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Post Pandemic Trends in Study Designs

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ABSTRACT

From the conventional method of having fixed study designs to the most recent trends, adaptive design model, the clinical trial industry has come a long way. The adaptive model allows for flexibility and optimization, which in turn speeds up the future procedures, by permitting alterations to subsequent study activities based on interim evaluation.

Faster and more effective findings are achieved by using a single Master protocol with numerous sub studies and/or "parent-child" studies. Additionally, using this method enables the sponsor to carry out numerous dose tests and evaluate the outcomes concurrently.

This paper will discuss the various data gathering and mapping procedures used by vaccine studies to apply the sub-study concept, including (a) dividing the Master Database into several sub-studies and (b) combining the database of a prior study and (c) handling re-screening scenarios in parent-child studies.

INTRODUCTION

During the covid pandemic many pharma companies came up with COVID vaccine for the initial known variant. However, we saw that the effectiveness wanes over a period of months, especially with respect to evolving variants of the virus. From the beginning of the pandemic, several variants emerged triggering infection rates despite taking the available vaccines. Due to this there was a need to have additional booster doses to be administered for better effectiveness against the variants.

This led the vaccine companies to begin clinical trials with modified vaccines. This could be possibly achieved by conducting several parallel studies with the same initial strain, and combining with modified strains to evaluate the safety, tolerability, immunogenicity, and efficacy of these combination drugs, with various dosing levels and also with different age groups.

This made way to have a master protocol design with multiple sub-studies being conducted in parallel on different groups of participants. Let’s go through few of the methods followed in the recent past by vaccine studies.

MASTER PROTOCOL

Master protocols are being used more frequently across the clinical research enterprise, including in cancer research and in response to the covid-19 pandemic for vaccine research. Master protocols generally refer to a central design divided into sub-studies to evaluate multiple hypotheses, with the goal of improving overall efficiency in clinical trial research. "A collection of trials or sub-studies that share key design components and operational aspects to achieve better coordination than can be achieved in single trials designed and conducted independently" are employed in the implementation of a master protocol.

ADVANTAGES OF MASTER PROTOCOL

The advantages of the master protocol listed as follows:

- ✓ Flexibility and efficiency in drug development
- ✓ Reduce trial time and cost from a long-term perspective.
- ✓ Increase benefits of the participants in the clinical trial by adapting to the most rational therapy/treatment based on the participants characteristics.

- ✓ They could collect a lot of high-quality data and engage and educate clinical trial professionals for stable employment, shared trial infrastructure projects with identical standard operating procedures established across sub-studies.
- ✓ Rather than beginning a new clinical trial, master protocols enable adding a new therapeutic discovery after one has commenced and more effectively implementing recent modifications to clinical practices.
- ✓ The rapid growth of precision healthcare mandates the development of increasingly rigorous medicines that require speedy evaluation. Consequently, the approach of using Master protocol setup would continue to take precedence considering the existing research attempts to test several treatments or diseases simultaneously.

CHALLENGES OF MASTER PROTOCOL

Few challenges of implementing master protocol are as listed below:

- ✓ These master protocol designed clinical trials are more complex in nature than the traditional clinical trials.
- ✓ The master protocol may also present challenges in study conduct and analysis that, if not properly addressed, may increase risk to humans or delay drug development.
- ✓ Master protocol trials require more costs than the budget in traditional clinical trials to establish the needed trial infrastructure and the increased upfront planning and coordination.
- ✓ The intricacy of master protocols has a few risks and issues that are either novel or already visible in the conventional trials and are challenging to manage.
- ✓ The abuse of over-complex clinical trial designs might result in unethical conduct of studies and weaken regulatory independence.
- ✓ This approach may undergo constant changes based on interim analysis, this in turn increases the criticality in planning and budgeting the ongoing adjustments. This also brings up the challenges in all the study documents to be amended accordingly and thereby requiring approvals and carry out all these processes all over again.

