Master Protocol and Combination Products Development: A Step Closer to Precision Medicine

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This article discusses the challenges and benefits related to using the "master protocol" and "platform" study design in conducting clinical trials of combination products, trials where the product is comprised of two or more regulated components. The authors speculate on regulatory challenges arising from employing alternative clinical trial procedures and processes and examine changes in FDA policy regarding clinical trials with combination products.

Introduction

Combination products are defined as "a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically or otherwise combined or mixed and produced as a single entity."[1] Combination products present researchers and manufacturers with unique regulatory challenges. FDA assigns review of new combination products to a specific center, but this process can be problematic when the Primary Mode of Action (PMOA) is difficult to determine.

With increased utilization of precision-based medical approaches, more adaptive scientific methods and processes have become increasingly necessary. The master protocol is a study design based on the concept of using an overarching protocol to answer multiple questions. The Platform Trial is one type of master protocol. It is conforming and self-correcting and could be the answer to the combination product question.

Current Product Development

Since the mid-1940s, the Randomized Clinical Trial (RCT) has been frequently utilized to demonstrate the safety and/or efficacy of new pharmaceutical and medical device products.[2] As further scientific discovery evolved, so did developments in ethics and statistical methods. All of this innovation led to an upsurge in clinical development, which brought hundreds of new products to market in the US. However,

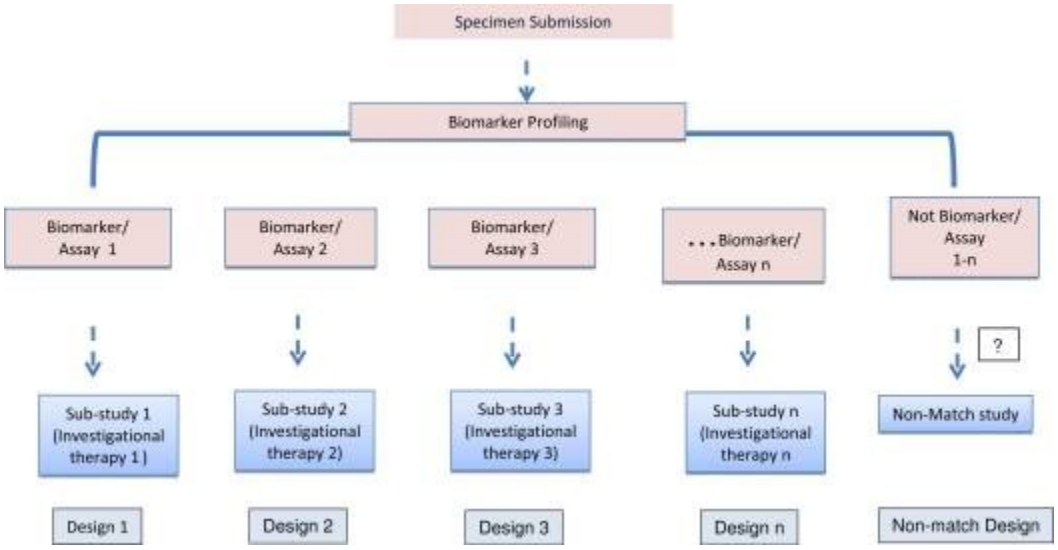
for the past two decades, the number of new products approved by FDA has slowed considerably as compared to previous decades, despite a significant increase in research and development spending by companies. Recent clinical trial failure rates are high: 36% for Phase 1, 68% for Phase 2, and 40% for Phase 3.[3] This elevated failure rate may contribute to the slowing of innovation, as re-evaluation or repeating of trials showing limited results can become costly. Traditionally, clinical studies have been designed to evaluate a single treatment in a largely homogeneous population. Currently, with new advances in genomics and biomarker identification and a desire for more precision medicine, many diseases and conditions can be classified as "rare" due to the uniqueness of therapies needed to treat them. This makes the single disease/single hypothesis clinical study design impractical, slow and costly. Innovation begins to outpace the completion of such trials, thus rendering them obsolete and their data outdated.

