engage Industry

How can the process mapping be used to increase efficiencies for industry, asked an international regulator, "so that you can convince your colleagues internally…that there's an added benefit for [you] in using a platform trial?"

A platform could save 15 or 20 million dollars in startup costs as well as time associated with setting up sites, etc., said an industry representative. But independent of the savings and efficiencies, if a pediatric platform trial under a PIP and PSP had a streamlined regulatory process that allowed products to be plugged into the trial with minimum effort, that alone

would make it worthwhile. "A lot of factors come into play here," said a second industry representative, who argued that sharing company SOPs is not the problem. The real question is what process led to the design of the platform study, who was involved in its design, "and who are the regulatory agencies that have weighed in that it's the reasonable design approach? That's really the process piece that would be important to us."

> **"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***

It's essential for industry to be involved in the process mapping, said an academic investigator. In many of her interactions with industry partners, she said, "after multiple Zoom calls…we finally realized what had been holding it up was just a misunderstanding." The academic partners make certain assumptions of how industry makes decisions and vice versa, and each needs to understand what they are doing that is problematic for the other. These areas of friction could be built into the process map, she said, including questions around issues like accessing the drug, seeking regulatory approval, data ownership, IP, financial arrangements, and data sharing.

Separate Paths, Common Strategies for Moving Forward

Regarding the three disease areas, participants agreed that each area will have to do its own process mapping. However, although there is no global approach to the process, there are common strategies and conveners, such as the World Health Organization (WHO), ITCC, TransCelerate, or Critical Path Institute, which could help move these efforts forward.

This workshop is a first step, and other conveners will have to take the work forward. An industry representative offered to assemble a small group to write a short, high-level proposal indicating what a public-private partnership would look like for MDD and present it to the Critical Path Institute, with the goal of forming a consortium under their purview.

The WHO has several opportunities at the global level that could be leveraged for this effort, said one participant. Work that began as WHO guidelines on clinical trials[92] is evolving into

[92] See https://www.who.int/publications/i/item/9789240097711 (accessed on February 12, 2025).

training packages, frameworks for clinical trial sites, and other tools; there is also an effort to incorporate the pediatric perspective into that broader body of work. A second opportunity is directed at regulators. Meetings of the WHO Paediatric Regulatory Network (PRN)[93] provide an opportunity to address global regulatory issues, and this participant offered to engage with the PRN on reviewing or helping to develop work related to this group. Regarding the third opportunity, she noted that the Critical Path Institute and other potential conveners are members of the Global Accelerator for Pediatric Formulation (GAP-f).[94] GAP-f has focused on medicines for several pediatric diseases, including cancer and TB, but is expanding into new non-communicable disease areas. One component of GAP-f's effort relates to "clinical trial design and innovation in clinical trial methodologies," she added, "which we would love to develop in conjunction with others."

> "There is an opportunity for us to come together across disease areas with a pediatric-specific lens to try to tease out some specific enabling policies, tools, and activities that might be of value across disease areas." – *UN Agency Representative*

Some Persistent Concerns about Pediatric Platform Trials

In their final discussion, participants wrestled with some of the more difficult questions and roadblocks to getting platform trials off the ground for these three diseases.

When Should Pediatric Trials Start?

There is a "Goldilocks moment" when it's neither too early nor too late in a product's lifecycle from an IP perspective to start testing in children, said an industry representative. Pediatric platform trials could start as soon as "people are convinced they have a marketable adult product" based on the first-line results from the adult program, which could potentially shave a year off the timeline.

Waiting for first-line results in adults is "not consistent with the timeframe that we should all be reaching for," argued an attendee. Instead, drugs should enter pediatric trials as soon as

[93] See https://www.who.int/initiatives/gap-f/who-paediatric-regulatory-network (accessed on February 12, 2025).
[94] See https://www.who.int/initiatives/gap-f (accessed on February 12, 2025).

the data show "that they have a real prospect to benefit" and that they can be studied safely. In oncology, she said, "we hear time and time again from parents…that they can't wait." The Goldilocks moment, she said, should be "when we have sufficient proof of concept and information in adults to decide what the clinical trial should look like."

