REVIEW

The Role of Master Protocols in Pediatric Drug Development

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Abstract

Master protocols are innovative clinical trial designs that enable new approaches to analytics and operations, creating value for patients and drug developers. To date, the use of master protocols in pediatric drug development has been limited, focused primarily on pediatric oncology with limited experience in rare and ultra-rare pediatric diseases. This article explores the application of master protocols to pediatric programs required by FDA and EMA based on adult developmental programs. These required programs involve multiple assets developed in limited pediatric populations for registrational purposes. However, these required programs include the possibility for extrapolation of efficacy and safety from the adult population. The use of master protocols is a potential solution to the challenge of conducting clinical trials in small pediatric populations provided that such use would improve enrollment or reduce the required sample size. Toward that end, Janssen and Lilly have been working on a collaborative cross-company pediatric platform trial in pediatric Crohn's disease using an innovative Bayesian analysis. We describe how two competing companies can work together to design and execute the proposed platform, focusing on selected aspects—the usefulness of a single infrastructure, the regulatory submission process, the choice of control group, and the use of pediatric extrapolation. Master protocols offer the potential for great benefit in pediatrics by streamlining clinical development, with the goal of reducing the delay in pediatric marketing approvals when compared to adults so that children have timelier access to safe and effective medications.

Keywords Master protocol · Pediatrics · Crohn's disease · Guselkumab · Mirikizumab · Bayesian design

Master protocols are innovative clinical trial designs that enable new approaches to operations and analytics, potentially creating value for patients and drug developers. This article will build on the experience with master protocols in pediatrics and explore the application of these approaches to the pediatric studies required by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) when there is a corresponding adult developmental

program in the same indication/condition. When multiple assets are being developed for an adult disease, sponsors may be in a situation of needing to conduct similar pediatric studies in the same, relatively small population, often incorporating a plan for extrapolation of efficacy from the adult studies. These studies may take years to complete. Multi-sponsor master protocols may serve to streamline these studies operationally, leading to more timely generation of data for prescribers. Master protocols may also incorporate Bayesian analyses, leveraging data from adult studies and potentially from other studies of drugs with the same mechanism of action in the same population. This article will discuss considerations when planning master protocols, including incorporation of extrapolation and the importance of infrastructure. In addition, we describe a collaborative cross-company pediatric platform trial in pediatric Crohn's disease in which two competing companies are working together to design and execute a master protocol, focusing on selected aspects—the usefulness of a single infrastructure,

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the regulatory submission process, the choice of control group, and the use of pediatric extrapolation.

The definitions of a master protocol and its subtypes vary considerably in the medical literature [1]; however, it is reasonable to adopt the definitions proposed by the FDA [2, 3]. A master protocol includes multiple coordinated substudies or "intervention-specific appendices" (ISAs) and is designed to evaluate one or more drugs in one or more diseases and or disease subtypes. There are three types of master protocols: umbrella, basket, and platform. An umbrella trial is designed to evaluate multiple drugs in the context of a single disease. A basket trial studies a single drug for multiple diseases or disease subtypes. A platform trial studies multiple drugs for a single disease, as in an umbrella trial, but allows drugs to enter or leave the platform based on a decision algorithm [2]. A platform trial could also incorporate features of a basket trial [4]. Thus, a platform trial could be sustained in perpetuity; however, this concept of perpetuity may not need to be a necessary component of the definition of a platform trial [1]. The 2018 FDA guidance uses the terminology of master protocol in lieu of platform trial, thus collapsing the concept of perpetuity into the descriptions of both an umbrella and basket trial [3, 5]. The platform trial can be understood as an adaptive umbrella trial where substudies involving either treatment arms or study populations can be added or dropped during the trial [6]. Although the 2018 FDA guidance on master protocols focuses on the development of oncology drugs and biologics, some of the approaches and concepts are relevant to other products and diseases.

When planning a pediatric master protocol, at least four aspects of the trial design and execution should be considered including: (1) the context of pediatric drug development, (2) the choice (or not) of a common control group, (3) the benefits of a single infrastructure for the conduct of the master protocol and the associated substudies, and (4) the FDA regulatory submission process.

