Being the Master for A Master Protocol Study

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Abstract

As a new paradigm for clinical research, master protocol studies, either basket, umbrella, or platform trials, demonstrate increasing benefits and reveal promise especially in oncology drug development. The beauty of designing a master protocol study does not only lie in the fact that it can support the evaluation of multiple compounds with/without common controlled arms in different tumor types simultaneously, but also it provides the possibilities that allow patients to move from one investigational drug to another if deem appropriate. On the other hand, given these appealing features, it is also important to realize that compared with traditional clinical trials, to conduct such attractive master protocol studies, there are quite a few challenges on data collection, result presentation as well as analysis. For instance, how to handle patients who are crossing over investigational drugs or rescreened multiple times? How to develop and design analysis datasets to support requested analysis in a master protocol study? What will be the most appropriate and efficient approach to do pooled analysis with data from different sources? In this paper, the author will use a single arm, open label platform trial that tests multiple investigational drugs as a case study to discuss the main challenges that are encountered from data collection to result presentations and further open the discussion for an optimum solution.

Key words: master protocol study, oncology, data collection, SDTM, analysis, ADaM, result presentation

Study design: The case study used in this paper is a single arm, open label platform trial with a single sponsor. This study starts with three investigational drugs (A, B and C) in combination with standard of care X. In reality, there could be more drugs to start with and existing drugs can "graduate" if meet or fail study endpoints; new drugs can also join later during trial conduct, which in practice brings in considerable uncertainties and impose great challenges on study planning. Within each investigational drug, there are four different cohorts - a, b, c, and d. Cohort a and b have patients with tumor type 1 and 2 respectively. Excluding patients with tumor type 1 and 2, cohort c and cohort d have patients with biomarker 1 and biomarker 2 positive respectively (Figure 1). In other words, in this particular study, to simplify clinical operation, each cohort within treatment modules has exclusive population and no re-/randomization is involved. In order to enter the study, the patients need to sign the master inform consent and meet the inclusion/exclusion criteria for the "master study" first. In addition, in order to be enrolled and treated with particular investigational drug, the patients have to sign the inform consent and meet the inclusion and exclusion criteria for corresponding modules as well. Further, patients can move across treatments if considered beneficial as is mentioned earlier.