Focusing on the concept of precision medicine, doctors are leading the charge with more complex treatment regimens to address the diversity and particular needs of their patients. Patients are demanding more of their healthcare professionals and, indirectly, also demanding more of those who develop and manufacture their treatments. As part of the trend toward precision medicine, combination products play an increased role. Their ability to deliver a number of therapies easily and inexpensively can lead to better medicine. And, to make the development of these products as efficient as possible, the path to market seems best paved by the use of the multi-arm platform Phase 3 the foundation for which is the master protocol.[4]

The Master Protocol and Platform Trials

The master protocol design is one of an overarching protocol addressing many questions. The general idea is to provide a platform for assessing multiple agents simultaneously in patients with specific conditions. Once the patient is evaluated for a biomarker, they are assigned to a sub-study within the master protocol.[5] Master protocols are divided into three distinct types: the Umbrella Study, which addresses multiple targeted therapies in the context of a single disease; the Basket Study, looking at a single therapy in the context of multiple diseases and the Platform Study, which studies multiple targeted therapies in the context of a single disease, in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.[6] The ease with which this study design allows for simultaneous evaluation and for elements to enter or leave the platform makes it more efficient to assess multiple characteristics. **Figure 1** illustrates a generic biomarker-driven master protocol design.[7] It is a more generalized version of the Umbrella Study, but is also modified slightly to become the Platform Study (**Figure 2**). As the master protocol is a variation on a Bayesian adaptive design, it can make changes based on testing outcomes. It is also what makes the study design easily altered for use in product evaluation. The Platform Study design is most easily adapted to combination product development.

Figure 1. Generic Biomarker-driven Master Protocol Design



For the concept of the master protocol to be successful, two innovative ideas must be well-established. First, there must be an infrastructure in place for data collection, storing and sharing. This type of study, where elements are constantly being introduced and removed, and massive amounts of data are being generated simultaneously, would not work if researchers and reviewers were constantly "reinventing the wheel." Second is the use of a common protocol incorporating statistical approaches to study design and data analysis that are innovative and allow for a wider set of objectives to be attained than would be permitted by independent studies.

Platform trials feature a number of factors that make them attractive in a clinical research setting. The multi-arm aspect makes them useful for exploring combinations of treatments and for comparing treatments to get a best outcome. These trials also require sharing resources among researchers, investigators and sponsors—all of whom can help reduce costs and increase statistical efficiency. The trials can be comprised of either a fixed number of treatments or an adaptive number in which treatments can be added or dropped during the course of the trial. Because of this capability, endpoints can be reached quickly with fewer resources, and the data "muddied" less by extraneous testing done in the name of redundancy to adhere to old standards.

Regulatory Challenges of Combination Products

Combination products includes products that are packaged together or packaged separately, yet designed to work together. Because of their complex nature, these products pose a challenge to the regulatory field.

At the beginning of the new product development process, several difficult decisions must be made. Among those is which regulatory agency center will be responsible for guiding the product along its regulatory pathway? How is that decision made? Since that decision is very commonly made by looking at the Primary Mode of Action (PMOA) of the device, it seems very straightforward. But with a product where the PMOA is not clear, things are not so clear.

Further along in development, during the preclinical and clinical phase, new regulatory questions may arise as products are tested and additional safety or efficacy concerns come to light. Although a particular regulatory agency center has been assigned, all components of the product must be tested for safety and efficacy. Currently, while guidance documents exist, they often must be modified to address the nature of combination products, as the components of these products must be assessed individually,

and then as they function together.[8] Adaptation can lead to ambiguity and less trustworthy application of regulations and guidelines.

FDA Statement Helps With Clarification

To address the confusion concerning Primary Mode of Action and classification as it pertains to combination products, on 14 May 2018, FDA issued a statement regarding a proposed rule intended to help clarify regulations, streamline the product classification process and better align with legislation.[9] In an effort to spark innovation and encourage companies to develop combination products, this rule will better explain what procedures apply to sponsors when the classification of their product is unclear or in dispute. Opponents of the new rule are concerned about some of the provisions the new rule will be removing. ne specific concern is the change that will remove the existing pathway for product sponsors to request FDA to reconsider a product classification determination. FDA calls the existing reconsideration process "confusing and inefficient," but opponents of the new rule say that process is invaluable in situations where information in the initial request was incomplete or overlooked.