The Context of Pediatric Drug Development

Data to support safe and effective treatments to guide prescribing in pediatrics is required by legislation in both the United States (US) and the European Union (EU). Under the US Pediatric Research Equity Act (PREA), first passed in 2003 and made permanent in 2012, FDA requires all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain an assessment (e.g., any necessary non-clinical and clinical studies) of the new product in the relevant pediatric population unless the applicant has obtained a waiver or deferral [7, 8]. The EMA also requires a Paediatric Investigational Plan, addressing the dosing, safety and efficacy in children of all age groups absent a waiver

[8, 9]. For both FDA and EMA, the required pediatric plan must be agreed upon prior to the submission of the pediatric and/or adult application which generated these requirements.

Pediatric studies pose ethical and operational challenges, such as the use of placebo and ensuring that there is the potential for clinical benefit to justify exposure to the risks of the investigational drug. Ethically, pediatric studies should enroll the minimum number of participants necessary to answer the scientific question [10, 11]. In support of this approach, extrapolation of efficacy from adults should be utilized for pediatric labeling when the disease and response to therapy are sufficiently similar in adults and children [12, 13]. From a parent/patient perspective there is a need to minimize the number of patients required to take placebo (e.g., some pediatric cancers, rare progressive genetic diseases) [14]. In addition to ethical concerns, there are many barriers to enrolling children in clinical trials, including relatively small numbers of potential participants, technical limitations related to blood draws and procedures, parental willingness to permit their child to participate, and the ability for physicians to prescribe the investigational treatment outside of a clinical trial (i.e., off-label) [15, 16]. Multiple companies enrolling pediatric and adolescent patients into trials of drugs in the same disease or with the same mechanism of action is not efficient. Multiple trials with drugs that are second or third in class may also raise ethical concerns given the known safety and efficacy of a drug that is already approved in adults.

Use of master protocols in pediatric drug development must also consider the role of the extrapolation of data concerning dosing, safety, and efficacy from the reference (usually adult) to the target pediatric population. Generally understood, extrapolation uses known facts as the starting point from which to draw inferences or conclusions about something unknown. The regulatory use of extrapolation was first introduced in the 1994 FDA Pediatric Labeling Rule [17] but did not have much of an impact until the US pediatric incentives were established in 1997 and 2003 [12]. In the United States, the extrapolation of efficacy from adults to children is defined by legislation [18]. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) has a similar definition: "an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric [target] and reference (adult or other pediatric) population." [19] In effect, information from the reference population can be borrowed or leveraged to support inferences in the target population, thereby reducing the need for additional data from a new clinical trial. This process is both stepwise and iterative whereby what is known is synthesized into an extrapolation concept, including the degree

of certainty or uncertainty surrounding what is known and the gaps in existing knowledge. Based on this synthesis, an extrapolation plan is formulated which focuses on generating the new data required to establish the safety and efficacy of a product in pediatrics. [19]

A Shared Placebo Arm: A Benefit or Not?

Particularly where off-label treatment options exist and delays in treatment can affect the disease course, use of a placebo even during a lead-in phase is problematic due to the lack of equipoise with respect to the use of the investigational drug once efficacy has been established in adults [20]. What are some of the implications in using study designs based on pediatric extrapolation in the context of master protocols in pediatric drug development? Many programs lack a concurrent control and instead rely on a comparison to a historical control, whether placebo or active. As such, the lack of a shared concurrent placebo control group eliminates one of the advantages of using a master protocol in which multiple arms can share a single control arm and thus reduce overall placebo exposure. However, this lack of a shared concurrent control group does not undermine the operational advantages of a shared infrastructure and protocol. In addition, there are interpretive or analytical advantages to having multiple treatment arms within a single master protocol whether to support a Bayesian analysis (thereby allowing for a smaller sample size) or to simply contextualize a descriptive comparison to either an active or placebo control.

The Importance of Infrastructure and Laying the Groundwork

Delays in regulatory approval of pediatric therapeutics are exacerbated by operational inefficiencies and multiple programs recruiting participants within the same disease space. Building pediatric trial infrastructure and a framework for companies to conduct pediatric platform trials would accommodate cross-company platform trials to assess drugs for the same disease, or with the same mechanism of action. The COVID-19 pandemic led to many examples of dramatic deployment of resources and advances in clinical trial designs to deliver critical data for societal needs [21–24].