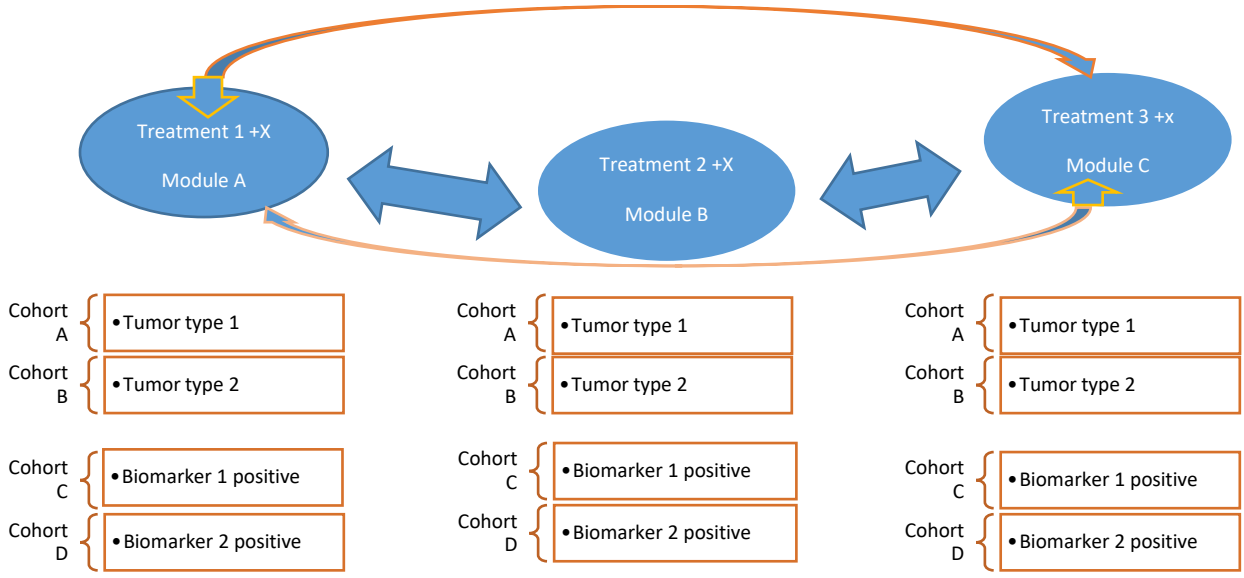

Figure 1 Overview of platform trial

Main challenges:

Challenge 1: handling patients moving from one treatment to another/rescreening patients. As is mentioned earlier, one of the attractive features of conducting master protocol study is to allow patients to cross over from one treatment to another, so that patients can have more opportunities to be exposed to investigational drugs and achieve most benefit. Under these circumstances, it would become more common that quite a few patients will cross treatments and are treated with multiple drugs. However, in reality, this "planned cross-over" has brought in great challenges for clinical operation as well as data collection and presentation. In addition, the nature of master protocol studies might lead to high possibility of rescreen/re-randomization, which will add another layer of complexity.

To handle aforementioned potential scenarios, there are two proposed options:

Option 1: one USUBJID but with different SUBJIDs if re-screen/re-randomization to get initial treatment. For example, if patients screen fails three times, this patient will have one USUBJID but three different SUBJIDs. FDA study data technical conformance guide endorses this approach (March 2019)

Option 2: one USUBJID associated with same SUBJID for the entire study period.

The first option is the approach that is recommended by FDA TCG regarding how to handle re-screen or re-randomized patients, which already becomes the industry well accepted convention. As has been already discussed quite a lot, patient information for successful or primary enrolment, such as SUBJID, inform consent date will be in DM. For screen failures, instead of creating a custom domain similar to DM as is recommend in FDA TCG, we propose to utilize existing available domains and submit related information to SUPPDM.

In terms of handling the situation of moving across treatments, patients will still have the single unique identifier across the entire study period. However, for SUBJID, we recommend to keep the same

identifier since strictly speaking, this is not a re-screen or re-randomization to get into the study in a traditional sense. Checking treatment module specific inclusion/exclusion criteria is to make sure patients are qualified and eligible for another regimen after failing previous therapies. Furthermore, from operational perspective, this approach can also reduce the complexity for sites as well as data management.

In DM domain, ARM/ARMCD/ACTARM/ACTARMCD retain the treatment information that are initially planned; cohort information together with subsequent treatment modules will go to SUPPDM. Inform consent date will be the date that patients sign for the master study. Inform consent for each individual modules will go to SUPPDS. Likewise, for a randomized study, the randomization date that is associated with patients' successful enrollment into study will be in DS. All the rest will go to SUPPDS.

Below are some examples from the case study. Patient MASTER-XXX-001 enrolled another treatment module C after no longer benefit from initial treatment A. Patient MASTER-YYY-002 enter the study after being screened for the second time.

Example 1: handling crossover and re-screen patients:

DM:

STUDYID	USUBJID	SUBJID	RFICDTC	ARM	ACTARM
MASTER	MASTER-XXX-001	XXX-001	2018-07-31	A+X	A+X
MASTER	MASTER-YYY-002	YYY-002	2018-08-31	B+X	B+X

SUPPDM:

STUDYID	USUBJID	IDVAR	QNAM	QLABEL	QVAL
MASTER	MASTER-XXX-001	USUBJID	COHORT1	Dosing cohort for initial module	1
MASTER	MASTER-XXX-001	USUBJID	MODDTC1	Inform consent for initial module	2018-08-01
MASTER	MASTER-XXX-001	USUBJID	MODULE2	Second Module	C+X
MASTER	MASTER-XXX-001	USUBJID	COHORT2	Dosing cohort for second module	1
MASTER	MASTER-XXX-001	USUBJID	MODDTC2	Inform consent for second module	2019-07-31
MASTER	MASTER-YYY-002	USUBJID	PSUBJID1	Previous Subject Identifier 1	YYY-001
MASTER	MASTER-YYY-002	USUBJID	COHORT1	Dosing cohort for initial module	3
MASTER	MASTER-YYY-002	USUBJID	MODDTC1	Inform consent for initial module	2018-09-01

DS: For demonstration purpose, only records that are relevant to the topic are included. Other milestones, such as termination of treatment module, are also part of the DS.

