Master protocols: New directions in drug discovery

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ABSTRACT

A master protocol is a unifying study construct that includes multiple subgroups and substudies, with patients having same or different diseases and that employ one or multiple drugs to treat it. Initially designed for oncology, master protocol trials are intended to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same overall trial structure. The ability to use a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, speeds up drug development and makes it more efficient. Thus, it is important for the clinical trial professionals to understand both the basic principles of master protocol trials and the way innovative trial designs are starting to change the landscape of clinical research.

1. Introduction

In 2006, the unprecedented approval of Novartis’ Imatinib Mesylate for five new indications based on a single-phase 2 clinical trial [1] bewildered the pharmaceutical sector. The FDA not only approved a drug without the customary two pivotal phase 3 trials, the drug was also cleared to treat a record number of cancers (one solid and four hematologic). It was an open-label, single arm prospective study that enrolled just 186 patients with 40 malignancies with evidence of expression/activation of imatinib-sensitive tyrosine kinases. In five of 40 malignancies the responses were robust, they became the genesis of the NDA applications and subsequent approvals. Remarkably, most of the studied groups had 10 patients or less. At the time many had wondered how Novartis accomplished so much with so little.

2. From oncology to wider application

The Imatinib story is a great illustration of a biomarker-driven precision medicine trial designed using the principles of master protocols. The growth in the use of master protocol studies is a reflection of a shift in drug development processes triggered by the increasing focus on targeted therapies for difficult to treat conditions, genomics and personalized healthcare. Master protocol trials have most ly been utilized in biomarker-driven studies where the use of a single platform to evaluate multiple treatment targets allows for more resourceful and more precise assignment of patients into appropriate and most relevant substudies.

This new approach has emerged as the need to investigate multiple biomarker targets across multiple tumor types has intensified. Since Imatinib, the number of master protocol trials has been growing exponentially. The discovery of specific tumor mutations has allowed for the development of targeted, less toxic therapeutics that have high affinity for cancer cells and are anatomically agnostic.

While to date the use of master protocols has been almost exclusive to oncology, with biomarkers enabling development of more targeted therapeutics now spreading to other therapeutic areas, new trial designs will undoubtedly become more prevalent across multiple therapeutic indications. There are already several large-scale trials in Alzheimer’s disease [2], pneumonia [3], influenza [4] that utilize master protocol principles and other novel trial design approaches. Thus, it is important for the clinical trial professionals to understand both the basic principles of master protocol trials and the way innovative trial designs are starting to change the landscape of clinical research.

3. Master protocol trials: Definitions and types

A master protocol is a unifying study design that includes multiple subgroups and substudies, with patients having same or different diseases and that employ one or multiple drugs to treat it. Initially designed for oncology, master protocol trials are intended to simultaneously evaluate more than one investigational drug and/or more than one disease type within the same overall trial structure. The ability to use a single infrastructure, trial design, and protocol to simultane-

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ously evaluate multiple drugs and/or disease populations in multiple substudies speeds up drug development and makes it more efficient \cite{5,6}.

4. Types of master protocols

4.1. Basket

A protocol employing a single therapeutic in multiple patient populations divided into parallel substudies (Fig. 1). Subgroups with robust responses may be expanded to achieve statistical significance.

The aforementioned Imatinib trial was a basket design trial where multiple cancers, both hematologic and solid, were treated with one drug.

4.2. Umbrella

A protocol with more than one targeted therapy studied for a single disease (Fig. 2). Patients are divided into multiple parallel treatment arms, receiving different drugs or drug combinations. Such studies usually include a control arm. Umbrella design studies may include multiple doses of the same drug for dose-finding purposes.

4.3. Platform

A protocol employing multiple treatments for a single disease, with these treatments allowed to enter/exit based on the decision algorithm \cite{7} (Fig. 3). Another name for such trials is Adaptive Platform Trials (APTs). APTs have some similarities with umbrella trials in that a single condition is usually studied through multiple interventions. However, unlike umbrella trials where all the subgroups go the initial predefined distance irrespective of the outcome, in APTs the information generated early in the trial is used to adjust its subsequent flow. The main tools utilized by APTs include the use of response-adaptive randomization (RAR) rules to preferentially assign interventions that perform most favorably, rules to trigger the addition or termination of a study arm, or rules to transition from earlier study phase to later phase. As data accrue from enrolled patients, they are used to iteratively update a pre-specified model. The updated results of the model trigger thresholds for the end of an experiment and provide updated randomization instructions for the ongoing APT.