One example is a pragmatic platform trial of critically ill patients with COVID-19 (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]), funded by 2 pharmaceutical companies developing IL-6 inhibitors. In the platform, both drugs were compared with standard of care. The primary outcome was analyzed using a Bayesian cumulative logistic model, incorporating evidence accumulated in the trial and the prior probability distribution (the assumed previous knowledge). The two anti-IL-6 drugs both met the primary outcome [25].

Despite the plethora of master protocols during the COVID-19 pandemic, there were noted problems with data quality due to lack of existing infrastructure. FDA assessed that the vast number of global clinical trial arms in these protocols were not randomized or adequately powered. The clinical trial ecosystem lacked a screening mechanism for identifying and directing candidates to an appropriate arm. The system also lacked the ability to generate highly actionable information of sufficient quality [26]. Pediatric platform trials could leverage Bayesian statistical analyses, as well as operational efficiencies, to streamline the process for data generation and analysis. This would be enabled by building the infrastructure necessary to generate high quality and interpretable data acceptable to health authorities.

Multi-sponsor Master Protocols and the Regulatory Submission Process

There are early challenges associated with launching a platform trial that must be addressed carefully, particularly in a multi-company platform trial. Pediatric development requires an a priori agreement with health authorities regarding a plan that will result in pediatric labeling. When more than one company participates in a trial using a master protocol, there must be company agreement on Master Protocol elements, which may require modification of health authority agreements. Operationally, collaboration agreements can be challenging. The process for data handling and statistical analysis must be kept confidential to each company. There must be alignment of timelines for companies developing drugs with a similar mechanism of action, and health authorities must agree to the proposed plans. Typically, platform trials are conducted under a single investigational new drug (IND) application, but it is possible to conduct cross-company collaborative trials under separate INDs by establishing distinct "platform" and "ISA" level protocols. Use of a centralized platform institutional review board (IRB)/ethics committee (EC), but separate Drug Safety Monitoring Boards for each company's ISA, might also be needed.

A Master Protocol in Pediatric Crohn's Disease

The pediatric experience with the use of master protocols has largely been in the field of oncology [27]. As summarized by Khan and colleagues (2019), the master protocols are primarily early phase trials focused on dose finding, safety, and an estimate of pharmacologic activity with the goal of carrying selected candidates forward in more

definitive phase 3 trials [28–38]. The experience outside of pediatric oncology is more limited.

Drug development in pediatric inflammatory bowel disease (IBD) presents many of the challenges discussed above. Pediatric approvals in the US and in Europe for infliximab and adalimumab in pediatric Crohn's disease and ulcerative colitis lagged between six and eight years after the adult approvals [39]. These trials were performed when there were limited competing products, while the field is becoming increasingly crowded. Most, if not all, of the adult development programs in IBD are associated with a requirement for pediatric studies. As a result, there are many more products for which there are pediatric requirements. For example, as of May 2021, there were twelve products involving six different classes which have active pediatric investigational plans listed on the EMA website, of which four are IL-23 inhibitors. These data are likely an underestimation of the challenge, given the number of publicly listed industry-sponsored clinical trials in adult Crohn's disease (i.e., 328 studies found on ClincalTrials.gov on May 13, 2021). As such, the length of time to recruit pediatric IBD clinical trials will only increase, leading to further delays in access to safe and effective drugs for pediatric IBD patients.

At an FDA meeting, investigators presented registry data estimating about 750 pediatric Crohn's disease patients and 490 pediatric ulcerative colitis patients in the US who would be eligible for a clinical trial (assuming moderate-severely active disease, which is a common inclusion criterion). There is a need for data supporting dosing and safety in young children with IBD; however, only approximately 20% of pediatric IBD patients are under twelve years of age and eligible patients less than six years of age are quite rare [40]. For comparison, the current sample size being required by regulatory agencies is between 90 and 120 pediatric participants, age 2 to < 18. At the same meeting, patients and physicians cited challenges related to pediatric IBD trial enrollment: families may be unaware of trials; most patients are managed in community settings rather than specialty centers; trials do not offer home visits or telemedicine to ease travel burden; families may not be ready to enroll in a trial at the time of diagnosis; trials may require patients to have failed 1 or more therapies; clinicians may prefer to avoid long washout periods required by clinical trials, and lack of benefit to participating in a trial vs. off-label prescription [40]. Physicians, caregivers, and drug developers call for a greater use of extrapolation from adult to pediatric studies, given the accepted similarity of disease and expected response to therapy in adult and pediatric forms of IBD. However, health authorities continue to require relatively large studies to fulfill postmarketing requirements [41].

