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Managing Deliverables in Oncology Basket Trial

Hong Qi, Merck & Co., Inc., Rahway, NJ, USA.
Mary Varughese, Merck & Co., Inc., Rahway, NJ, USA.

ABSTRACT

Basket trials have emerged as a novel approach to expedited clinical development of innovative oncology products. A basket trial examines safety and efficacy of a single drug or drug combination across multiple cancer populations. It could support a wide range of development needs with hundreds to thousands of data analysis reports for individual or combined cancer populations at each interim analysis. This brings new challenges to resource and technical management for reasons that are uncommon in traditional clinical trials, such as complexity of analysis datasets, a large number of analysis reports, and multiple in-parallel activities (including regulatory submissions) within and across IAs. In this paper, the authors discuss strategies and approaches to project planning, communication/ documentation, and automation for improving efficiency and productivity of analysis, reporting, and submission activities in oncology basket trials with multiple deliverables.

INTRODUCTION

As an innovation in oncology drug development, a basket trial is often used to examine an anti-cancer therapy, either a single agent or combination of agents, across multiple cancer populations in solid or hematologic malignancies. The study populations in a basket trial may be grouped into different cohorts by cancer type, or by biomarker regardless of the cancer type/origin/location. This allows exploration of the same therapy on patients with various cancer types or biomarkers, thereby accelerating the identification of effective treatment and subsequent regulatory approval for multiple indications and bringing innovative medicines earlier to patients in need.

Although the benefits are evident, there are still substantial challenges associated with basket trials from the analysis and reporting (A&R) perspective. Examples of such challenges include generation of complex analysis datasets and a large number of reports, and coordination of multiple parallel activities for regulatory submissions within and across interim analyses (IA). To overcome all these difficulties, we develop strategies and approaches for project planning, communication, documentation, and automation, aiming at improving efficiency and productivity of analysis, reporting, and submission activities in oncology basket trials with multiple deliverables. The main work on this regard is summarized in this paper.

The contents in this paper are based on an oncology basket trial with cohorts for 10 cancer types of solid tumor and four biomarkers of interest. In the seven years of the basket trial, sixteen IAs were performed to generate results for early evaluation and prediction of endpoints, external conference presentations (e.g., ASCO), journal publications, agency requests, and most importantly submissions to multiple regulatory agencies. For example, the submissions to the US Food and Drug Administration (FDA) for approval comprised two biomarkers, i.e., microsatellite instability - high (MSI-H) and tumor mutation burden (TMB), and three cancer types/indications, i.e., cervical, endometrial, small cell lung cancer. The scope of deliverables for each cohort includes data analysis and reporting (A&R) of all the cohorts in the first 10 IAs, and the remaining cohorts in the follow-up stage or with enrollment catching up in the later IAs. For the regulatory submission, there are often in-parallel submission activities ongoing for multiple indications, and/or for multiple agencies with tight timelines. Some of these are involved in different agency's innovative submission programs, e.g., the FDA real-time oncology review (RTOR), ORBIS, etc. Usually, hundreds to thousands of A&R reports are generated for each IA that can be 3-month to 16-month apart from another IA. To handle these requests on a timely manner with limited resource, we established a system discussed below for project management and planning, communication and documentation, and automation. Among multiple challenges, we will only focus on several key aspects in this paper. Of note, ideas described in this paper can also be applied to clinical trials with other novel trial designs such as umbrella trials and platform trials when similar situations are encountered in these studies.

PROJECT MANAGEMENT AND PLANNING

Under the general guidelines and standards, an agile and compliant project management is essential in a basket trial. From the process perspective, a robust plan should be built as a road map guiding the team to support the A&R and submission deliverables in the subsequent IAs.

