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Kraft Precision Medicine Accelerator

MEETING SUMMARY

April 11, 2019

MAKING NON-PROFIT AND PHARMA MASTER PROTOCOL COLLABORATIONS WORK

KEY TAKEAWAYS

- Master protocols offer the promise of more productive clinical trials.
- There is a “sweet spot” for master protocol partnership between industry and nonprofits.
- Proactive risk mitigation gives a master protocol the best chance of operating smoothly and working successfully.

THE KRAFT PRECISION MEDICINE ACCELERATOR

works to solve problems: to speed the development and delivery of therapies by improving the business processes that surround them. While oncology remains the focus of precision medicine efforts in healthcare, the field holds great promise for many other disease states as well.

The Kraft Accelerator's work is centered on four workstreams: direct to patient, data and analytics, clinical trials, and investment/venture. In all four workstreams, the philosophy is the same: engage leading experts, identify best practices, and promote collaboration to advance development.

On April 11, 2019, the clinical-trial workstream of the Kraft Accelerator convened a roundtable discussion on improving the ways in which nonprofit organizations and pharmaceutical organizations collaborate on master protocols.

IF WE KEEP LOOKING AT THE WAYS OF THE PAST, IT'S DIFFICULT. WE HAVE TO DISCUSS OPENLY WHAT WE CARE ABOUT: CLEARNESS AND INTEGRITY OF DATA.

GIOVANNI ABBADESSA, AVP, SANOFI-GENZYME

INTRODUCTION

Master protocols promise to accelerate precision medicine with efficient, broad and flexible hypothesis testing. However, the field has yet to define when and why master protocols work best, and how to undertake one with the greatest likelihood of success.

This workshop is perhaps the first in precision medicine to take on this dual mission. For the first time, partners from both sides of collaborative master protocols — nonprofit and industry — met for an honest discussion about the real tension that often exists, and to define the right circumstances, and the right risk-mitigation strategies, for effective research. Participants included nonprofit executives leading the most exciting master protocol efforts, as well as, pharmaceutical executives directing master protocols and nonprofit research collaborations.

KEY THEMES

- The "sweet spot" for master protocol partnership between industry and nonprofit is a situation that meets one or more of the following conditions:
  - Therapeutic indications where there is both clinical unmet need, and an opportunity for commercial development.
  - Therapeutics that are being investigated for secondary indications, rather than core or first indications for the commercial partner.
  - Studies that investigate indication expansions or complex combination therapies, especially in immuno-oncology.
  - Simple or modular master protocols that can more rapidly advance therapeutics to proof-of-concept, especially for biotech partners requiring funding.

- Risk mitigation in a well-designed master protocol should focus on four areas, which the team outlines and offers advice for inside:
  - Legal agreements, including questions of liability, ownership of patient samples and intellectual property.
  - Fundraising, while an everyday reality for nonprofits, a particularly challenging one for unproven efforts like an organization's first master protocol.
  - Business development, to obtain the best assets and partnerships for a master protocol.
  - Execution, to successfully manage the inherent complexity of a master protocol including the number of arms, data management and study leadership.

YOU CAN'T DESIGN A GOOD PLATFORM TRIAL IN THREE MONTHS. THESE DESIGNS TAKE TIME BUT ARE WORTH THE EFFORT.

VICTORIA MANAX RUTSON, MD, CHIEF MEDICAL OFFICER, PANCREATIC CANCER ACTION NETWORK

OVERVIEW

A recent overview of precision-medicine trials published in *Cancer Treatment Reviews* (Cecchini, M, et al, Clin Cancer Res. 2019) found 48 master protocols that were "planned, ongoing and completed umbrella and basket trials in oncology" as of July 2018. The paper noted, "Precision medicine trial designs fuel new hopes for identifying best treatments, but there is also the potential for hype. The benefits and challenges associated with their use will need continued monitoring."

The April 11 meeting sought not only to discuss the benefits and challenges of Master Protocols, but to share the expertise of the participants to assist future researchers by specifically identifying the circumstances best suited for these trials, and the areas of focus most critical for risk mitigation and a successful study. The discussion reflected the Kraft Initiative's own analysis of current and planned master protocols (Smith B, et. al, Applied Clinical Trials May 8, 2018) as well as the warning provided by Cecchini et al.