The use of master protocols is among the potential solutions to this problem provided that such use would either improve enrollment or reduce the required sample size. Toward that end, Janssen and Lilly have been working on a collaborative cross-company pediatric platform trial in pediatric Crohn's disease using an innovative Bayesian analysis. The platform trial will involve a master protocol with separate ISAs for each compound, guselkumab and mirikizumab. We describe how two companies in the pharmaceutical industry have been able to work together to design the proposed platform. We focus on selected aspects of the program, highlighting the usefulness of a single infrastructure, the regulatory submission process, the choice of control group, and the context of the use of pediatric extrapolation.

The How

The initial inspiration for a master protocol was based on the recognition that there were multiple compounds being developed which targeted the IL-23 pathway. Following informal conversations with colleagues in different companies, Janssen and Lilly decided to work together toward formulating a master protocol for the study of two IL-23 p-19 inhibitors in pediatric Crohn's disease (Janssen investigational agent = guselkumab; Lilly investigational agent = mirikizumab). Janssen established a GitHub® site for collaborative coding and an external facing SharePoint® site for document management and storage. With appropriate agreement(s) in place, Janssen and Lilly collaborated in developing and submitting (1) a meeting request to the FDA Complex Innovative Design pilot program, (2) a briefing package to the EMA Scientific Advice Working Party, (3) FDA Type C meeting request and briefing package, and (4) request for clarifications and responses to the advice received from both FDA and EMA. Confidentiality was maintained by submitting the Investigator Brochures under separate cover (EMA) and cross-referencing the company specific INDs (FDA).

Discussions of the appropriate legal and operational structure took place in parallel with the development of the master protocol. Early on, there was a decision not to seek an independent third-party to hold the master protocol IND as this would effectively cede control of the platform. This approach deviates significantly from the predominant model by which an independent third-party holds the master protocol IND and brings the various sponsors together. FDA provided feedback on the regulatory submission process, which required separate yet coordinated submissions by each company. As there would be no sharing of data from each ISA between companies, the overall program would be run by an independent Contract Research Organization (CRO) and statistical group to perform the Bayesian analysis.

The companies have put in place agreements to govern the collaboration and address key issues for the conduct of

the platform study, such as financial responsibility, data handling, regulatory communication, and study operations. This agreement creates a structure for shared governance of the master protocol (e.g., steering, protocol, regulatory, and operational committees) and for joint contracting with the CRO.

The What

The master protocol covers the screening and randomization process into one of the two ISAs. To ensure the comparability of the populations enrolled in each ISA, the master protocol includes all the necessary inclusion and exclusion criteria. Study participants then will be followed according to the schedule of activities of the ISA to which they are randomized. The schedule of activities of the two ISAs have been harmonized to the greatest extent possible to reduce the possibility of a perceived difference in the burden of participation, as assignment to each study intervention (i.e., ISA) is not blinded. The platform-level analysis is based on the endpoint of clinical remission and endoscopic response at week 52. As such, the design of each ISA needed to be harmonized for those aspects which would impact on the week 52 endpoint, such as disease activity, responder and loss of response definitions, rescue medications and exit criteria. This harmonization was achieved through a collaborative process by which the master protocol was written jointly, as well as close communication as each company finalized their ISA.

Pediatric clinical trials in Crohn's disease often lack a concurrent control group. The totality of evidence used in support of efficacy include comparisons to both the adult placebo rate and the adult response to the active study intervention. Absent an agreement to share clinical trial data on the adult response for either guselkumab or mirikizumab, the design of the platform-level analysis focused on the comparison to a meta-analysis of the adult placebo control. The modeling was performed using public data on the adult placebo response rate in Crohn's disease trials, and there is an agreement to share any available adult placebo response data. Whereas the comparison to the adult active control will be performed separately at the ISA level by each company, the platform-level analysis will be performed by an independent statistical group so that patient level data does not need to be shared between companies.