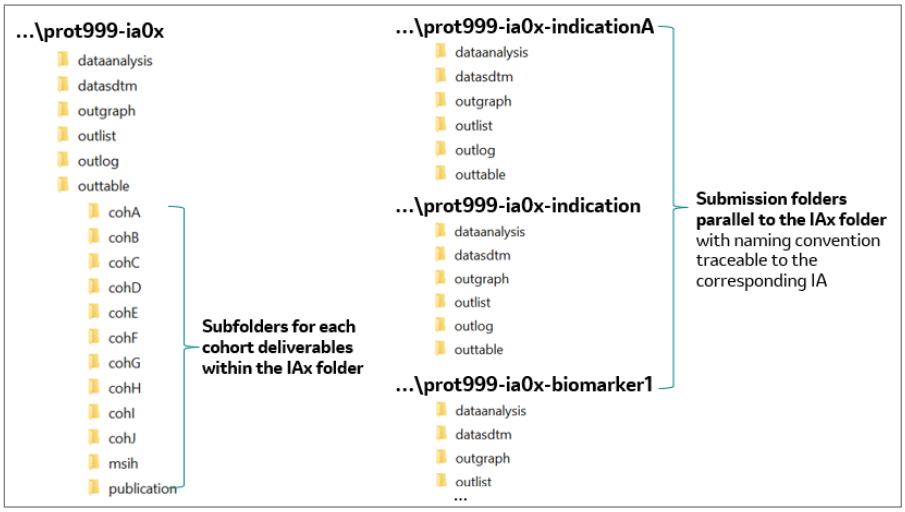
1. RESOURCE

To manage the dynamic deliverables for a basket trial, a flexible Statistical Programming (SP) project team size with both dedicated and flexible resources is proven to be a good strategy. A dedicated SP lead is necessary, to be responsible for collaborating with management and multi-functional areas for resource planning and meanwhile, coordinating technical design and development, process management, team mentoring, and oversight of all the IA and submission deliverables. A couple of dedicated technical SP members are also needed for the protocol-level template and macro program development and validation, and key A&R deliverables for each IA and some submission packages. Flexible resource should be planned in case if additional SP support is required for, e.g., multiple submissions based on one IA, the preparation of the Oncologic Drugs Advisory Committee (ODAC) meeting, etc.

2. STUDY FOLDER STRUCTURE

The folder structure for a traditional clinical trial usually supports deliverables for one disease population per IA, e.g., …\prot999-ia0x. In a basket trial, additional planning is needed for the folder hierarchy and naming conventions to properly organize and support the broad deliverables and provide traceability to the context of each folder. Besides traditional IA folders, subfolders within the IA folder, and folders parallel to the IA folder for the submission of certain disease indication with proper naming convention may be required. Some examples for study folder are illustrated in Display 1 for a basket trial.

As general practice, subfolders for each cohort are created under the output folders in the main IA folder to store the A&R deliverable output. Output folders usually include “outgraph” for graphs, “outlist” for listing, “outlog” for log files, and “outtable” for tables. This helps the study team locate the output and automate the output generation with ease. For the indication or cohort planned for a submission, a folder dedicated for the filing activities is created with naming convention of …\prot999-ia0x-indicationA. These facilitate the organization of submission data, program, and documents, simplify the story board for audit preparation, and clarify which IA’s data are included in Indication A’s submission.



Display 1 Example of Study Folder Structure and Naming Convention in a Basket Trial

3. ADaM SPECIFICATION/DATASET

The data collection and analysis requirements, and course of therapy may vary among participants of different cancers. For example, (1) somatic short-variants pertaining to DNA polymerase epsilon catalytic subunit mutations (POLEMUT) are only available for the tissue samples that had POLE mutations for a limited number of participants (around 4‰), (2) derivation rules are different for the number of prior line of therapy among study populations with different cancer types, (3) different prior therapies may be administered to patients with specific cancer types, such as Bevacizumab injection given as the first-line treatment of unresectable, locally advanced, recurrent, or metastatic non-squamous non-small cell lung cancer (NSCLC) before enrollment of participants in the basket trial, and (4) Unconfirmed response based on RECIST 1.1 per independent review committee (IRC) assessment needs to be derived in early stage of the trial for exploratory purpose. Moreover, different cancer types are identified for submission in different IAs. All of these add complexity to the ADaM specification and datasets in a basket trial. Thus, a basket trial may need unique dataset(s), variable(s), and variable derivation for certain cancer/biomarker population besides the common ADaM datasets and variables applied to all participants.