Figuring out the right time to conduct early-phase pediatric trials is part of the mapping process, and it will vary significantly depending on the therapeutic area, said an academic investigator. The industry representative clarified that what would constitute a Goldilocks moment for MDD "has nothing to do with pediatric oncology. Zero."

The Regulatory Response Can be Unpredictable

Citing the attendee's remark that pediatric platform trials should start earlier because patients cannot wait, an industry representative said she continues to receive comments from the FDA that "they do not want to entertain discussion on our pediatric programs until they have the top-line adult data." While it's reasonable to adjust the timing based on particulars of the disease and the mechanism, she cautioned against making blanket statements, noting that "sometimes these early negotiations on our pediatric plans are completely useless…they are huge resource wastes…it's very, very case dependent." The attendee countered that it is often the research proposal that proposes to wait until top-line data are available from the adult program, and while "that may make sense in some cases," it often seems too slow, particularly for pediatric oncology.

> "I'm not saying you should put the cart before the horse and design a trial before you have the scientific knowledge upon which to base it, but depending upon the target, depending upon the promise of the drug and its mechanism of action, you could see it happening very early." – *Attendee*

"That's where the process mapping comes in," said an international regulator, "can we create a process where we do it differently…less burdensome…faster," including regulators and all the different stakeholders, "to show that there is efficiency in doing a platform, within the drug development life cycle, of a drug where there's a requirement to develop?"

One participant recalled how in the first workshop session, participants imagined a model platform trial with multiple drugs, willing partners, optimal timing, adult approval, and no IP constraints to block industry participation. She suggested that the FDA look at potential opportunities and facilitate this type of lower-risk trial, because "if we get a win there…that's going to really move things forward."

"Procedurally, we have to get to a smarter place" regarding the regulatory review and agreement process, said an industry representative. "There's an ability to introduce pilots, to be smarter about how we're agreeing to our pediatric plans that could move really efficiently," but this requires alignment among researchers, companies, and regulatory review authorities. An attendee strongly supported the idea of pilot studies aimed at improving the current system.

Drug Companies Must Engage

"We can create a system to efficiently evaluate drugs…and drug companies don't show up," said an academic investigator. Pediatric representatives within industry express interest, but their companies don't provide the drugs. "What problem are we trying to solve for the various pharmaceutical companies…what is the gap between the pediatric Center of Excellence and the regulatory affairs office," he asked, and how can the trial be de-risked while meeting timelines, so that companies will participate? This will be a key component for process mapping, and it goes to the decision-making processes within a company, he said, adding that "we never feel like we're talking to the right people."

"We can meet with the pediatric representatives from pharmaceutical companies that express enthusiasm for the mission of what we're trying to do, but the drugs don't materialize." – *Academic Investigator*

Introducing Efficiencies Between Industry and Regulators

There needs to be a general conversation about how to introduce efficiencies and "more thoughtful, pragmatic approaches" in how companies engage with regulatory agencies to arrive at agreement on their pediatric plans, said an industry representative. As one example of this, she noted that agreeing to a pediatric plan is a 210-day process in the US, with 90 days of review on both ends followed by 30 days of alignment. However, there may be specific indications that have enough research, patient, industry, and regulatory support for a specific platform design that the protocol is "a true plug and play," in which case a new asset would need to be vetted for safety and not much else. In that case, it may be possible to shorten the process from 210 days to 90 days.

This is a procedural discussion that needs to happen across a broad set of companies and the regulatory agencies, and it does not need to involve academic representatives, said the industry representative. Mapping is important, said an academic investigator, because it clarifies where academic involvement is not needed, so the academic collaborator knows their boundaries and is not surprised when they aren't invited to the table.