TYPES OF MASTER PROTOCOLS

Master protocols emphasize the use of a common infrastructure and standardized procedures to promote uniformity and are often categorized as basket trials, umbrella trials and platform trials.

Basket trial - A master protocol designed to test a single investigational drug or drug combination in different populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics.

Umbrella trial - A master protocol designed to evaluate multiple investigational drugs administered as single drugs or as drug combinations in a single disease population.

Platform trial - A trial designed to study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform based on a decision algorithm.

CASE STUDIES

SINGLE MASTER PROTOCOL DESIGN WITH MULTIPLE SUB-STUDIES

A protocol that includes several sub studies, each with potential distinct goals (endpoints), and coordinated efforts to assess one or more novel drugs in one or more disease subtypes within the framework of the overall trial. Each sub study's data collection is done collectively, using a single CRF, and each sub study's database setup is handled collectively.

Each sub study had a unique analysis even though the data was collected together for all the sub studies. Consequently, by dividing the raw data in accordance with each sub research's distinct participants, the SDTM standardization was carried out independently for each sub study. These studies' primary presumption is that participants won't overlap between the sub studies.

Each participant is considered unique within the sub studies. The screening attempts are applicable only within the sub studies. The below points cover the challenges faced during the SDTM standardization.

1. When a subject is part of more than one sub study, the screening attempts details for the that subject was not able to be traced completely, because of the assumption of unique participant.
2. The same subject in multiple sub studies were given different unique subject identifier, depending on the screening attempts within the sub study.
3. Even though the data is collected in a single database, the combined study data should follow the integration process rather than simple append of data.
4. Difficulty in summarizing the screening attempts for each participant of the database, when they are part of multiple sub studies.

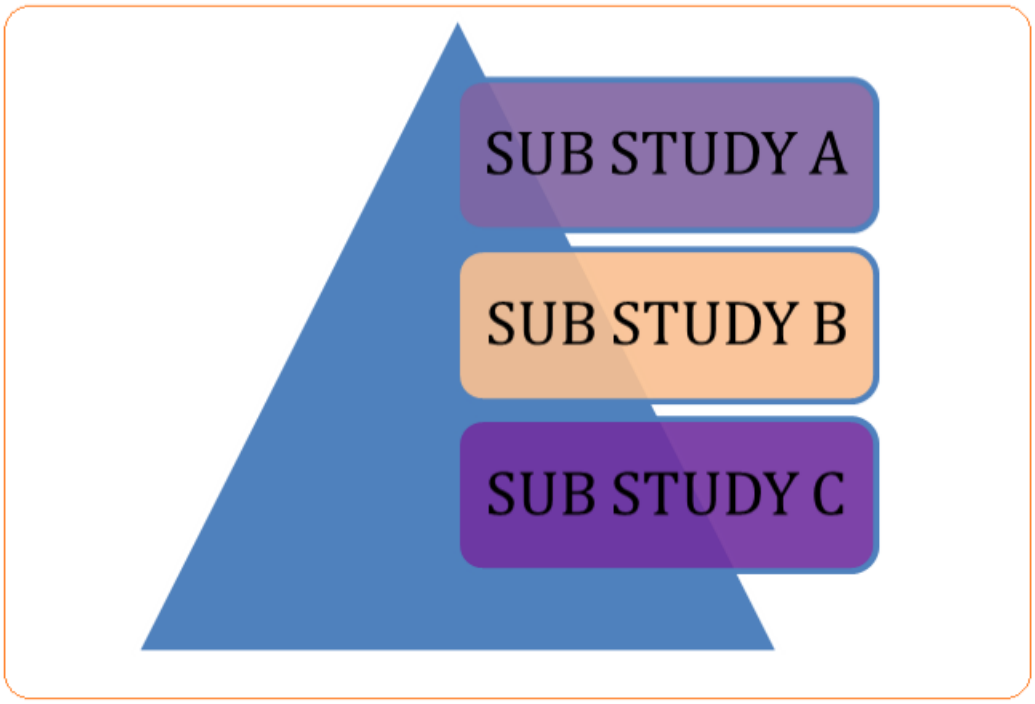

Figure 1. Illustration of the Single DB with Multiple Sub Studies

Another scenario of this case study will be a single database with multiple cohorts where some cohorts are extension of the previous cohorts. The participants from the other trial are split into multiple cohorts for the current trial and the final cohort will be a combination of participants from the previous cohorts within the current trial. Depending on the analysis requirement, the cohorts are split, and split participant details are considered for the SDTM and analysis datasets. There is a possibility that the analysis might be one or more cohorts at a time.

