

Master protocol studies: Embracing the “new normal”

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Abstract

In a post-pandemic world, master protocol studies will be an integral part of the “new normal” for clinical research and play an important role in providing actionable data to support health policy and resource allocation. Medical writers and study teams alike will be expected to be fluent in the development of clear and coherent protocols to support these studies. Here we provide a brief orientation on master protocol study designs, protocol structures, and methods to support medical writers through the protocol development process.

Introduction

The emergence of COVID-19 has had a considerable global impact, including extensive disruption to ongoing clinical research and patient care.¹ In response, the global research community embarked on thousands of clinical studies to not only understand disease pathology but also identify safe and efficacious treatments. As researchers and patients engaged in this process, the absence of a coordinated response and the ensuing fragmented approaches impeded health policy decision-making and appropriate resource allocation.

Current estimates suggest that only 6% of COVID-19 clinical studies in the US are expected to yield actionable data to support decision-making.² The primary barriers for achieving actionable data were poor enrolment due to overlapping and competing studies for similar patient populations, and studies conducted without the robustness needed for regulatory approval.^{2,3} However, during the pandemic, master protocol study designs have been shown



to be a more structured and sustainable approach to clinical study evaluation.⁴ By adopting a master protocol study design, enhanced efficiency and uniformity (by standardising study design and

operation procedures) facilitate the parallel development and parallel evaluation of multiple interventions.^{3,4}

From a historical perspective, the origins and

early use of master protocol studies in oncology targeted prevalent biomarkers and genetic subtyping to address multiple clinical questions within the same overall study structure. Until recently, the use of master protocol studies has steadily increased and branched out into other therapeutic areas; examples include Alzheimer’s disease (DIAN-TU), Ebola (PREVAIL II), and community acquired pneumonia (REMAP-CAP). Then, in early 2020, COVID-19 accelerated the adoption trajectory of master protocol studies as governments and researchers established far-reaching master protocol studies to address the public health crisis. While the list of studies is long, notable contributions include: the World Health Organization’s Solidarity Trial – a master protocol study to investigate repurposed antiviral drugs for COVID-19; ACTIV network – the US National Institutes of Health’s (NIH) four fast-track focus areas for the treatment of COVID-19; ANTICOV – the largest COVID-19 study

conducted in Africa; and RECOVERY – the UK platform study that received international recognition for demonstrating dexamethasone and tocilizumab improved survival of hospitalised COVID-19 patients.^{4–9}

Defining a master protocol study – in all but name

Clear definition and classification of **master protocol studies** remains a key challenge that has obstructed widespread adoption of such designs. Although key opinion leaders and regulators agree that master protocol studies are characterised by multiple parallel substudies that share a common overarching framework, how these studies are defined and categorised has not yet reached maturity. Definitions of a master protocol study from the United States Food and Drug Administration (FDA), the European Economic Area Heads of Medicines Agencies (HMA) Clinical Trials Facilitation and Coordination Group

(CTFG), and EU Patient-centric clinical trial Platforms (EU-PEARL) show a continuing evolution in understanding, with the most comprehensive description recognised by EU-PEARL (Table 1).^{10–15}

In relation to the protocol document itself, terminology is equally evolving, with only the CTFG and EU-PEARL providing descriptions for master protocol content and platform study content, respectively.^{12,13} In order to differentiate between the master protocol study design and the protocol document content, we propose the use of **core protocol** vs **subprotocol** descriptors for common and substudy-specific content, respectively.

The seminal work by Woodcock and LaVange from the US FDA provided the initial classification of master protocol studies as **basket**, **umbrella**, or **platform** designs (Table 2).^{10,11} Real-world application of these definitions suggests that the initial classification was incomplete, with only 57% of studies included in a recent systematic review being correctly classified.¹⁶ More recently, EU-PEARL further expanded the definitions to include a **matrix** design and a **multi-arm multi-stage** (MAMS) analysis framework.