5. Benefits

Master protocols offer a powerful new approach to drug development allowing for flexibility and creativity in the highly regulated clinical trial sector. They can be used to incorporate biomarker development, genetic subtyping and therapies with different mechanisms of action. Master protocol trials provide an opportunity to effectively expedite the development and delivery of innovative treatments across many therapeutic areas. Some of the benefits are explored below:

Time saving: Ability to test hypotheses quickly and effectively and to evaluate and compare drug combinations particularly in complex diseases. Master protocols also allow companies faster activation of new studies and substudies by plugging into existing infrastructures and cohorts.

Cost saving: Master protocols have the potential to bring about cost savings through cost-sharing with partners. They can reduce costs in several trial areas including start-up and site recruitment, site monitoring, administration, and control arms by leveraging shared infrastructure and reducing redundancies.

Continuous learning and sharing of real-world evidence: Master protocols typically bring together leading research and clinical experts in the area of complex and difficult to treat diseases e.g. certain difficult to treat cancers, Alzheimer’s disease. This allows for the sharing of the latest scientific and real-world evidence between stakeholders.

Patient benefits: Master protocols offer patients personalized treatment driven by their genetic subtype and biomarker makeup. There is also a reduction of the placebo exposure from the usual 1:1 ratio to 1:5 or even 1:10. Additionally, they allow for nonresponding

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Fig. 1. Example of basket trial design.

Fig. 2. Example of umbrella trial design.

Fig. 3. Example of PlatformTrial design.
patients to be offered more than one treatment giving those with previously untreatable or life-threatening diseases more shots on goal.

**Benefits for researchers:** Master protocols allow researchers to collaborate with other investigators. They can help them to collect observational data, create natural history cohorts, and quickly test clinical hypotheses.

**Advocacy group benefits:** Master protocols can enable patient advocacy groups to accelerate translation of preclinical research into novel treatments for the patient groups they represent.

6. Challenges

The multiple benefits associated with these new trial designs, not only for pharmaceutical companies but also for patients, researchers, non-profit and governmental stakeholders, are widely acknowledged. However, there has been some hesitancy in adopting these models on a wider scale. This is due to the relative complexity of these trials, concerns about cost and funding, competition between pharmaceutical companies and issues concerning guidelines and definitions.

The high complexity of master protocol trials frequently requires third party management. They may also be considered time-consuming in both its design, preparation and execution. They purposely include multiple interim analyses that increase the study duration and, somewhat paradoxically, may require larger patient cohorts. In addition, it is unlikely that a single company would have enough drug candidates with similar indications and at the same stage of development to warrant using these models. The exception is the basket trial design where a single drug candidate can be studied in multiple indications.

There are also issues surrounding competition and control whereby individual companies may be unwilling to create a platform study which may benefit its direct competitors. Hence, to date all the master protocol trials have been mostly run by independent organizations, non-profits, government agencies or the combinations thereof.

Other considerations include the fact that some of these new designs are reminiscent of head-to-head superiority trials that are not always palatable for risk-averse pharmaceutical companies. In situations where there are few treatment choices, it may be easier to run a classic randomized control trial (RCT) and compare one drug candidate to one standard of care (SOC) regimen.

Funding for master protocol trials can also be challenging as these trials are frequently open-ended and perpetual, without a set number of patients, with unclear duration of interventions and are subject to evolving standards of care. Potential variance in budgets associated with these trials may be unattractive to pharmaceutical companies and other parties accustomed to strict budgetary constraints who may prefer the relative predictability of traditional designs.

7. A rising tide in favour of complex innovative designed trials

Despite these considerations support for innovative and complex trial designs is growing as has been endorsed by several international governing bodies including the FDA in the US. In a 2017 *New England Journal of Medicine* article on new trends in clinical research, FDA affiliated authors Janet Woodcock, M.D. and Lisa M. LaVange, Ph.D., concluded “As the targets for new drugs become more and more precise, there is no alternative but to move forward with these coordinated research efforts.” [6] In 2019, the FDA cemented its position relating to complex study designs by issuing a draft guidance on master protocols [8]. In 2019, the EU’s Heads of Medicines Agencies (HMA) led by Danish authorities, launched guidance to support the adoption of complex trial designs [9] “in recognition of the fact that the development of personalized medicine is gaining ground and clinical trials with trial subjects are becoming more and more complex”. In January 2020 in the UK, the National Institute for Health Research (NIHR) along with health departments in Scotland, Wales and Northern Ireland put forward recommendations to support further development and adoption of Complex Innovative Designed (CID) trials including master protocol trials [10]. These moves suggest a groundswell of support for the wider adoption of complex design trials beyond oncology and into previously hard to treat conditions. In addition, demand for innovative design trials is growing in tandem with a shift towards precision medicine and personalized healthcare.