To ensure consistency and swift turnaround across IAs and submissions, we keep the required ADaM datasets/variables for all participants in each IA for all the study participants, and work with the unique scenario for the related cancer type/population submission as listed in Table 1.

Table 1 Data Scenarios and Solutions in a Basket Trial

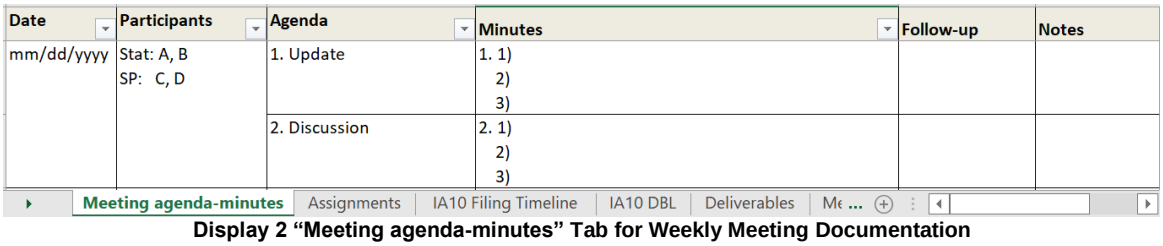
Scenario	ADaM Dataset Specification	ADaM Dataset	ADaM Variable
Data for limited number of participants, e.g., POLEMUT	Specify only for participants with data in a specific cohort submission	Stand-alone dataset in a submission, e.g., ADPOLE	Only required variables
Different variable derivation rules among cancer types	• Specify derivation rules for each cancer type for all participants (main specification • Keep only the corresponding derivation rule for the cancer type for submission (cohort specification)	• Main dataset with the variable for all cancer types • Cohort dataset with the variable for the cancer type for submission	e.g., ADSL.PRIORLN (Number of Prior Line of Therapy (N)) • For each cancer type in the main ADSL • For the cancer type for submission in the cohort ADSL
Prior therapy unique to certain cancer type, e.g., Platinum for SCLC	• Leave the variable out from the main specification • Specify in the specification for the cancer type for submission	• Main dataset without such a variable • Cohort dataset with such a variable	e.g., ADSL.PLTSENS (Platinum Sensitive/Refractory Status) • not in the main ADSL • in the ADSL for SCLC
Information for exploratory analysis, e.g., unconfirmed response based on RECIST 1.1 per IRC assessment, per investigator	• Specify in the main specification • Remove from the specification for submission cohort as the response has been confirmed	• Main dataset with the data value • Submission cohort dataset without the data value	e.g., • ADRS.PARAM=" Best Overall Response, unconfirmed (Radiology)", • ADRS.PARAM="Best Overall Response unconfirmed per RECIST 1.1 (Investigator)"

This helps streamline an ADaM data development and validation process with compliance, accuracy, and efficiency for a basket trial with multiple IAs and submissions.

COMMUNICATION AND DOCUMENTATION

During the long study journey, a basket trial could have a lengthy log of discussions, numerous decisions, and many non-standard reports to support requests from both internal and external customers. Good communication and documentation practice is the key to keep the team informed, providing a reference for team alignment, and helping new team members to speed up with the project essentials and progress. An Excel tool is developed to fulfill this purpose of communication and documentation within the basket trial project team. Two tabs from the Excel tool are highlighted below.

Meeting agenda and minutes (Display 2): This documents the regular meeting agenda and minutes between statisticians and programmers. The standing items contain updates on project decision/timeline, standards and guidelines related to A&R, follow-up on the team assignments, discussion of issues, upcoming tasks, and resource. Comparing to meeting minutes in separate Word documents, this provides a much easier forum to search any agenda topic in regular meetings.

