Innovative use of master protocols for pivotal studies in rare diseases

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Abstract

Recent years have seen the development of clinical study protocols that introduce more complex design features into the usual gold-standard randomised controlled trials (RCTs). Complex protocols are potentially useful for drug evaluation in the setting of rare disease indications, to optimise the efficiency of investigational drug development. They often involve a development of a master protocol alongside disease-specific sub-protocols. This article describes an approach used to develop a complex protocol for a Phase 3 trial involving an investigational treatment being studied for use in two distinct rare diseases. In a somewhat unusual approach, detailed subprotocols were developed that contained all information required by the investigator, while the master protocol highlighted differences between the subprotocols and provided rationale justifying use of a complex study design. Use of complex study designs aims to promote efficiency in the clinical investigation process but also needs to offer optimal clarity to both study investigators and regulatory reviewers.

Clinical trials in rare diseases

Rare diseases affect around 400 million people globally; however, 95% of these diseases lack an approved treatment.[1] According to an analysis of clinical trials in Europe, the USA, and Japan in 2018, most clinical trials into rare diseases consider rare cancers.[2] Costs and other challenges involved in undertaking such clinical trials are increasing, with evaluation of investigational treatments being particularly difficult when patient recruitment is limited by the small numbers of individuals affected. Other challenges that can limit clinical trials for rare diseases include: poor understanding of disease course and characteristics; difficulties in following regulatory guidance in the context of small patient numbers; issues with manufacturing and supply of investigational drugs; as well as safety and financial risks.[3] This means that undertaking randomised controlled trials (RCTs), the established gold standard for evidence of drug efficacy and safety, can be difficult in the rare-disease setting.

Agents intended to treat rare diseases are usually termed orphan drugs. A major factor that compromises the development of orphan drugs is the cost of the process and small market potential. These issues require the use of novel approaches to optimise treatment options for this underserved groups of patients.

This article describes our recent experience using a somewhat novel approach to complex protocol design that was used to assess a treatment in the rare-disease setting. In this case, the protocol was for a Phase 3 trial involving an investigational treatment being studied for use in two distinct rare diseases.

Use of novel master protocols to date

Recent years have seen the development of clinical study protocols that introduce more complex design features into the gold-standard of RCTs, to optimise the efficiency of investigational drug development.[4] There is potential for some of these complex-design approaches to help bring treatments to market for individuals with rare diseases.

The use of master protocol designs has led to great advances in cancer therapy. For example, this approach was used to investigate the activity of imatinib in treating 186 patients with 40 different malignancies ranging from solid tumours to haematologic cancers.[5] The study was conducted as a basket trial, in which a common treatment combination was investigated across multiple disease cohorts and outcomes were assessed in the context of relevant genetic mutations; multiple disease types were in effect collected together in a "basket".

Another approach uses an umbrella trial whereby multiple therapies are evaluated for a single disease. National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) was an umbrella trial that investigated whether treating cancers according to their molecular abnormalities was effective; NCI-MATCH enrolled an impressive 1,593 participants who were each assigned to one of 38 sub-protocols.[6]

> Matrix studies involve multiple clinical interventions and patient populations, and in effect can be considered a combination of a basket and an umbrella study.

Platform studies are designed to prospectively add or discontinue sub-studies. As such they have a fluid structure, which allows multiple targeted therapies to be studied in populations with similarities such as a common disease. An example of a platform study is the Systemic Therapy for Advancing or Metastatic Prostate Cancer (STAMPEDE) trial in men with newly diagnosed advanced prostate cancer. From its start in 2005, STAMPEDE included almost 12,000 participants; the trial is ongoing, but recruitment is now closed.[7] The first results demonstrated improved disease control and life expectancy by adding docetaxel or abiraterone to treatment regimens; however, since then the fluid structure of the study has allowed many other strategies to be tested.

Matrix studies involve multiple clinical interventions and patient populations, and in effect can be considered a combination of a basket and an umbrella study. In common with platform studies, matrix studies can remove interventions and include new interventions as the study progresses. Matrix studies need not have a fixed duration or sample size.

These various types of studies offer a range of design options that can be incorporated into large

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and complex protocols. While cancer has been the clinical setting that has most frequently utilised novel study protocols, other areas of clinical research are also embracing this change.

A survey in 2021 found that master protocols had been used in infectious disease, neuroscience, immunology, and rare disease settings, with the most common design being basket trials.[8]

