

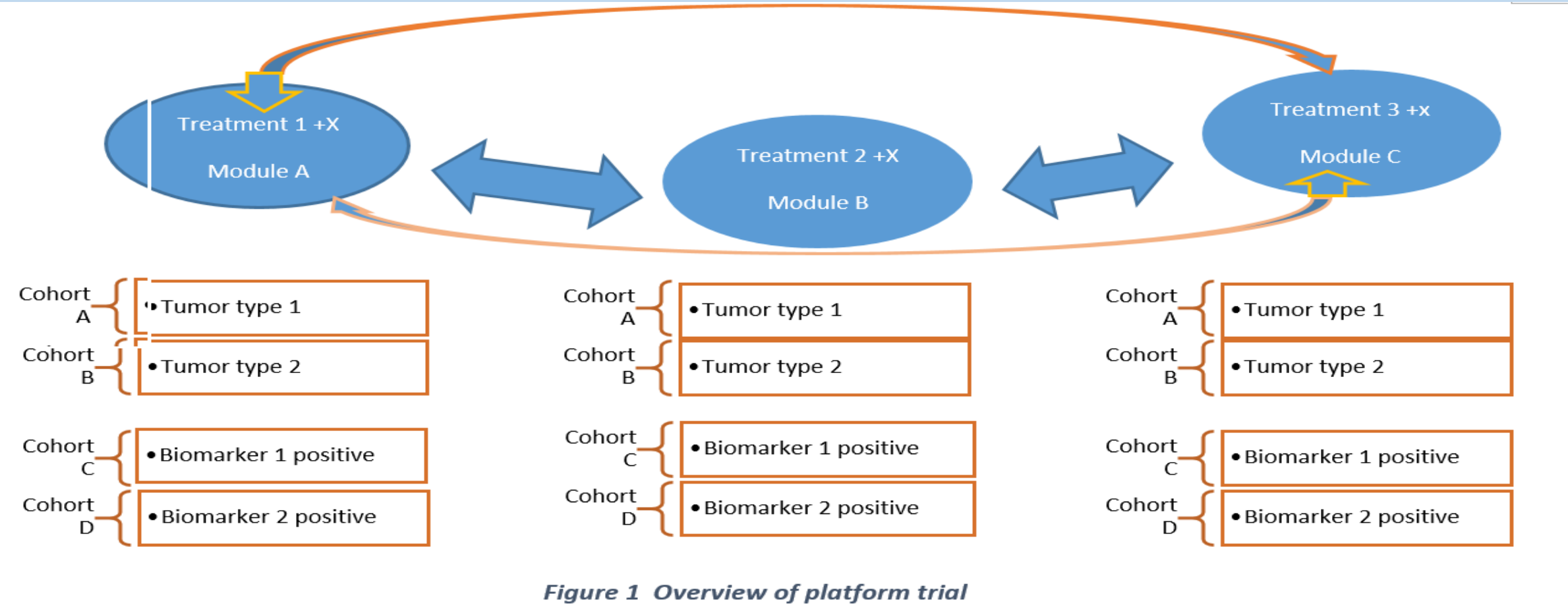
PP09 Being the Master for A Master Protocol Study

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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. 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. This poster 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 poster 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.



Major 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.

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.

Example : 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
	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:

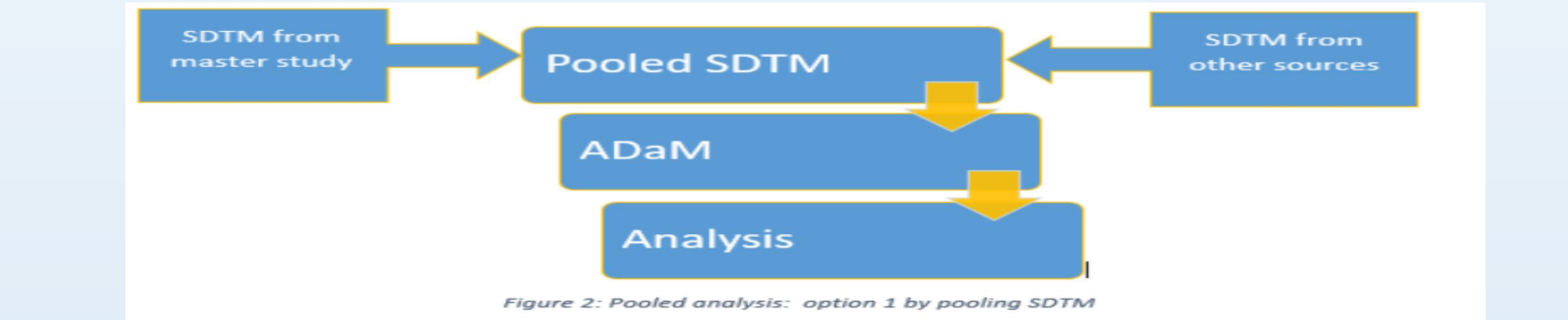
	STUDYID	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
	MASTER	MASTER-YYY-002	DSSEQ	1	PSUBJID1	Previous subject identifier 1	YYY-001

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.

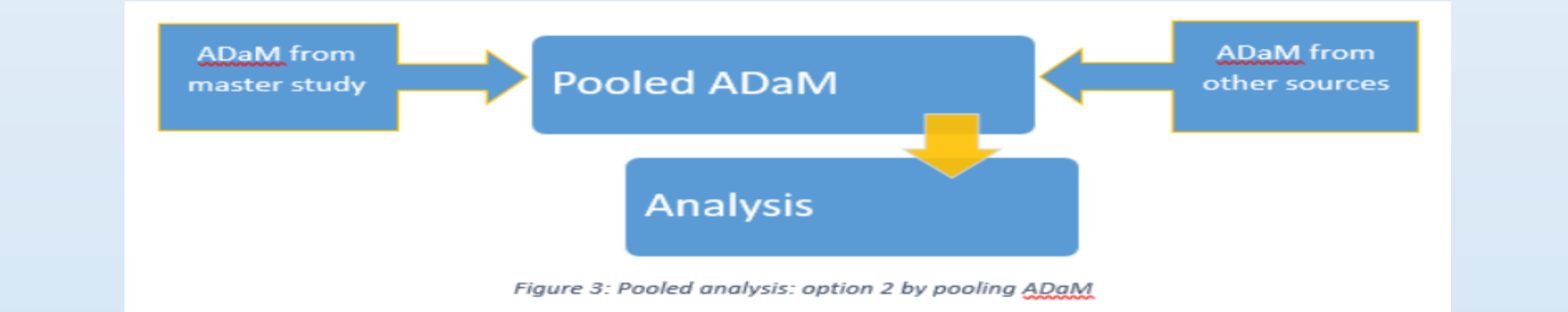
Proposal: All treatment modules/sub-studies within this platform trial will share one ADSL and one ADSE. ADSE has other structure and records the details for a patient’s journey in this platform study, including screening, starting initial treatment, having dose reduction, wrong dose taken, etc. Each 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.

Challenge 3 : Pooled analysis for cohorts in and outside the master study for aggregated analysis. 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. It is crucial to realize that there are

no one-size-fit-all solutions. 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. Option 1: Pool SDTM first and build analysis datasets;



Option 2: Pool analysis datasets from all modules/sub-studies;



Option 3 : A hybrid way of pooling both ADaM and SDTM depending on the specific situation

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

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
...		

Conclusions: Master protocol study design is gaining popularity in current drug development due to its efficiency and great benefits patients can get. However, 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, the poster proposes several potential handling approaches and aims to open further discussion for seeking optimum solutions.

References :

CDISC, *Analysis Data Model Implementation Guide*, February 2016
FDA, *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics: Guidance for Industry (Procedural)*, September 2018
FDA, *Study Data Technical Conformance Guide*, March 2019