Four major master-protocol trials that are currently in preparation, or underway, include: Beat AML, GBM Agile, MyDRUG, and Precision Promise. These four trials (from, respectively, the Leukemia & Lymphoma Society, the Global Coalition for Adaptive Research, the Multiple Myeloma Research Foundation, and the Pancreatic Cancer Action Network) illustrate the variability in master protocol design and organization impacting the opportunities and risks of the master protocol approach.

Characteristics	Beat AML	MyDRUG	GBM Agile	Precision Promise
Bayesian/ Frequentist	Frequentist	Frequentist	Bayesian	Bayesian
Number arms	11 arms	6 arms	2 arms	3+ arms
Number sites	13 sites	17 sites	Global trial sites	14 sites
Funding	Pharma	Hybrid (foundation/pharma)	Hybrid (foundation/pharma)	Hybrid (foundation/pharma)
Biomarker driven (patient selection)?	yes	Yes	Yes	can be incorporated but retrospective to start
Registration?	No/Signal finding with registration preparations	No	Yes	Yes
Existing Organization?	Yes	Yes	No at start	Yes
Existing site network?	Yes	Yes	No at start	Yes
Internal legal resources?	Yes/ outsourced contracting	Yes	No at start	Yes

As a result, the promise of master protocol trials to advance research has yet to be fully realized, as risks are introduced by a variety of issues. This meeting undertook to not only to delineate the problems, but to specify the "sweet spot" with the greatest likelihood of success, and the specific areas of risk mitigation that can make the most difference. The panel of experts considered situations in which nonprofit organizations hold the sponsorship of an Investigational New Drug application and evaluated common situations in a forthright discussion.

Pharmaceutical and biotech manufacturers, and nonprofit organizations, share the goal to take advantage of the speed and flexibility of master protocols to improve research in precision medicine and bring new, safe and effective drugs to patients. However, while their end goal is the same, their priorities often differ. Nonprofits prioritize research and data-sharing and are looking to provide access to the best drugs for their patients. Manufacturers are generally concerned with data quality and trial infrastructure to aid in advancing drugs to registration, hoping to drive the widest possible access to patients.

Discussion participants from both commercial and nonprofit organizations agreed that interpersonal relationships are vital to advance development of collaborative master protocols. Partners must be willing to earn and demonstrate trust in each other's capabilities and expertise. This trust will come as both sides demonstrate the ability to deliver, but also from personal leadership and relationships from dedicated staff. Therefore, it's vital to have the right team on board. For nonprofits, this includes having an adequate structure, track record, staffing level and experience.

To find the right people on both sides of the partnership, nonprofit representatives advocated having a willingness to accept that not every organization will be interested, or right, for the project.

In addition to trust, partners must proceed throughout the study development process with dexterity and flexibility. Being nimble and agile allows partnerships to continue to work successfully together. For example, being open to hybrid clinical trial models can make it possible to start up faster, increase comfort levels, and build trust through models that redefine roles and responsibilities. In addition, while some have advocated that trials should always start with many arms, the panel agreed that it can be best to start with only a few arms, in order to kickstart interest that can be followed with additional partners and arms.

THE "SWEET SPOT" FOR MASTER PROTOCOLS IS WHEN ONE OR MORE OF THE FOLLOWING CONDITIONS ARE MET:

- **High unmet need plus development opportunity.** These are areas in which earlier treatments have failed to show benefit but may also be areas that have been addressed to some extent, but gaps remain, leaving some patients behind. In either case, the area must hold commercial opportunity in the appropriate stage of clinical development to make it a viable target for the pharmaceutical or biotech partner.

- **Combination therapies or indication expansions.** Master protocols can be an efficient approach to explore how treatments work together, particularly in immuno-oncology.

- **Secondary or niche indications.** Due to the complex and nature of master protocols and potential lack of control in a collaboration, a commercial partner may not feel that a core indication is the ideal scenario for an important asset. It's more likely that a master protocol will suit developers looking for additional indications for an approved drug, in niche or secondary indications.

- **Rapid proof-of-concept.** The potential flexibility and speed of an adaptive master protocol can help biotech organizations, who need to demonstrate progress and PoC to investors, to learn more, faster, than they might with a traditional trial design.