STUDYID	USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	DSSTDTC
MASTER	MASTER-XXX-001	1	MASTER INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOAL MILESTONE	2018-07-31

STUDYID	USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	DSSTDTC
MASTER	MASTER-XXX-001	2	INITIAL MODULE INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOAL MILESTONE	2018-08-01
MASTER	MASTER-XXX-001	3	SECOND MODULE INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOAL MILESTONE	2019-07-31
MASTER	MASTER-YYY-002	1	MASTER INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOL MILESTONE	2018-08-15
MASTER	MASTER-YYY-002	2	MASTER INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOAL MILESTONE	2018-08-31
MASTER	MASTER-YYY-002	3	INITIAL MODULE INFORM CONSENT OBTAINED	INFORM CONSENT OBTAINED	PROTOCOAL MILESTONE	2018-09-01

SUPPDS:

STUDYID	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
MASTER	MASTER-YYY-002	DSSEQ	1	PSUBJID1	Previous subject identifier 1	YYY-001

Challenge 2: designing and developing analysis datasets to support master protocol study. Analysis needs to support master protocol study drive the design of analysis datasets. In this particular case study, the purpose is to assess the efficacy of combination of investigational drug with standard of care X. Similar to traditional oncology studies, important endpoints include but are not limited to objective response, duration of response, disease control, progression free survival, overall survival, etc. The primary analysis will be conducted within each treatment module based on the initial treatment assigned. If patients move across treatment modules, additional sensitivity analysis might be performed based on the needs. Safety analysis including AE and LAB data presentation will be according to actual treatment when the events occur.

How can we design analysis datasets to best support analysis requested in a complex master protocol study? Can we use the same approach in traditional clinical trial and create one set of analysis datasets for all treatment modules? This concept is intuitive and straightforward. However, it might not be efficient nor easier to implement especially when an increasing number of investigational drugs are in the study. Both structure-wise and content-wise, it will become more and more challenging and require high maintenance. On the other hand, to certain degree, individual treatment module itself in a master protocol study can be considered as an independent study, in particular in this example; analysis will be mainly done within their own treatment module. In this case, shall we design and create separate sets of analysis datasets for each individual module? This approach provides sufficient flexibility especially taking into account that potential ad hoc analysis could come in and different modules might have diverse reporting schedules. However, one point to consider is a master protocol study is still a single

study that consists of groups of individual sub studies with the same STUDYID. Current ADaM IG (v1.2) recommends only one ADSL for one study. In this sense, to create separate sets of ADS for individual treatment module is not strictly consistent with this rule. Moreover, the advantage of having one ADSL is that it can serve as a central place to provide a comprehensive overview about subject level status. Individual ADS within treatment module might not be able to capture the holistic picture of the entire journey patients, in particular those who move across treatment modules, have been through in the study. Therefore, an alternative comes into place and we propose this so-called hybrid approach - all treatment modules will share one ADSL and one ADSE. ADSE has other structure and records the details for a patient's journey in this platform study, including screening, starting initial treatment, having dose reduction, wrong dose taken, etc. (Example 2). On the other hand, each individual treatment module can have their own module specific analysis datasets to support efficacy and safety analysis. Below is a sample list of proposed core analysis datasets for a master protocol study. The list is not exhaustive, and can be expanded per specific analysis needs.