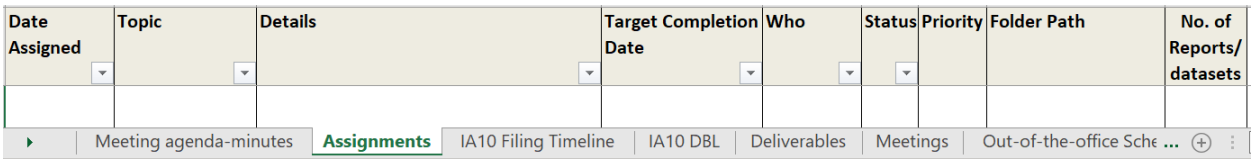


Date	Participants	Agenda	Minutes	Follow-up	Notes
mm/dd/yyyy	Stat: A, B SP: C, D	1. Update	1. 1) 2) 3)		
		2. Discussion	2. 1) 2) 3)		

Meeting agenda-minutes | Assignments | IA10 Filing Timeline | IA10 DBL | Deliverables | Me ...

Display 2 "Meeting agenda-minutes" Tab for Weekly Meeting Documentation

Assignments (Display 3): This tracks the A&R requests that do not go into the standard tracking tools for the normally planned deliverables. It shows the status, location, and progress of each request and team's workload, helping address new requests using the previous similar work recorded in this tab.



Display 3 "Assignments" Tab for Documenting the Information and Assignments for the Request

We exercised different communication approaches for different situations. For example, ODAC request claims to be always overwhelming and urgent, and may come at any time while the project team prepares the presentation. To get quick support, an instant message group was formed to post the resource need for the team to sign up.

AUTOMATION

Automation plays a critical role in improving efficiency, quality, and productivity for a basket trial with overwhelming and competing activities. It also motivates team members to be an innovative process builder. Several automation approaches in this basket trial are described below.

1. MASTER A&R TEMPLATE PROGRAMS

Master A&R Template programs are developed for parallel submissions of certain cohorts, as well as for subsequent IAs. Under different folders for various deliverables, some of these programs can be executed directly and some others need to be slightly modified based on special requirements for the submitted cohort and/or different IAs. For example, ADSL.PRIORLN can be simply updated for SCLC submission by removing the derivation rules applied to other cohorts. This tactic saves the time of A&R program development and validation, making a submission with integrated efficacy datasets and analysis reports possible with four-week notice.

2. TEMPLATE/MACRO PROGRAM TO SUBSET SDTM DATASETS FOR STUDY COHORT

In our process, the Study Data Tabulation Model (SDTM) datasets are extracted from the clinical database together for all the study cohorts of a basket trial. This allows the one-time effort for submission-ready SDTM processing, including versioning, business rule application, data enrichment, and ADaM dataset generation for all the cohorts. Meanwhile, in each IA, we often have various submissions for certain indication(s)/biomarker(s). The SDTM and ADaM datasets in a submission package should only include the target screened participants. Therefore, SDTM datasets need to be subset accordingly. A template/macro program is developed to fulfill this task.
The program automates the subset of all SDTM domains, except the trial design domains, to include study participants with the indication/biomarker for submission and those failed screening. Retaining all the attributes, the SDTM subsets are submission ready for the corresponding indication/biomarker. This template/macro approach ensures the consistency, quality, and efficiency in creating the SDTM subsets comparing to subsetting each SDTM dataset with an individual program.

3. DATE DERIVATION MACRO

Several ADaM date variables and parameter values are derived from multiple SDTM datasets with similar programming approach, e.g., UCLKADT (Uncut Last Known Alive Date), DTHDT (Date of Death), UCDTHDT (Uncut Death Date with Imputation), UNCUTDT (Date Beyond Cutoff), LKALDT (Date of Last Known Alive Prior to Cutoff). Some of these variables are repeatedly included in more than one ADaM datasets for A&R purpose. Keeping the code deriving these variables and parameters in each ADaM dataset program will cost additional work of development and validation if the code needs to be updated. Hence, a protocol-specific macro is created for date derivation at USUBJID (Unique Subject Identifier) level and is read into adsl.sas and adintdt.sas with a simple macro call, i.e., %apr0last0date, to streamline the process.