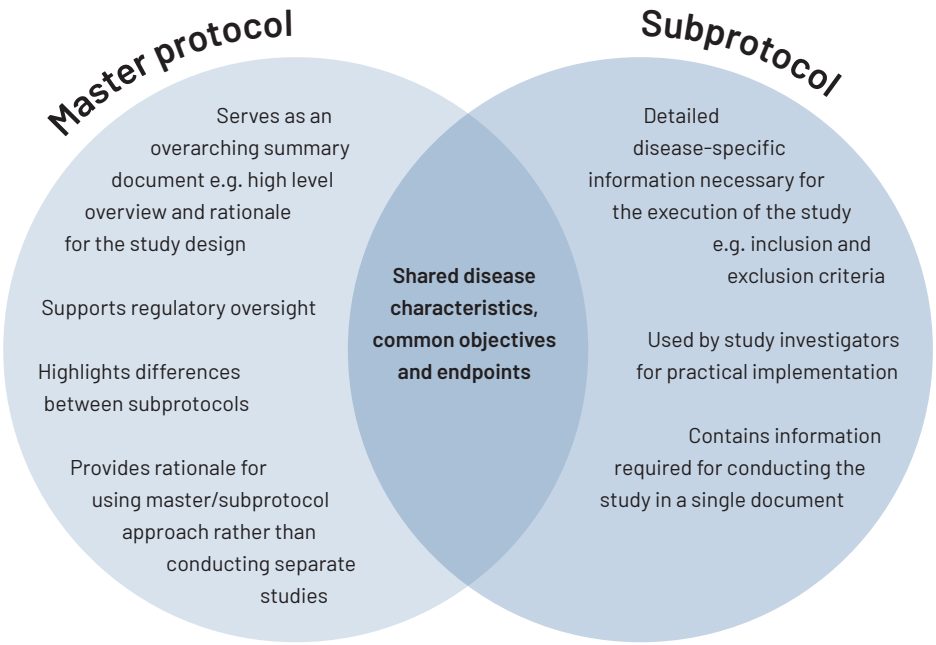

Figure 1. Venn diagram showing how the master protocol and sub protocols interacted within the complex protocol design

Available guidance on the use of master and sub protocols

Assistance in developing master protocols is available in the form of templates, such as those provided by EU Patient centric clinical trial platforms (EU-PEARL).[9] More detailed guidance is also available from sources such as the US FDA[10] and TransCelerate Biopharma.[11] However, how useful these templates are depends upon various factors, including the disease setting and experience and expectations of the study development team. Guidance documents generally describe the development of a master protocol that includes detailed description of clinical study design; the associated subprotocols then describe disease-specific aspects to highlight the differences between subprotocols.[9,10,12]

Experience in developing master and sub protocols in the rare-disease setting

A protocol was required for a pivotal Phase 3, double-blind, randomised, multicentre, placebo-controlled study, whereby two rare diseases were to be investigated with the same therapeutic agent. This led to developing master and sub protocols (Figure 1).

Our approach was to prepare detailed disease-specific sub protocols (rather than a detailed

Similarities	Differences
Share similar disease characteristics, faciltating the use of many common endpoints	Each subprotocol has its own control group, due to potential differences in disease progression profiles or rates between the conditions under study
Common database setup	Sample size calculation
Comparable visit/assessment schdules between subprotocols	Stratification variables
Use of single independent safety monitoring committee	Disease inclusion and exclusion criteria

Table 1. Summary of the similarities and differences between the disease-specific sub protocols.

master protocol) that included all the usual information expected in a protocol for an RCT; the master protocol then served as a summary document that presented an overview of the study, highlighted differences between the two subprotocols, and provided the rationale for use of the master/subprotocol approach rather than conducting separate studies. In this setting, the subprotocol becomes a document that is predominantly used by the investigator, with the master protocol supporting regulatory oversight.

Development of detailed subprotocols was considered to promote clarity for study investigators, as all information required for conducting the study was included in a single document (rather than having to consult a master protocol for common aspects and the subprotocol for disease-specific aspects). Use of the complex study approach was intended to rationalise operational aspects, allowing for a common database set-up, comparable visit/ assessment schedules between subprotocols, and use of a single independent safety monitoring committee. In addition, conducting a single study in multiple rare-disease populations can help with accrual of a more substantial body of safety data for the investigational treatment. In the rare-disease setting, these considerations can help overcome some of the challenges associated with drug development in very small patient populations.

Comparison of the two subprotocols highlighted differences that would be expected, primarily reflecting different disease inclusion and exclusion criteria, sample size calculation, and stratification variables (Table 1). In this particular study, numerous similarities in disease characteristics facilitated use of many common endpoints.

In addition, conducting a single study in multiple rare-disease populations can help with accrual of a more substantial body of safety data for the investigational treatment.

A major difference in approach, compared with many other complex-design studies, was that each subprotocol had its own control group. Use of a common control group across sub-studies is often used, to facilitate accrual of a larger body of data relating to the investigational agent and to ensure that as many participants as possible receive the potentially beneficial investigational treatment. In the context of rare diseases, it can be applicable to include individual control groups given the potential for the disease-progression profile or rate to differ between the conditions under study.

The protocol was submitted as part of a Clinical Trial Application by the Sponsor of the clinical study through the Clinical Trials Information System (CTIS) and subsequently approved. Regulators comments were as expected for a Phase 3 protocol with minor changes required. The structure of a master protocol and subprotocols was approved without resistance to the concept. The master and sub protocols will all be registered as one clinical study. The clinical study is due to start in 2025 and the protocol will be submitted to additional countries and regions globally.

Conclusions

Conducting clinical trials into new investigational agents to treat rare diseases that provide robust evidence of safety and efficacy can be difficult, expensive, and timely to perform. The use of a master protocol with disease-specific subprotocols has the potential to improve the efficiency of drug development for such indications. We describe experience developing a clinical trial with a master protocol/subprotocol design, whereby a single investigational drug was assessed in two rare diseases. The approach taken in developing the master/subprotocols aimed to promote efficiency of the clinical investigation process and offer optimal clarity in both process and design to both study investigators and regulatory reviewers.

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Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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