8. Case studies of master protocol trials

8.1. GBM AGILE trial (glioblastoma multiforme adaptive global initiative learning environment)

GBM AGILE is an international phase 2/3 clinical trial of adult patients with newly diagnosed or recurrent isocitrate dehydrogenase wild-type glioblastoma multiforme [11] (Fig. 4). The first patient was enrolled in July 2019 with a plan to recruit over 3000 patients worldwide. The study will have two stages: an adaptively randomized ‘learn’ stage to identify effective interventions and associated biomarker-defined signatures, with a seamless “graduation” to a fixed randomized ‘confirm’ stage for interventions that show positive signals of efficacy. The primary endpoint of GBM AGILE is overall survival, and the statistically significant data from the second phase will be used for New Drug Applications (NDAs).

![GBM AGILE](image)

Fig. 4. Gbm agile trial design.
8.2. REMAP-CAP trial (randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia)

REMAP-CAP is an international phase 4 platform design clinical trial evaluating multiple SOC treatment combinations and experimental treatment options for adults diagnosed with severe community-acquired pneumonia (CAP) [3] (Fig. 5). The design of REMAP-CAP allows to simultaneously assess for multiple interventions. If patients are ineligible for randomization into one subgroup, they are immediately evaluated for other subgroups. REMAP-CAP is launching with four domains that examine different antibiotics, the use of steroids and the use of different ventilation strategies. The study is designed in a way that additional interventions within each subgroup as well as additional subgroups can be added. The trial is enrolling in multiple geographies and plans to evaluate and address both SOC and real-life differences in CAP management.

8.3. BATTLE-1 TRIAL (The biomarker-integrated approaches of targeted therapy for lung cancer Elimination-1)

Initiated in 2006 and completed in 2009, BATTLE-1 trial is the first prospective biopsy-mandated, biomarker-based, adaptive randomized clinical trial for patients with advanced non-small cell lung cancer (NSCLC) [12] (Fig. 6). The clinical program consisted of one umbrella trial and four parallel phase II studies with biomarker-based, targeted therapies in patients with advanced NSCLC who had been previously treated with chemotherapy and subsequently experienced disease relapse. The treatments were chosen to target each of the four selected gene pathways in NSCLC that were of the highest scientific and clinical interest at the time when the trial was designed. After initial equal randomization into one of the four treatment arms based on their marker group membership an outcome-adaptive randomization scheme was employed. Adaptive randomization allowed to use the updated knowledge to guide the assignment of patients to treatment arms as the trial continued. As a result, more patients received the more efficacious treatments as the study progressed.

9. Conclusion

As precision medicine, with its focus on targeted and increasingly complex medical interventions, continues to gain traction, the role of master protocol trials in drug development is set to grow. The trend towards expansion of master protocols beyond oncology (e.g. REMAP-CAP) has already begun and is likely to continue. The support of regulatory authorities who have recently made moves towards harmonizing definitions and issued guidance on these new approaches to trial design is clear. Thus, the future looks bright for master protocol trials which is good news for industry, patients and healthcare systems worldwide. While there are still challenges associated with the application of master protocols and further work to be done in terms of harmonizing standards and safety associated with new trial designs, its further development and adoption is anticipated. This will be particularly welcomed by patients living with complex diseases and the

*RSA – Region-Specific Appendix
*DSA – Domain-Specific Appendix

Fig. 5. REMAP-CAP trial design.
scientific community researching effective treatments for the same. Wider adoption of the principles of master protocols may also be welcomed by those in the clinical research organization (CRO) sector as the complexity of the trials will necessitate third party expertise in recruitment of patients and management of studies. By working through the challenges and opening up to more collaborative approaches to drug development pharmaceutical companies can accrue significant benefits from master protocols including saving costs and time, sharing risks and accelerating the delivery of promising new therapies to patients in need.

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Declaration of competing interest

The author declares that he has no competing interests.

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