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Table 1. Terminology

Definition	Description	Reference
Master protocol study	A single overarching design developed to evaluate multiple hypotheses , and the general goals are to improve efficiency and establish uniformity through standardisation of procedures in the development and evaluation of different interventions. Under a common infrastructure, the master protocol may be differentiated into multiple parallel substudies to include standardised study operational structures, patient recruitment and selection, data collection, analysis, and management.	EU-PEARL 2020 Park et al 2019
Protocol scaffold	A visual aid to help plan for how the protocol content will be distributed between the core and subprotocols. A protocol scaffold is most easily presented by extracting the protocol template’s table of contents and indicating whether content is located in the core vs subprotocols, whether content is repeated, or whether content is complementary.	N/A
Core protocol (document)	Protocol document describing content for the overarching study design that is applicable to all substudies. Common content examples include: a general introduction to the master protocol study, common objectives and endpoints/estimands, rationale for conducting the master protocol study, and common administrative, regulatory, and operational elements. Also referred to as “master protocol”.	N/A
Subprotocol (document)	Protocol document or content that is specific to an individual substudy. Synonyms include: “intervention specific appendices”, “domain specific appendices”, “study modules” and “comparison protocols”.	N/A

Abbreviation: EU-PEARL, EU Patient-centric clinical trial Platforms

In essence, master protocol studies that are designed with a fixed number of populations and/or interventions can be categorised as a basket (single intervention, multiple populations), umbrella (multiple interventions, single population), or matrix (multiple interventions, multiple populations) study. If the study is designed with the ability to prospectively add or stop substudies, the study is categorised as a platform study.

Clinical study protocol structure – choosing the right fit

An overly complex study protocol can have long lasting and potentially devastating results on a study. An overly burdensome protocol can lead to study sites redirecting participants to other more preferable studies and participant dropout rates in excess of 30%.¹⁷ The body of guidance for conducting master protocol studies has focused

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on the operational implementation of the study protocol; yet, little credence has been given to the protocol structure – a process that makes decisive contributions to how multiple substudies are submitted, updated and reported. In 2015, Hollingsworth recognised the need to introduce flexibility into the protocol’s structure to accommodate master protocol study designs.¹⁸ In the years since Hollingsworth’s publication, adoption of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations and the TransCelerate Biopharma Common Protocol Template have consolidated industry protocols around a common framework that is more amenable to standardised document structures for master protocol study designs.^{19,20}

The complexity and variability in master protocol study design currently precludes a “one

size fits all” approach. The protocol structure chosen will need to balance the study needs against the resultant trade-offs, a decision process that can impact study conduct and data integrity if done poorly. In the most simplistic structural interpretation, where the subprotocol content is minimal, a standard protocol structure would be most appropriate. However, this approach can soon become complex and difficult to understand as more content is added. Appendix/annex and independent subprotocol structures offer comparative clarity for larger studies with more substudies, as well as studies with few substudies of substantial subprotocol content. In addition, independent subprotocol structure offers additional flexibility when recurrent or parallel amendments are anticipated throughout the life of the study. A review of the current literature does not indicate preferred structures for the protocol document by study design; nevertheless, field experience from the STAMPEDE and FOCUS4 platform studies support appendix/annex or independent subprotocol structures for platform studies.²¹

Table 2. Classification of master protocol studies

Name	Description	Reference
Basket	A study designed to test a single intervention in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics	Woodcock & LaVange 2017 FDA 2018
Umbrella	A study designed to evaluate multiple interventions administered as single drugs or as drug combinations in a single disease population .	Woodcock & LaVange 2017 FDA 2018
Platform	A study designed to evaluate multiple interventions 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.	Woodcock & LaVange 2017
Matrix	A study that is both an umbrella study and a basket study , including analyses in multiple disease subtypes. Many platform studies are matrix studies with the additional feature that as the study progresses and interventions leave the study, new interventions may enter, and the study does not have an initially fixed duration or sample size.	EU-PEARL 2020
Multi-Arm Multi-Stage (MAMS)	An analysis framework that can be used in combination with Umbrella or Platform master protocol study designs. This framework analyses study results in a Group Sequential framework and controls overall Type-1 Error and is attractive for studies intended for regulatory submission. This framework avoids features that are more problematic for regulatory submission such as response adaptive randomisation, sub-group analysis, and Longitudinal Modelling.	EU-PEARL 2020

Abbreviations: EU-PEARL, EU Patient-centric clinical pLatforms; FDA, Food and Drug Administration