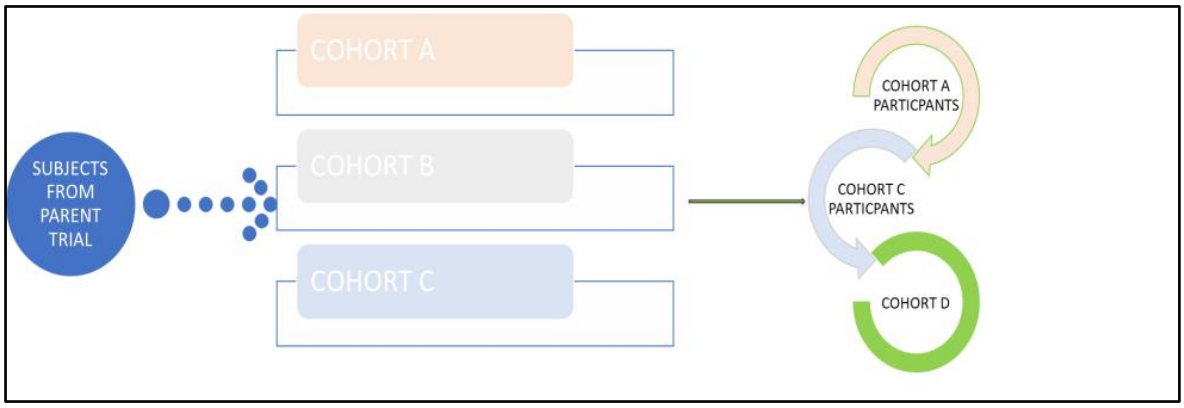

Figure 2. Illustration of single DB with Multiple Cohorts

The challenges in these trials are as follows:

1. The initial cohorts can be reported for regulatory submissions by appending the SDTM Datasets.
2. By integrating the initial cohorts and the final cohorts' SDTM datasets, all the cohorts can be reported for regulatory submissions.
3. Addition of DC- Demographics as Collected Domain is an essential work for the integration of the SDTM Datasets.
4. As the participants are from another trial (parent trial), the effort is needed to trace them back to the parent trial twice.

PARENT STUDY ON INITIAL STRAIN FOLLOWED BY CHILD STUDIES

This scenario, mostly applicable to the new disease or the new objectives of the previous clinical trial. The initial study will be the parent trial, where huge volumes of participants will be enrolled/treated as a part of the trial. the subsequent studies will be the subset of the participants from the parent trial. The huge population from the parent trial will be split into multiple studies to achieve different objectives of the research.