Designing the Platform: Getting Everyone in the Room

It is often the case that industry and regulators negotiate the details of a PIP or PSP between themselves, said an academic investigator, before approaching the academics who will contribute patients and/or conduct the trial. Not having the academics in the room makes it a game of telephone, said an industry representative, with academics and regulators only able to communicate through the industry partner. "Having the experts and the academics and the research networks present as much as possible has been only of benefit, in terms of efficiencies," she said. She noted that the legislation in Europe is changing and processes for

interacting with regulators will be discussed; she encouraged both companies and academics to participate in that discussion.

All voices need to be engaged in the trial design, agreed an international regulator. In the triangle of industry, academia, and regulators, one side is broken because regulators, as part of the PIP discussion process, don't talk to the academics sponsoring the study, but only to industry. This may not be necessary for process, said the regulator, but "when we talk about design considerations…it's fundamentally important to have everyone around the table." Furthermore, he added, if regulators could discuss the feasibility of a particular platform design with the academic sponsor, they might be able to reach a regulatory decision more quickly.

Transparency: Patient Advocates Want It, Agencies Can't Provide It, and Industry is Conflicted

"There is a deep need for collaboration and transparency and a new way of working," said a patient advocate. "We've had decades where we are reflecting back and saying, 'We wish we had done things sooner'…The only way to move forward is to really take a critical look at how we're currently operating." She encouraged "a collaborative and more transparent working relationship across all of the stakeholders."

> **"Patients and advocates, that's what we're asking for: To increase partnership and transparency, and being open to working in a new way." – *Patient Advocate***

""The FDA…would probably need an act of Congress to reveal what is in a PSP," said an industry representative, and the EMA reveals very limited information about trials. "So, this comes to industry," he said. "The platform assumes that we all have the same design…we should be willing to share our designs." He advocated making PIPs and PSPs public after excising information that risks IP.

> **"We should compete on products, not on design. We should be willing to share our designs." –*Industry Representative***

"It's all a big 'it depends,'" countered a second industry representative. For drugs that are already in use, greater transparency may be possible. But information about investigational agents will not be willingly shared, she said, because the adult program for which these agents were designed are "the value driver for the company." Everyone in this room believes in platform trials, and the companies are looking for efficiencies too, but "within reason, to protect those innovations that…require protection," she said. Timing is very important.

> "There is a degree of information that could be shared and should be shared, but there's also a lot of information that shouldn't be shared and won't be shared." – *Industry Representative*

"I think we can be in a space where more details are shared," said a third industry representative. "It's about knowing the level of information that's being provided and to whom," countered the second. "For therapeutics that are investigational, the actual decision makers…are not going to be sharing their information in a public domain if it potentially undermines the value of their product, but they will be willing to talk about what information could be shared." She cautioned against being too "blue sky." "Let's find a way to do it, in a way that it can actually be done," she said.

There is precedent for releasing information that was previously confidential, said one participant, noting the new Clinical Trials Regulation legislation in Europe,[95] which requires more transparency about clinical trials while protecting commercially sensitive information. Similarly, said another, when the EMA said they would post clinical study reports a decade ago, industry was concerned because these contained commercially confidential information, but they were redacted and shared, and now it is current practice.

The Statisticians' Report

Speaking for the three statisticians in attendance, one participant remarked that "many of the barriers that we see were not discussed in detail here." As a next step, she said, the statisticians planned to develop a white paper for this group that lays out, from a statistical perspective, design and logistical challenges and their proposed solutions.

Next Steps

"Everybody here…wants to see a through-line to getting this done," said Dr. Bierer, and the next steps are well-defined:

[95] See https://accelerating-clinical-trials.europa.eu/newsroom/news/launch-revised-ctis-transparency-rules-2024-04-22_en (accessed on February 28, 2025).

- Develop a process map. Some pieces will be generic and others disease-specific, as each disease will have its own challenges.
- Produce a summary of this meeting.
- Reconvene the central and disease-specific planning committees.