Dataset	Structure	Purpose
Across treatment module		
ADSL	Subject level analysis dataset	Provide a comprehensive overview about subject level information
ADSE	Other	Provide detailed information for patients' progress during the entire study.
Within treatment module		
ADAE	Occurrence	Analysis dataset for AE
ADLB	BDS	Analysis dataset for lab
ADINDT	Other	Intermediate date dataset
ADTR	BDS	Intermediate dataset containing tumor burden related information
ADRS	BDS	Intermediate dataset containing response related information
ADTTE	Time to event	Intermediate dataset containing time to event related information
ADEFF	Other	Analysis dataset to support efficacy analysis
ADEX	BDS	Analysis dataset for exposure
ADMH	Occurrence	Analysis dataset for medical history
ADCM	Occurrence	Analysis dataset for concomitant mediation
ADVS	BDS	Analysis dataset for vital signs
ADDV	Occurrence	Analysis dataset for protocol deviation
…		

Table 1 A list of proposed analysis datasets in a master protocol study

Example 2: An example of ADSE: Content-wise, to have one ADSE across all treatment modules provides a comprehensive view about patients' milestones in the entire study. Meanwhile ADSE also serves as the basis for exposure and AE analysis by providing detailed dosing information, such as dose escalation, dose reduction, wrong medication taken, etc. Structurewise, ADSE mimics SDTM SE domain, but with additional details. In this case, patient MASTER-XXX-001 has one dose reduction- from high dose of A to medium dose after being treated for two cycles. After no longer having benefits, the patient switched to treatment C and treated at high dose. While on treatment C, by mistake, the patient took treatment C at low dose once.

STUDYID	USUBJID	ETCD	AELEMENT	SESTDTC	SEENDTC	AEPOCH
MASTER	MASTER-XXX-001	10000000	Screening for master study	2018-07-31	2018-08-01	SCREENING
MATER	MASTER-XXX-001	10000001	Screening for module A	2018-08-01	2018-08-02	SCREENING
MATER	MASTER-XXX-001	C2000001	TRTA **high** dose + X	2018-08-02	2018-08-03	TREATMENT
MATER	MASTER-XXX-001	10000042	Off - drug	2018-08-03	2018-08-23	OFF DRUG
MATER	MASTER-XXX-001	C2000001	TRTA **high** dose + X	2018-08-23	2018-08-24	TREATMENT
MATER	MASTER-XXX-001	10000042	Off - drug	2018-08-24	2018-09-13	OFF DRUG
MATER	MASTER-XXX-001	C2000002	TRTA **medium** dose +X	2018-09-13	2018-09-14	TREATMENT
…						
MATER	MASTER-XXX-001	C2000002	TRTA **medium** dose +X	2019-04-30	2019-05-01	TREATMENT
MATER	MASTER-XXX-001	10000042	Residual effect period	2019-05-01	2019-05-31	TREATMENT
MATER	MASTER-XXX-001	10001001	Treatment A follow up	2019-05-31	2019-07-31	LONG TERM FOLLOW UP
MATER	MASTER-XXX-001	10000003	Screening for treatment C	2019-07-31	2019-08-01	SCREENING
MATER	MASTER-XXX-001	C4000001	TRTC high dose	2019-08-01	2019-08-02	TREATMENT
…						
MASTER	MASTER-XXX-001	C4000003	TRTC **low** dose	2019-08-31	2019-09-01	TREATMENT
MASTER	MASTER-XXX-001	10000042	Off-drug	2019-09-01	2019-09-22	OFF DRUG
MASTER	MASTER-XXX-001	C4000002	TRTC high dose	2019-09-22	2019-09-23	TREATMENT
MATER	MASTER-XXX-001	10000042	Residual effect period	2019-09-23	2019-10-24	TREATMENT
MATER	MASTER-XXX-001	10001003	Treatment C follow up	2019-10-24	2019-12-31	LONG TERM FOLLOW UP