4. TUMOR TYPE DERIVATION MACRO

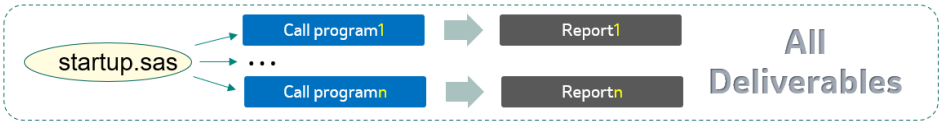
The variable denoting tumor type (ODDTYP) in ADSL is required for tumor identification among participants of all-cohorts combined and biomarker cohorts. However, it is not necessary for a single-tumor-type cohort. To save the effort on taking the variable derivation in and out of adsl.sas when generating ADSL for a single cohort, the following steps are taken: (1) Macro oddtype.sas is developed to derive ODDTYP at USUBJID level; (2) A macro parameter &oddtyp is defined in %macro adsl. Only when &oddtyp is specified as Y can ADSL.ODDTYP be generated. Through this macro approach, the update in ADLS is not needed for different cohorts.

5. FURTHER STANDARDIZATION AND AUTOMATION OF STUDY REPORT GENERATION

Tremendous effort has been invested in the standardization and automation for the generation of clinical trial study reports. Macros developed by the standards and project team have laid a solid foundation to increase the

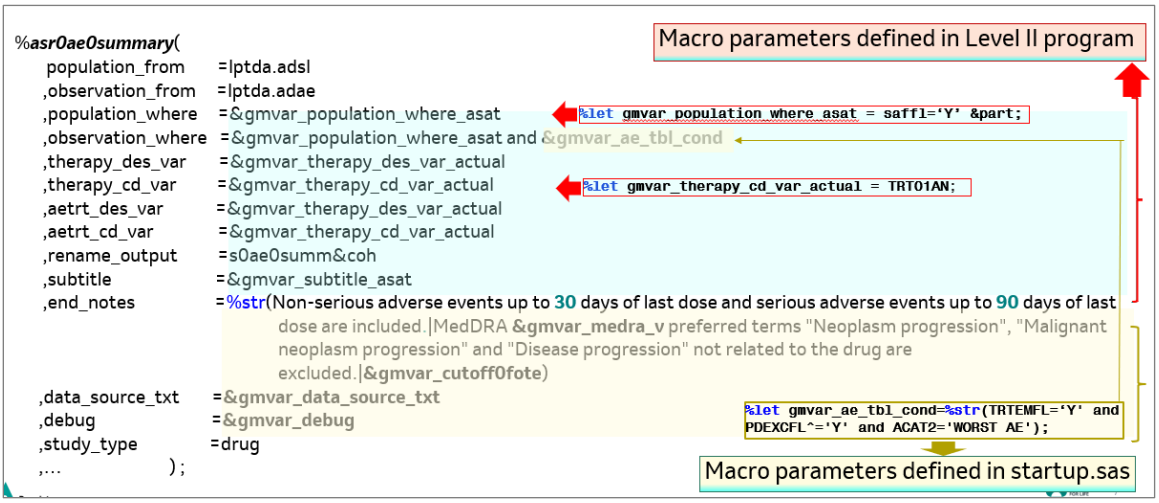
productivity. While working on a basket trial, opportunities to further enhance the standardization and automation have been identified and implemented.

Study reports are traditionally generated by using one macro call program per report, meaning 1000 macro call programs to generate 1000 reports when 100 reports are needed for each of the 10 cohorts, as shown in Display 3.