"The art to getting this done is to have the right people in the room at the beginning," said Dr. Bierer. This means expanding the square of academia, industry, regulators, and funders to a pentagon or hexagon that includes patient advocates and, in some cases, physicians/community providers. The process will start with FDA/EMA, but it will need to incorporate Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, MHRA, and other agencies, she said, "earlier rather than later."

In closing, the workshop met its objectives of further developing the principles, ethical foundations, and operational considerations upon which platform trials can be pursued for studies of pediatric investigational products. Roughly 80 pediatric and platform trial experts from Europe, the UK, Asia, Australia, and the US attended this hybrid, 2-day event. The discussants were successful in identifying knowledge gaps and practical challenges that impact clinical trial planning and execution.

The workshop also strengthened individual, institutional, and stakeholder relationships. Attendees left the workshop committed to continuing the work and were energized by the series of discussions that evolved over the two-day workshop. Finally, each of the 3 disease-specific breakout groups successfully recommended actionable approaches to address identified issues, and the respective groups continued to meet to take concrete steps to further the momentum created at the workshop. The MRCT Center remains actively involved in the work for each disease-specific subgroup in carrying forward the next steps from this workshop.

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Appendix 1: Workshop Agenda

Advancing Pediatric Platform Trials: Streamlining Development, Maximizing Impact

Workshop agenda

Day 1: Tuesday, October 29, 2024

Time	Topic	Speaker
8:00 – 8:30 AM	**Breakfast** (on-site)	
8:30 – 8:45 AM Room Location: Art Gallery	**Welcome**	**Lisa Koppelman** The Multi-Regional Clinical Trials Center of Brigham & Women's Hospital and Harvard
8:45 – 9:45 AM Room Location: Art Gallery	**Keynote Address**: Platform Trials for Children: History, Common Goals, and a Path Forward	**Dr. Danny Benjamin** Duke University
9:45 – 10:45 AM Room Location: Art Gallery	**Keynote Address**: Intellectual Property Considerations in Platform Trials	**Dr. Melissa Rones** Ropes & Gray
10:45 - 11:00 AM	**Coffee/tea break**	

11:00 AM – 12:00 PM Room Location: Art Gallery	**Panel Discussion and Q&A** Multi-stakeholder Perspectives for the Design and Implementation of Pediatric Platform Trials	**Dr. Barbara Bierer** (Moderator) The Multi-Regional Clinical Trials Center of Brigham & Women's Hospital and Harvard **Dr. Danny Benjamin** Duke University **Dr. Suzie McCune** PPD Clinical Research Business of Thermo Fisher Scientific **Dr. Melissa Rones** Ropes & Gray
12:00 – 1:00 PM	**Lunch** (on-site)	
Breakout Sessions: Disease-area experts will discuss study design, operational considerations, & legal implications of implementing pediatric platform trials.		
1:00 – 4:30 PM	**Breakout Sessions** **See specific disease-area agendas for additional detail*	**Disease-Area Co-leads & Breakout Groups**
5:30 PM	**Group Dinner** (Mission Dupont)	

Day 2: Wednesday, October 30, 2024

Time	Topic	Speaker
7:30 – 8:00 AM	**Breakfast** (on-site)	
8:00 – 9:00 AM Room Location: Art Gallery	**Keynote Address:** Designing a platform trial for depression: Experience from EU-PEARL	**Prof. Dr. Stefan Gold** Charité – Universitätsmedizin Berlin
Breakout Sessions: Disease-area experts will discuss study design, operational considerations, & legal implications of implementing pediatric platform trials.		
9:00 – 10:45 AM	**Breakout Sessions** **See specific disease-area agendas for additional detail*	**Disease-Area Co-leads & Breakout Groups**
10:45 – 11:00 AM	**Break**	
All Attendees Reconvene in the Main Room Room Location: Art Gallery		
11:00 AM – 12:30 PM Room Location: Art Gallery	**Breakout Session Report Outs** Thematic learnings from breakout sessions, which include identified issues, causation, barriers, and identified solutions	**Co-leads & Breakout Groups**
12:45 – 1:30 PM	**Lunch** (on-site)	