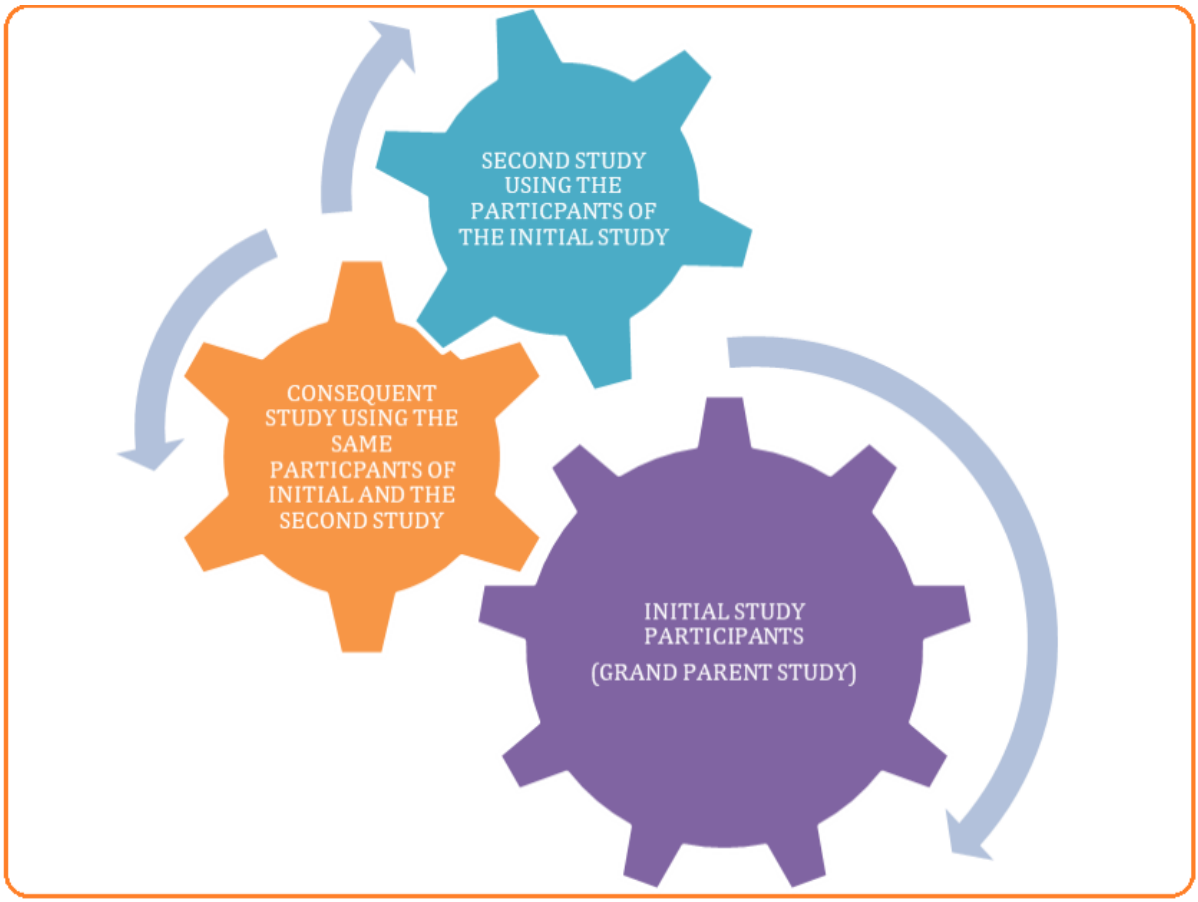

Figure 3. Illustration Parent - Child Studies

The USUBJID will be derived based on the participants' details from the parent study. The daisy chain model is implemented for the USUBJID derivation. The USUBJID will be derived based on the participant details when he was enrolled first time for these trials. The intermediate studies participant details can be mapped to the supplementary demographic dataset to make sure the traceability is not lost during these implementations. There is a high possibility of data entry error in these scenarios. The level of studies should be correctly assessed for the USUBJID derivation.

STUDY - I	SUBJID - I	SITE - I	STUDY - II	SUBJID - II	SITE - II	STUDY - III	SUBJID - III	SITE - III	USUBJID
A9999	11561156	1156	B9999	10361009	1036	C9999	10141069	1014	A9999 1156 11561156
			B9999	10361041	1036	C9999	10141070	1014	B9999 1036 10361041
						C9999	10141070	1014	C9999 1014 10141070
A9999	11561156	1156				C9999	10141069	1014	A9999 1156 11561156

Table 1. Data Showing Participant Details from Different Trials

COMBINING DATABASES OF STUDIES INTO ONE

These situations arise when database capacities are insufficient to accommodate the expansion of data from the same study. In the first step of the SDTM mapping, the raw data is appended from both studies databases. It is important to ensure that those who participated from the primary study are included in the data from the extension studies, meaning that the participants will be consistent across the two studies. Any information gathered for the non-participant in the primary study's extension study will be ignored and reported to data management to undertake further cleaning. Extending the time and visit details for the same subject from the primary study should be the outcome of the combination.