Table 3. Protocol structure

Protocol structure	Description & structure example	Benefits	Risks
Integrated subprotocols	<p>Description: Substudy protocol content is integrated within the core protocol structure</p> <p>Structure example: Section 5: Study Population 5.1: Inclusion Criteria (IC) 5.1.1: IC for Substudy 1 5.1.2: IC for Substudy 2 5.2: Exclusion Criteria (EC) 5.2.1: EC for Substudy 1 5.2.2: EC for Substudy 2</p>	<ul style="list-style-type: none"> ● Easy to implement ● Maintains standard protocol structure ● Reduced structural complexity (compared to other structures below) ● Minimal impact to protocol development processes and timelines ● Single document for future amendments 	<ul style="list-style-type: none"> ● Comprehension reduced with increasing substudy content ● Can substantially increase the length of the standard protocol structure if there are numerous substudies ● No single location for substudy information, requires detailed review and comprehension of the protocol for all study staff ● Difficult to amend if new substudies are required
Appendix/Annex subprotocols	<p>Description: Substudies are provided as separate appendices/annexes to the core protocol</p> <p>Appendix Structure example: Core protocol Appendices 1-9 Appendix 10: Subprotocol 1 Appendix 11: Subprotocol 2</p> <p>Annex Structure example: Core protocol with appendices 1-9 Annex Document 1: Subprotocol 1 Annex Document 2: Subprotocol 2 (Annex documents submitted under the same submission number)</p>	<ul style="list-style-type: none"> ● Clearer comprehension when there are multiple subprotocols with substantial content ● Maintains standard protocol structure ● Clear division for subprotocol information (useful when not all sites are enrolling across all subprotocols) ● Easy to amend if new substudies are required ● Single document for future amendments 	<ul style="list-style-type: none"> ● Redundant if substudy information is brief and/or there are few substudies planned ● Reduced flexibility for amendments with increasing number of substudies as substudies cannot be independently updated (amendments would be queued, e.g., subprotocol 2 could not be amended while subprotocol 1 was undergoing an amendment) ● Risk of repetition, redundancy, or conflicting statements in subprotocols compared to the core protocol if not managed correctly ● Moderate impact to protocol development processes and timelines ● Increased reporting complexity as a single study report is required ● Increased study disclosure complexity as all substudies need to be summarised and submitted simultaneously
Independent subprotocols	<p>Description: Substudies are provided as independent subprotocol documents and registered separately</p> <p>Structure example: Core protocol (submitted alongside subprotocol 1 and subprotocol 2) Subprotocol 1: EudraCT number: 2021-xxxxxx-01 Subprotocol 2: EudraCT number: 2021-xxxxxx-02</p>	<ul style="list-style-type: none"> ● Clearer comprehension for multiple subprotocols with substantial content AND where the core protocol information is limited to summary operational details (most common for platform and matrix studies) ● Maintains standard protocol structure ● Clear division for subprotocol information (useful when not all sites are enrolling across all subprotocols) ● Easy to amend if new substudies are required ● Subprotocols can be amended independently and submitted in parallel (if desired) ● Independent reporting of each substudy ● Study disclosure is less complex than summarising all substudies together 	<ul style="list-style-type: none"> ● Redundant if core protocol contains most of the content (appendix/annex substudies preferable) ● Core protocol updates impact multiple submissions that need to be updated in parallel ● Risk of repetition, redundancy, or conflicting statements in subprotocols compared to the core protocol if not managed correctly ● High impact to protocol development processes and timelines – more upfront planning and time requirements from team members ● Increased administrative burden if multiple amendments are conducted in parallel

An additional consideration for the protocol structure is the regulatory requirements of the study. There are limited submission guidelines available as only the FDA and the CTFG have released guidance on master protocol studies.^{11,12} Both recommend two submission structures: either a single submission with multiple substudy protocols under a single EudraCT/NCT number (integrated sub-protocols or appendix/annex subprotocols) or independent subprotocols, each accompanied by the common master protocol, submitted under individual EudraCT/NCT numbers. The submission strategy (integrated or appendix/annex vs independent subprotocols) will depend on the operational needs and long-term considerations for the overall master protocol study.

Directing protocol development – flexibility is key

Identifying the protocol development team

Although often not the responsibility of the medical writer, confirming study team members prior to protocol development is an important task to start gravitating individual expertise around the collective objective(s) of the study. This process can be challenging, in particular for study teams that are managing their first master protocol study. Unlike traditional study protocols, identifying all team members prior to protocol development may not be straightforward since the team structure is dependent on the overall ambition of the study design, number of interventions, patient populations, and countries involved. Examples for each have been provided below:

- **Study design:** The study design may include adaptive elements, decentralised components, or digital health technologies. Early engagement with the relevant expertise will minimise the risk of substantial changes late in the protocol’s development.
- **Multiple interventions/participant populations:** Depending on the organisation(s) involved, there may be multiple representatives for the same function. For example, a master protocol study that wishes to include multiple interventions may require representation from each of the intervention groups – such as medical professionals or study/programme leaders. Equally, a study with multiple participant populations will require adequate representation for each population to ensure the suitability and applicability of the study design.