1:30 – 2:15 PM Room Location: Art Gallery	**Group Discussion** (All Attendees) Commonalities and Differences Across Disease Areas	**Co-leads**
2:15 – 3:15 PM Room Location: Art Gallery	**Group Discussion (Cont.)** (All Attendees) Next Steps & Synthesis	**Dr. Barbara Bierer** *(Moderator)* The Multi-Regional Clinical Trials Center of Brigham & Women's Hospital and Harvard
3:15 – 3:30 PM Room Location: Art Gallery	**Closing Remarks**	**Dr. Barbara Bierer** The Multi-Regional Clinical Trials Center of Brigham & Women's Hospital and Harvard

Workshop Sponsorship

Johnson & Johnson, AstraZeneca, and Sanofi have provided sponsorship grants towards this independent program. Sanofi is part of the Steering Committee of the MRCT Center. Johnson & Johnson and AstraZeneca are part of the Executive Committee.

Appendix 2: Workshop Attendees

Name	Affiliation	Workshop Role
Muna Abu-Shaar	Biospark Intellectual Property Law	Attendee
John Alexander	U.S. Food and Drug Administration	Attendee
Rebekka Astudillo	LMU Ludwig Maximilians University, Munich	Attendee
Susan Andrews	GSK	Planning Committee
Trevor Baker	Multi-Regional Clinical Trials Center	Planning Committee
Kristen Bartlett	Multi-Regional Clinical Trials Center	Attendee
Danny Benjamin	Duke University Medical Center	Planning Committee Keynote Speaker
Carol Berkower	Freelance Writer, National Academy of Sciences	Attendee
Barbara Bierer	Multi-Regional Clinical Trials Center	Planning Committee
Lucinda Billingham	University of Birmingham	Attendee
Christina Bucci-Rechtweg	Novartis Pharmaceuticals Corporation	Planning Committee
Annie Buchanan	ViiV Healthcare	Attendee
Dana Cahill	Otsuka Pharmaceuticals	Attendee
Michelle Carr	Bristol Meyers Squib	Attendee
Dilip Chary	Otsuka Pharmaceuticals	Attendee
Ann Lee Collins	The Leukemia & Lymphoma Society	Attendee
Laurie Conklin	Johnson & Johnson	Planning Committee
Todd Cooper	Seattle Children's Hospital	Attendee
Christoph Correll	Hofstra/Northwell & Charité University	Major Depressive Disorder Core Group Member

Ramesh Dass	Otsuka Pharmaceuticals	Attendee
Sneha Dave	Generation Patient	Planning Committee
Melissa DelBello	University of Cincinnati	Major Depressive Disorder Core Group Member
Ralph DeMasi	ViiV Healthcare	Attendee
Martha Donoghue	U.S. Food and Drug Administration	Oncology Core Group Member
Willie Earley	Intra-Cellular Therapies Inc	Attendee
Ricardo Fernandes	Connect4Children	Attendee
Megan Fernandez	Ropes & Gray LLP	Attendee
Olimpia Ferreira Galvao de Araujo	Eli Lilly & Co (representing Transcelerate)	Attendee
Robert Findling	Virginia Commonwealth University	Major Depressive Disorder Core Group Member
Brian Gadbaw	Novartis Pharmaceuticals Corporation	Attendee
Anthony "Tony" Garcia-Prats	University of Wisconsin-Madison	Multi-Drug Resistant Tuberculosis Co-lead
Birgit Geoerger	Institut Gustave Roussy	Attendee
Jason Gerson	PCORI	Attendee
Stefan Gold	Charité – Universitätsmedizin Berlin	Keynote Speaker
Meg Grabb	National Institute of Mental Health (NIMH)	Major Depressive Disorder Core Group Member
Dionna Green	U.S. Food and Drug Administration	Planning Committee
Douglas Hawkins	Children's Oncology Group	Attendee
Anneke Hesseling	Stellenbosch University	Multi-Drug Resistant Tuberculosis Core