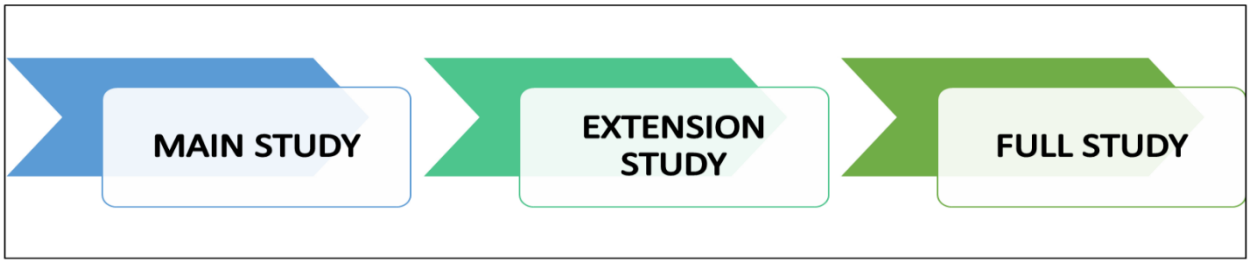

Figure 4. Combining DBs of Main and Extension Studies

These scenarios occur when the study design continues but a different participant population is utilized, and analysis will be performed for both populations jointly. Under these circumstances, the study databases will once more be accessed by appending the raw datasets and/or common variables, and the unique values of the variables will be kept for those specific participants wherever collected.

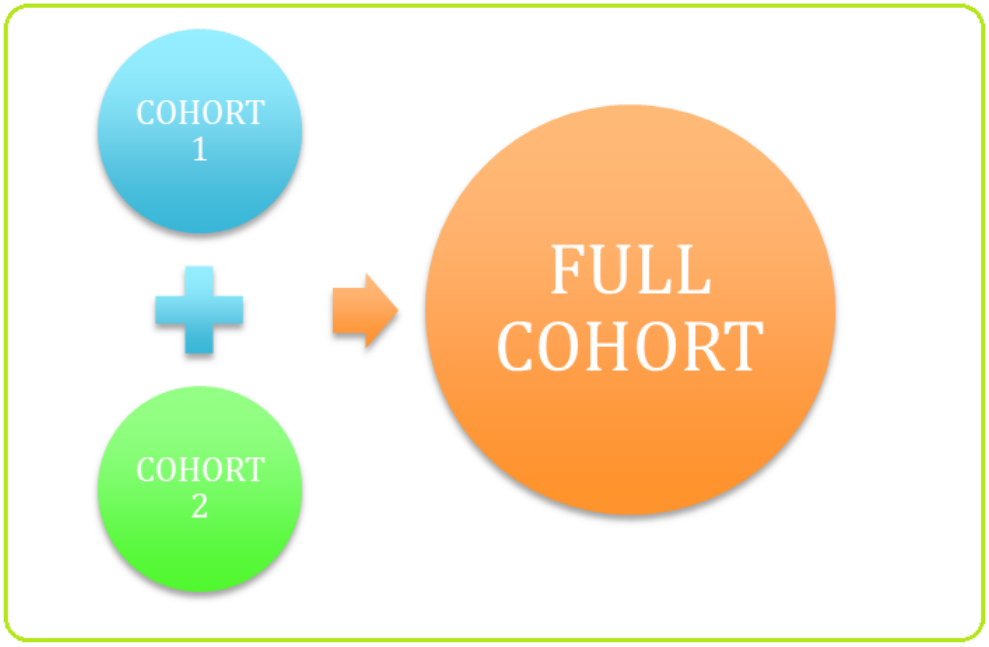

Figure 5. Combining DBs of different Cohorts or Study Designs or Countries Participants

When merging raw data from various snapshots or snippets for submission or analysis, the following scenario will be employed. The snapshots are further subset and then included to obtain the entire set of data needed for the purpose, depending on the requirement. To illustrate, suppose a snapshot was taken in accordance with the study's milestone. However, all the necessary efficacy data could not be gathered for that benchmark at the time of the snapshot. The efficacy data for that milestone may be identified in the second snapshot (at a later date). In these situations, the most recent efficacy data snapshot is linked to the safety data of the first snapshot, completing the collection of raw data for the deliverable.