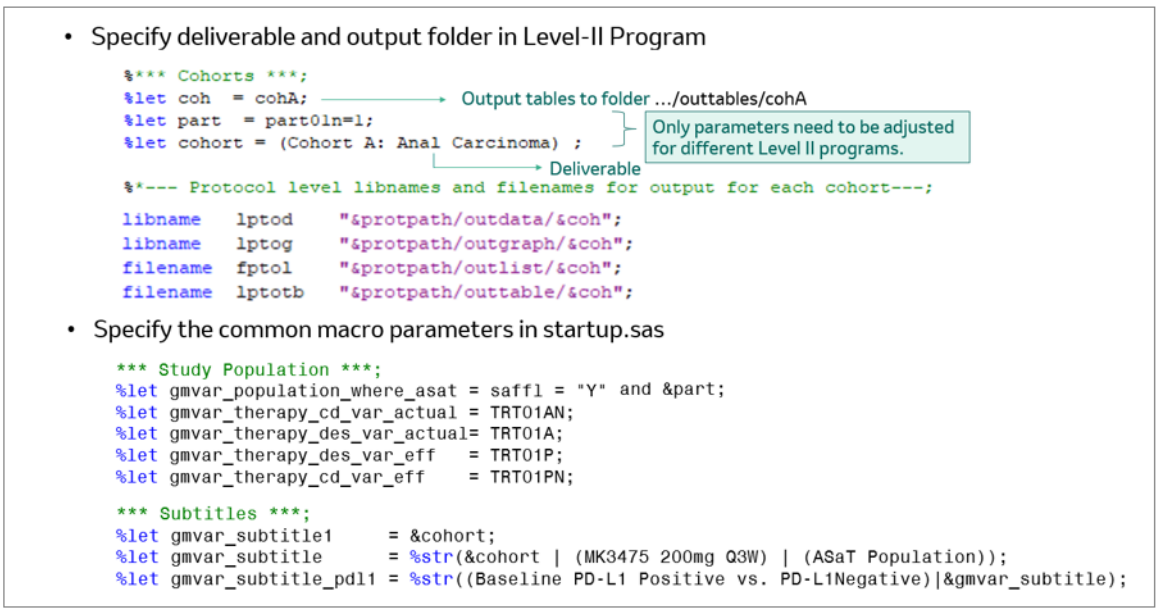


Display 3 Approach of One Macro Call Program Per Report Generation

For studies with common reports for multiple deliverables, such as different population, subgroups, multiple cohorts (especially in a basket trial), a simplified process design is needed to eliminate the repeat chore of setting up call programs with many common parameters and a few different parameters for the same macros over and over. An enhanced approach is to set up macro call program templates by specifying the common parameter values and leaving those that are different for different deliverables to be specified later in a Level-II program (Display 4 and 5).



Display 4 A Macro Call Program Template



Display 5 Macro Parameters Specified in Level-II Program and Startup.sas

Display 6 Reports Generated for Multiple Deliverables with Efficient Approach in a Basket Trial

To generate 100 common reports for each of the 10 cohorts with the method illustrated in Display 6, only 110 programs (100 standardized macro call programs and 10 Level-II program for 10 cohorts), instead of 1,000 macro call programs, can achieve the goal. This significantly saves programming resource and ensures quality when generating common reports for multiple deliverables.

CONCLUSION

A basket trial is often designed to study the safety and efficacy of an investigational product among patient populations with different tumor types and/or biomarkers, aiming at early identification of efficacious treatment for patients in need. The implementation of a backet trial usually requires frequent IAs for publications and/or multiple accelerated submissions across study cohorts in the same IA and/or across IAs simultaneously. The complexity of the trial design and conduct and a large volume of reports create significant challenges to A&R resource, process, and techniques. It is important to adapt an agile, flexible approach under the general guideline and SOP for the improvement of efficiency and productivity. We address these challenges through careful and innovative planning and implementation of resource, project management, and programming techniques. Some essential elements such as project management and technical approaches developed in this basket trial have also been used in other Phase III traditional oncology trials.

REFERENCES

1. Definition of basket trial - NCI Dictionary of Cancer Terms - NCI

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Hong Qi
Merck & Co., Inc., Rahway, NJ, USA
267-305-7589
hong_qi@merck.com

Mary N. Varughese
Merck & Co., Inc., Rahway, NJ, USA
267-305-6891
mary_varughese@merck.com