The platform-level analysis will use a Bayesian robust mixture prior in which each ISA is used as prior information for the other ISA. The amount of information that will be borrowed from one ISA to the other will depend upon the degree of similarity between the two response rates, which belongs to a class of Bayesian models known as commensurate priors. This use of the commensurate prior is an important feature as it does not assume that the two compounds will behave similarly (i.e., the two biological compounds are assumed different until proven similar) but rather allows the clinical data to drive the degree of borrowing. It is beyond the scope of this article to explore the details of the Bayesian modeling. Suffice it to say that a sample size of approximately 50 participants per ISA was sufficient to model acceptable operating characteristics at the ISA level with respect to the probability of success, false positive rates, and bias based on a 90% non-overlapping credible interval between the placebo and ISA response rates. This is approximately half the number of participants that would be currently required to enroll in a study of each individual drug. In addition, the operating characteristics with respect to the probability of a false positive rate (i.e., the chance of making a false positive conclusion about efficacy) was calculated for each compound (i.e., at the ISA level) and not for the overall platform trial [42, 43].

For different reasons, neither the EMA nor the FDA agreed that a sample size of 50 per compound was sufficient for a marketing authorization application. Accordingly, the platform program was redesigned to enroll an adequate number of participants to address both EMA and FDA concerns while maintaining the Bayesian platform design. The overall program will thus serve as an important proof of concept for the advantage of master protocols to potentially reduce the required sample size in the future. In addition, the absence of a common concurrent control group does not mean that there are no advantages to using a master protocol, such as is being done with this platform trial in pediatric Crohn's disease. There may be operational and financial advantages to using a single infrastructure (e.g., shared contract research organization) for conducting the clinical trial.

The Bayesian design with borrowing between the two ISAs, guselkumab and mirikizumab, assumes exchangeability of the data between the two ISAs. In other words, the platform trial assumes exchangeability among the ISAs whereby "units (patients or trials) are considered exchangeable if the probability of observing any particular set of outcomes on those units is invariant to any reordering of the units." [44] ISAs are considered exchangeable if the remission rate for any one ISA is no more likely to be larger or smaller than that of the other ISA. Given the shared mechanism of action, this is a reasonable assumption. In addition, patients will be randomized between the ISAs. Randomization, along with inclusion/exclusion criteria and disease activity measures defined at the platform level across ISAs, support that "patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other reindexing or re-numbering of the patients" [44]. As such, exchangeability

assumes that the individual ISAs have different but related treatment effects, and that this relationship is modeled through a common distribution [45]. Critically, exchangeability does not assume that the ISAs and investigational agents are equal, but that they are related [46]. By design, the platform approach supports the concept of exchangeability because the platform ensures that the ISAs are "similar enough in design and execution" and a priori "should not have any reason to believe that there are systematic differences among the trials in any given direction" [44].

If this assumption of exchangeability is violated, an expected result would be a large degree of heterogeneity between ISAs. The use of a commensurate prior assures that the degree of borrowing would be minimal if this exchangeability assumption turned out not to be true based on a differential response rate between the two active compounds. In addition, randomization of participants between the two ISAs also support exchangeability insofar as the two populations would be effectively the same. The possibility of heterogeneity between the two compounds in the clinical response has been incorporated into the simulation so that the results of the primary analysis are not overly reliant on the assumption of exchangeability. Of note, the concept of exchangeability is closely related to the use of extrapolation in pediatric Crohn's disease, where the adult placebo remission or response rate is considered an appropriate control group for the pediatric active group. In addition, this pediatric Crohn's disease platform proposal builds on the extrapolation concept of borrowing efficacy data across the 2 treatment arms (or ISAs).

Concluding Remarks

Master protocols offer the potential for great benefit in pediatrics by streamlining clinical development through, for example, utilizing shared control groups (whether active or placebo), creating efficiencies in clinical operations, and reducing the number of patients required to participate in trials through innovative analytical methods. However, the work necessary to implement pediatric master protocols should not be underestimated. Building the collaborative infrastructure for the design and implementation of pediatric master protocols would benefit the movement toward wider use and acceptance. The ultimate goal would be to reduce the delay in pediatric marketing approvals when compared to adults so that children have access to safe and effective medications in a timelier manner.

Declarations

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