		Group Member
David Holtzman	Bill & Melinda Gates Medical Research Institute	Attendee
Pauline Howell	Wits Health Consortium-Clinical HIV Research Unit	Attendee
Patrick Jean-Philippe	National Institute of Allergy and Infectious Diseases	Multi-Drug Resistant Tuberculosis Core Group Member
David Jenkinson	LifeArc	Attendee
Dominik Karres	European Medicines Agency	Planning Committee Oncology Co-lead
Pamela Kearns	University of Birmingham	Oncology Core Group Member
Olga Kholmanskikh	Federal Agency for Medicines and Health Products (Belgium)	Attendee
George Kirk	AstraZeneca	Oncology Core Group Member
E. Anders Kolb	The Leukemia & Lymphoma Society	Planning Committee Oncology Co-lead
Lisa Koppelman	Multi-Regional Clinical Trials Center	Planning Committee
Colette Kosik-Gonzalez	J&J Innovative Medicine	Attendee
Adam Levy	Bristol Myers Squibb	Oncology Co-lead
Wendy London	Dana-Farber Cancer Institute & Boston Children's Hospital	Attendee
Kellie Malloy Foerter	BMS	Attendee
Tiziana Masini	World Health Organization	Attendee
Susan McCune	PPD Clinical Research Business of Thermo Fisher Scientific	Planning Committee

Lindsay McKenna	Treatment Action Group	Multi-Drug Resistant Tuberculosis Core Group Member
Amanda Monteiro	The Leukemia & Lymphoma Society	Attendee
Grace Montepiedra	Harvard T. H. Chan School of Public Health	Attendee
Salvatore Morello	Takeda	Attendee
Gloriah Moses	ITPC Global	Attendee
Sumati Nambiar	Johnson & Johnson	Planning Committee Multi-Drug Resistant Tuberculosis Co-lead
Robert (Skip) Nelson	Johnson & Johnson	Planning Committee Major Depressive Disorder Co-lead
Gahan Pandina	Johnson & Johnson	Attendee
Hernando Patino	Johnson & Johnson	Attendee
Martina Penazzato	World Health Organization	Multi-Drug Resistant Tuberculosis Core Group Member
Jacqueline Phillips	Johnson & Johnson	Attendee
Adelaide Robb	Children's National Hospital	Attendee
Melissa Rones	Ropes & Gray LLP	Keynote Speaker
Amy Rosenfeld	AstraZeneca	Attendee
Nicole Salazar-Austin	Johns Hopkins University	Attendee
Samuel Schumacher	World Health Organization	Attendee
Tina Shah	Westat & We are TB	Attendee
Angeliki Siapkara	AstraZeneca	Attendee
Manpreet Kaur	University of California-Davis	Planning Committee

Singh		Major Depressive Disorder Co-lead
Bridget Stuart	Novartis Pharmaceuticals Corporation	Attendee
Eugene Sun	TB Alliance	Attendee
Lionel Tan	ViiV Healthcare	Planning Committee
Nidale Tarek	GSK	Attendee
Louvina van der Laan	Desmond Tutu TB Centre, Stellenbosch University	Attendee
Jasper van der Lugt	Prinses Maxima Centrum	Attendee
Gilles Vassal	Gustave Roussy	Attendee
Sabine Verkuijl	World Health Organization	Attendee
Charles Wells	Bill & Melinda Gates Medical Research Institute	Multi-Drug Resistant Tuberculosis Core Group Member
Lynne Yao	U.S. Food and Drug Administration	Planning Committee