- **Geographic footprint:** Like all multiregional studies, regulatory requirements for countries in which the study will be conducted may influence the protocol. Master protocol studies may require additional discussion and engagement with regulatory agencies or regulatory professionals during the protocol’s development.

Agreeing on the protocol structure

Ensuring all team members are aware of, and agree on, the protocol structure prior to initiating protocol development will reduce the risk that conflicting opinions on protocol structure arise (due to either unfamiliarity with the master protocol study designs, in general, or the particular study requirements) that may extend

review cycles or require additional document drafts. Both can damage the team’s decision-making ability and reduce overall team efficiency that, in turn, may not only extend development time but also reduce overall quality.

To support this task, the medical writer can initiate early discussions to identify the most suitable protocol structure. Points to consider/questions to ask:

- **Does the master protocol structure give optimal clarity and coherency for readers?** A common challenge for all protocol writing is the multidisciplinary audience with variable clinical experience and study involvement. Master protocol studies have audiences that may also engage with the content differently – not as a whole single study, but rather as separate individual substudies. This means that although two readers may be reading the same protocol document, each may be approaching the content with differing participant populations, interventions, or study schedules in mind. Therefore, does the chosen structure facilitate readers being able to identify relevant substudies easily?
- **Will information be repeated, or will a single source of information be cross-referenced throughout?** There is a strong argument for cross-referencing a single source rather than repeating information within or across the core and/or subprotocols – in that duplication breeds inconsistency – although this view is not shared by all. If the preference is to repeat information across multiple sections, it is important to clarify what essential content needs repeating (e.g., overarching objectives and endpoints, or eligibility criteria), how team members will comment on multiple repetitions of the same content, and how this will be controlled for consistency.
- **What information will be specific to the core protocol vs subprotocol?** What information will be applicable across all substudies and what will be specific to each substudy? For example, will each substudy follow the same schedule of assessments? Will there be a core set of eligibility criteria with additional criteria for each substudy?

After the provisional decision of the protocol structure has been made, the medical writer may wish to develop a **protocol scaffold** to aid the team’s understanding of what the protocol

structure will look like (Table 1). By using a simple tool to visualise the content distribution, the medical writer can minimise the risk of the study team rejecting the protocol structure during the team’s revision and thus, requiring substantial changes midway through the protocol’s development.

Establishing (and maintaining) timelines

In combination with agreeing on a protocol structure and protocol scaffold, upfront agreement on timelines is an important step in aligning expectations while allowing for sufficient protocol development time. We propose two approaches:

1. A **parallel approach** that follows a similar approach to standard protocol development (all content is developed together) with additional time included for content development and review.
2. A **staggered approach**: leading content (such as the core protocol) is submitted for review first, and then trailing content (such as the subprotocols) is submitted once the initial content has been reviewed.

Points to consider/questions to ask:

- **What approach should be followed?** In certain circumstances a parallel approach would be preferable e.g., where several indications are involved, and it is beneficial to engage all team members at the same time. By contrast, a smaller study team covering all substudies would likely benefit from reviewing in a staggered manner as this would mitigate reviewers being overburdened by the review requirements.
- **Parallel approach**: How long will the timelines be extended to account for the additional content to be reviewed while maintaining consistency? Will all team members need to complete the review within the timeframe, or will it only be key team members (i.e., will this approach fit all team members)?
- **Staggered approach**: What content should be leading and what content should be trailing? Will the team members be engaged and able to accommodate the review requirements over the whole review period

(i.e., are there any planned absences or work requirements that would interfere)? Will there be any periods where all content needs to be reviewed together (e.g., when the protocol is close to being finalised)?

Conclusions

Master protocol studies are highly complex. The complexity and variability in the accompanying protocol development process can test even the most experienced medical writer and study team. Standard protocol templates and approaches are often inadequate for addressing the complexity and multiple configurations of a master protocol study. We hope the guidance

provided herein will be of use in the development of clear and coherent protocols to support master protocol studies.

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

Conflicts of Interest

The authors declare no conflicts of interest.

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