Benefits of Integrating Master Protocols into Combination Product Development

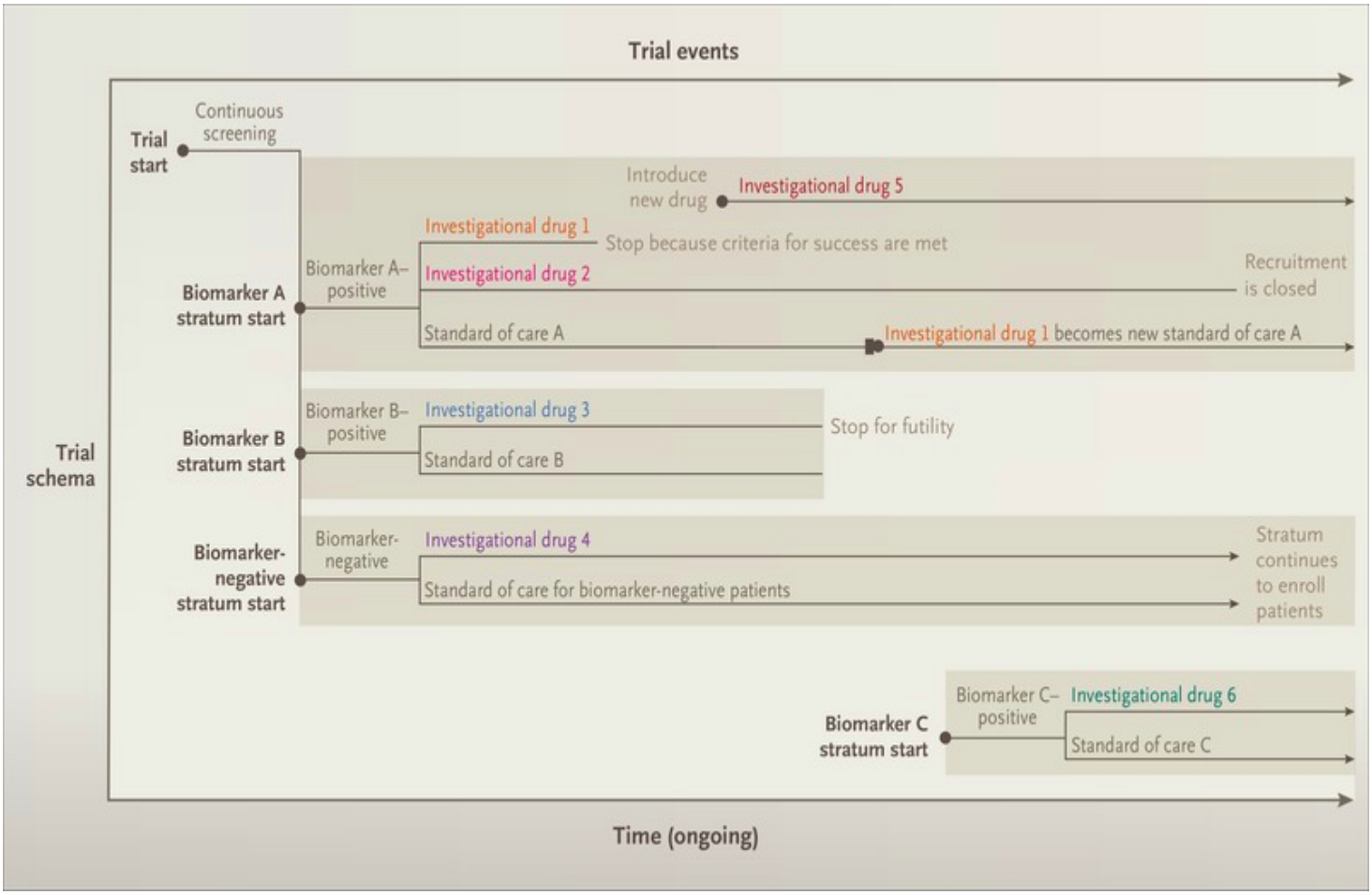
Regarding the proposed new FDA rule noted above, the implementation of a master protocol and adaptive design preclinical and clinical trials would be made even simpler by modifying the classification requirement, as this modification would mean that trials could continue smoothly and would not need to "fit" strictly into the structure of the assigned classification.

The master protocol is a variation on a Bayesian adaptive study design and employs an outcome-based adaptive randomization design.[10] What this means is, as a study progresses, the ratio of elements randomly assigned to an experimental arm versus the control arm changes over time from 1:1 to randomly assign a higher proportion to the study arm that is doing better. Not only can this change optimize sample sizes, but it can employ early stopping rules, ensuring that the study begins to select for effective outcomes while ineffective outcomes are eliminated. The master protocol provides a solid framework on which to build a study or assessment but, due to its flexibility, it is effective in assessing the complexity of combination products.

Figure 2 shows a framework for a platform trial master protocol.[11] There is no fixed stopping date, as the master protocol design is such that it is planned that strata will be added and dropped over time. In this example, patients undergo a screening for specific biomarkers (A or B) and are assigned to one of three strata. The first strata (Biomarker A-Positive) are randomly assigned to one of three groups, testing two drugs against the current standard of care. When drug number one meets the success criteria, that group is stopped and drug number one replaces the previous standard of care as the control. Randomization to a drug number five group is begun on the Biomarker A-Positive group, sharing the control group for patients with similar biomarker profiles. The drug number two group completes enrollment and stops. Entry of patients into the Biomarker B-Positive stratum is stopped when drug number three appears unlikely to provide benefit. When that occurs, new Biomarker B-Positive patients are assigned to the biomarker-negative group. A Biomarker C-Positive level is opened when a new biomarker assay and a new drug become available. At this point in the trial, patients are screened for Biomarkers A and C and assigned to the appropriate stratum. This is only one possible platform trial study scheme. This example

shows a randomized treatment assignment, sharing of common control patients and sequential analyses with the possibility of stopping early for success or failure, but also can be modified to meet the needs of a specific study.