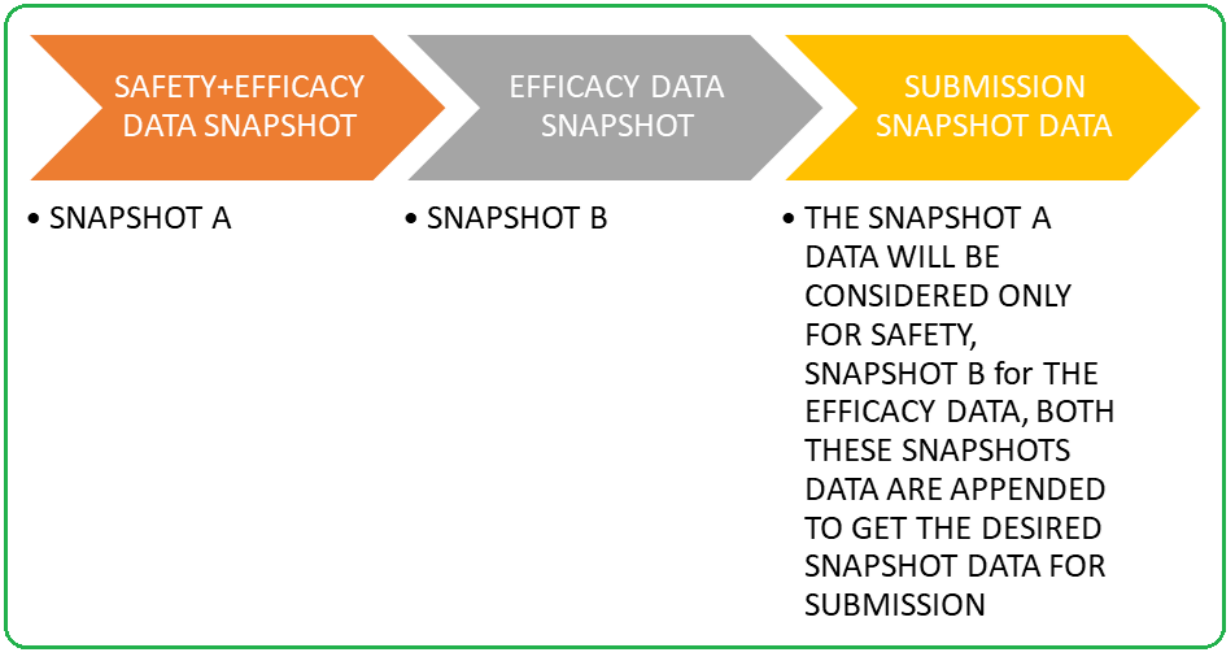

Figure 6. Illustration for Selective Data Combine

CONCLUSION

Master protocols accelerates the drug development trials by testing multiple treatments or multiple subpopulations simultaneously under a single protocol. The purpose of this work is to deepen the understanding of master protocols in various vaccine studies and to provide useful insights for the design and implementation of master protocols. A good example of the use of the master protocol is the platform trial method to accelerate the evaluation of treatment for COVID-19, which is a good way to respond to the urgent needs of new infectious diseases without effective treatment.

However, due to the complexity of the underlying protocols, many problems and risks that are not new or fundamental problems in traditional trials have emerged and are difficult to manage. Therefore, master protocols should be used judiciously when they cannot be avoided for scientific reasons. The master protocol must be carefully designed and limited to ensure subject safety, data integrity, or research quality.

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