PROACTIVE RISK MITIGATION

Proactive risk mitigation gives a master protocol the best chance of developing smoothly and executing successfully. These four areas are the most important to consider:

Legal and contracting. Legal and contractual issues, and in particular, issues of liability, and ownership of intellectual property (IP) and patient samples must be addressed. For example, liability arrangements may include, terms stipulating that companies are responsible for design and manufacturing defects, while sites are responsible for negligent acts, and nonprofits take responsibility for study data. IP ownership issues may include terms that give companies non-exclusive rights after database lock with an option for exclusivity. Addressing legal and contracting issues is helped enormously by the quality of the relationships between companies, non-profits and sites. However, having action-oriented milestones (public announcements, for example) can be very useful in motivating partners to work through delays.

Funding. Trust is as vital in funding as in all other aspects of research. A nonprofit's status as a trustworthy organization, can be useful in gaining this support. However, it can also be helpful to approach partners from a business mindset, with an understanding of their needs for finding cost and time savings, and even media attention.

Business development. Efforts in business development, or obtaining access to company partnerships and therapeutics, can be both logistical (ensuring drug availability, for instance) and strategic (ensuring long-term commitment to the collaboration). Skilled alliance management is key and can be advanced through the involvement of a participant without a vested interest. The attendees agreed that it's important to take the time to have the right conversations with the right people at the right time, considering different approaches based on the organization in question. It is important to understand that the right people to involve may be different in different organizations. Finally, opportunities for business development will depend greatly on the timelines and stage of development of an asset and organization.

IF WE'RE AFRAID TO WORK TOGETHER, THAT'S A WASTE OF MONEY. DOING EXPLORATORY ACTIVITY IN CONCERTED EFFORT MAKES MUCH MORE SENSE.

JUERGEN REESS, HEAD, CORPORATE INTERNATIONAL PROJECT MANAGEMENT, BOEHRINGER INGELHEIM

Execution. Despite the small number of executed complex master protocols available, representation in the workshop was provides from the BeatAML study and other operational executives. The group emphasized the importance of extremely disciplined project management, ideally led by a small and nimble team of managers unafraid of strong decision-making to keep the trial moving, to ensure data quality and to protect the reputation of the study and its partners. Master protocols may be launched with a small number of arms, expanding once study feasibility is established. The group finally focused on the critical importance of proper data management to ensure the usefulness of the results and the return on the investment.

IT WAS A LOT OF INVESTMENT UP FRONT, BUT IT HAS PAID OFF.

EDWARD CHA, MD, PHD, MEDICAL DIRECTOR, CANCER IMMONOTHERAPY, GENENTECH

CONCLUSION

Master protocols offer the promise of more productive clinical trials.

Speed is often touted as the priority for master protocols in research, but their true promise is broader than that. First, the goal is to be effective rather than rapid. Second, value may be measured in a variety of ways, depending on the priorities of the collaborators. The emphasis on efficiency may be focused on whether a particular decision or number of decisions are made, or when a milestone is reached.

As Janet Woodcock, M.D., Director for the FDA's Center of Drug Evaluation and Research, has noted, master protocols present two types of innovation: first, a streamlined logistical infrastructure that can improve the data output; and second, innovative statistical approaches that allow more objectives to be met. Therefore, the true promise of master protocols lies not only in speed alone – but in productivity. However, master protocols can be challenging, requiring time, resources and collaboration to get off the ground with often-conflicting priorities.

When considering a master protocol, it behooves industry and nonprofit partners to determine that the circumstances are right, and that they've taken the necessary steps to mitigate risk and ensure success. This roundtable was the first gathering to take on that challenge to provide research and development organizations with actionable guidelines to succeed with master protocols.

IN AN IDEAL WORLD, WE'D HAVE INFINITE DRUGS, AND INFINITE TIME. IN REALITY, WE DON'T HAVE THOSE CONDITIONS, WHICH IS WHY NEED MASTER PROTOCOLS.

BRIAN ALEXANDER, MD, MPH, DANA-FARBER CANCER INSTITUTE, GLOBAL COALITION FOR ADAPTIVE RESEARCH GBM AGILE