Figure 2. Potential Design of a Platform Trial Involving a Single Disease



The ability to enter new strata, as well as discontinue treatments or elements that are no longer producing an outcome, is easily tailored to the development of combination products. Each aspect of the device can be assigned to the initial strata. An example could be a contact lens that also delivers medication to treat glaucoma. This type of product presents a new challenge because it is impossible to determine its primary mode of action.[12] Because of the design of this study, there is no need to determine the PMOA as all aspects will be tested at their own strata. With the platform trial design, each characteristic of the product can be tested concurrently as different treatments are applied and either continued or ruled out. As data is gathered and stored, it can be utilized at various points during the study and throughout regulatory review. As much of the testing is done at the same time, and attention is focused on results and adaptation, the maximum amount of data is obtained and is likely of high quality. When strata are completed, with either positive or negative results, new aspects are introduced and assayed.

Integration Challenges

As with any innovation, master protocols present unique but not unsurmountable challenges. Although by design master protocols provide a solid foundation on which to build, implementation requires a significant amount of up-front planning. A study or review must be carefully managed before, during and

after for completeness, consistency and to ensure the safety of all participants. Complete and thorough training and preparation becomes paramount, so that all parts of the endeavor go smoothly. Data sharing and cooperation between all involved parties—from clinicians to patients to reviewers—is imperative. While it is understood that there is proprietary information and the privacy of study participants must be maintained, proper planning can help assure that what can be shared is shared.

Developing a central location for information (preferably digital information) that has leveled security to provide correct access could help make cooperation easier, while still satisfying the need for safekeeping of data. Additionally, especially with more complex products or for longer studies or reviews, the potential for more complicated study design increases. Because of the flexible nature of the master protocol construction, which allows for elements to be added or subtracted, for the ending and beginning of old and new strata, and its ability to handle many strata at once, there is potential for an investigation to get quite out-of- hand. However, with careful planning and continued oversight throughout the entire process, the simplest solutions will always be explored first and complications can be mitigated. And, lastly, there is the difficulty of establishing an end date early in the process. As components are added and removed, trials are altered, arms are ended and begun, and the ability to set endpoints becomes problematic. And determining these conclusions early becomes seemingly impossible. By allowing for more adjustability in these dates, and with some foresight on the part of the investigators and study conductors for these adjustments to be made, the impact on scheduling should be minimal.

Conclusion

Ideally, clinical studies are standard, double-blind and placebo-driven with strict protocols and predictable endpoints. They are conducted smoothly, with "clean data" collected and only encouraging results obtained. Everything is statistically sound and the road-to-market is clear. But, with innovative technology comes intricacy and complexity. Combination products are at the front of innovation and will be one of the main contributors to the further emergence of precision medicine.[13] Yet, even precision medicine is not predictable or smooth. The diversity of patients, and the conditions and diseases with which they battle, will likely make this personalization puzzling, and often ambiguous. Rather than fight against this and adhere dogmatically to the way things have "always been done," it would be in the best interest of product developers and researchers to design and implement systems allowing for more resilience and change in order to keep pace with the changing face of medicine and patient care.

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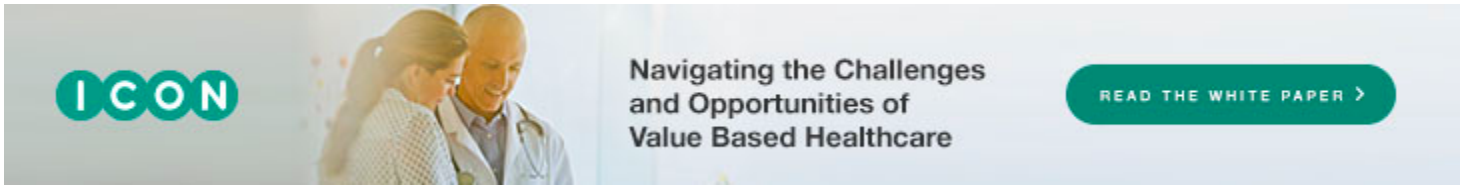

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