Challenge 3: pooled analysis for cohorts in and outside the master study. One of the challenges of working on a master protocol study is to do integrated analysis based on data from various sources. This task shares some similarities as integrated summary of safety (ISS) and integrated summary of efficacy (ISE) to certain extent. Currently there are two most popular options, which are listed below (Figure 2 and 3). Option 2 sometimes can be further extended by adding pooled SDTM if requested information are not available in ADaM. A brief comparison of strengths and limitations between these two options are provided as well. It is crucial to realize that there are no one-size-fit-all solutions and each one has its own advantages. Meanwhile it is also of equal importance to bear "fit for use" in mind and select the most appropriate and efficient approach. In this example, the study team lean toward

using pooled SDTM with the consideration that there are potential additional ad hoc pooled analysis in the future. Pooling SDTM provides sufficient flexibility to fulfill analysis needs.

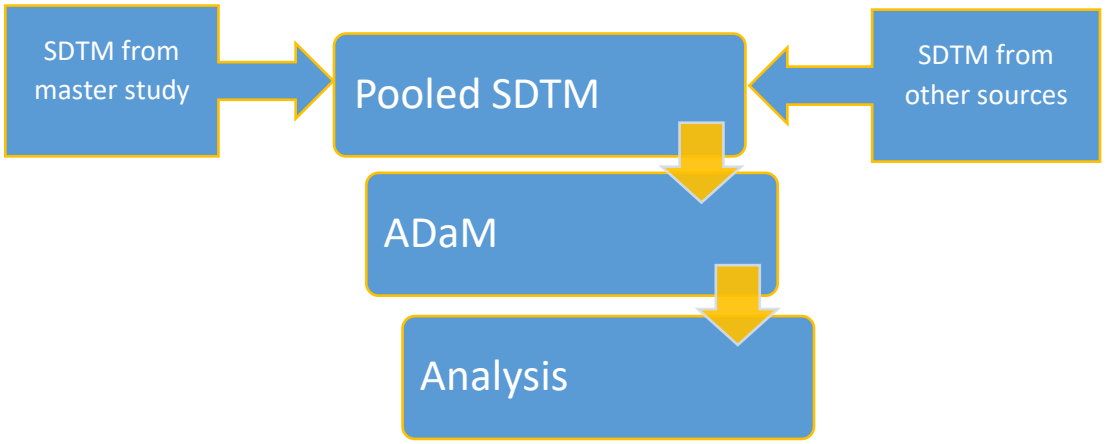

Figure 2: Pooled analysis: option 1 by pooling SDTM

Figure 3: Pooled analysis: option 2 by pooling ADaM

Table 2: A comparison of pros and cons of two options for pooled analysis

	Option 1: pooling SDTM	Option 2: pooling ADaM (+ SDTM)
Pros	• **Sufficient flexibility** at the level of building ADaM especially considering potential different trial designs, study focus as well as unexpected ad hoc analysis; • **No harmonization needs** at ADaM level	• Harmonization of SDTM are handled at each study level while building ADaM.
Cons	• Interpretation and implementation of SDTM across studies/different sources might not be the same. Harmonization /standardization will be time consuming.	• Analysis in the master protocol study and at pooled integrated level need to be the same for a meaningful pool. At integrated level, analysis might be more than in the master protocol study.

	Option 1: pooling SDTM	Option 2: pooling ADaM (+ SDTM)
		• Require consistent logic to be applied across studies, which in practice might be challenging. • Variables with the same names must carry the same meanings across studies. A significant amount of pre pre-planning is foreseen. • Might not be flexible enough to handle additional/ad hoc request at integrated level. • Analysis datasets from ALL studies need to be ready at the time of pooled analysis.

Conclusion

Master protocol study design is gaining popularity in current drug development due to its efficiency and great benefits patients can get. On the other hand, those attractive features of a master protocol study distinguish itself from traditional clinical trials and impose considerable challenges that are not common in a traditional trial that evaluates a single compound or a single tumor type. Using three main challenges as an illustration, in this paper, the author proposes several potential handling approach and aims to open further discussion for seeking optimum solutions.

Reference

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