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Breaking Barriers in Clinical Trials: Insights into Platform Designs

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Abstract

Platform trials are changing how clinical research is done by allowing multiple treatments to be tested at the same time within one trial, specially in Oncology. These trials use a shared structure called a master protocol, which makes them flexible and efficient. A single control group can be used for multiple treatments, saving time and resources. One of the defining features of platform trials is their adaptive design. New treatments can be added as the trial progresses, and ineffective treatments can be discontinued based on interim data, allowing researchers to rapidly focus on promising therapies. As medical research moves forward, platform trials are becoming a key tool for improving the way new treatments are developed and tested.

I will share the challenges we encountered while working on Platform Trial, the strategies and steps we took to address and resolve them, and the success we achieved through these efforts and experiences.

Introduction

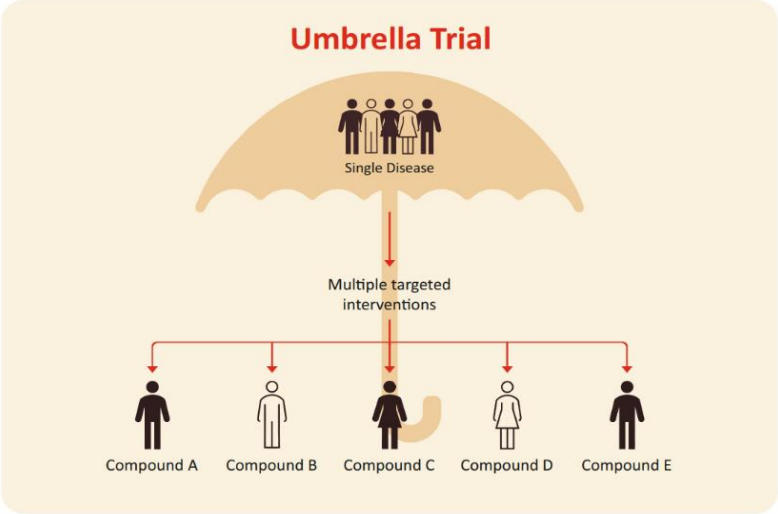
Currently, platform trials are being widely adopted across various therapeutic areas within the clinical research industry. Despite their growing popularity and promise, platform trials still need better guidelines and clearer ways to report results. Improving these standards is important to ensure the trials are consistent, transparent, and reliable. This will help industry embrace them more widely and enhance their impact on advancing medical research.

The purpose of this paper is to explain how GlaxoSmithKline (GSK) used the master protocol design in a study on multiple myeloma. It will highlight the best practices used during the study and share insights into the strategies that worked well. The paper will also discuss how the programming team dealt with challenges and the solutions they found to overcome them. This discussion will offer valuable lessons for future research and emphasize the importance of good protocol design in clinical studies.

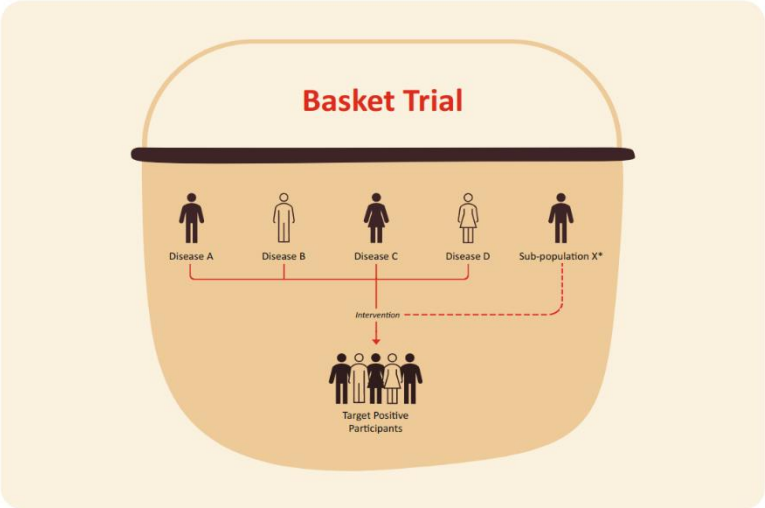
Decoding Master Protocols:

Platform trials are one type of master protocol. To understand them better, it helps to look at the different types of master protocols. These protocols create a broad framework for running clinical trials and generally fall into three main categories.

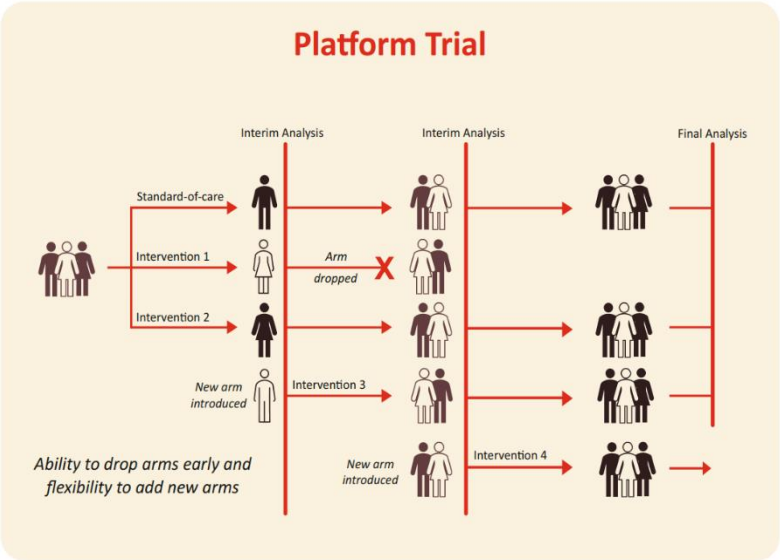
1. **Umbrella Trials**[1]**:** Umbrella trials focus on a single disease and test multiple treatments within that disease by targeting different genetic mutations or biomarkers. This master protocol enables researchers to evaluate how various subtypes of the disease respond to different therapies. Specifically, umbrella trials are designed to assess multiple investigational drugs or combinations of drugs in a single disease population, providing insights into which treatments or treatment combinations are most effective for specific disease types or indications.



2. **Basket Trials**[1]**:** A basket trial is a type of study that tests one drug or a mix of drugs in different groups of patients. These groups are divided by things like how advanced their disease is, what type of tissue is affected, how many treatments they've had before, their genetic traits, or other characteristics like age and gender. The goal is to see if a treatment that works for one kind of cancer might also work for other cancers that have the same genetic mutation.

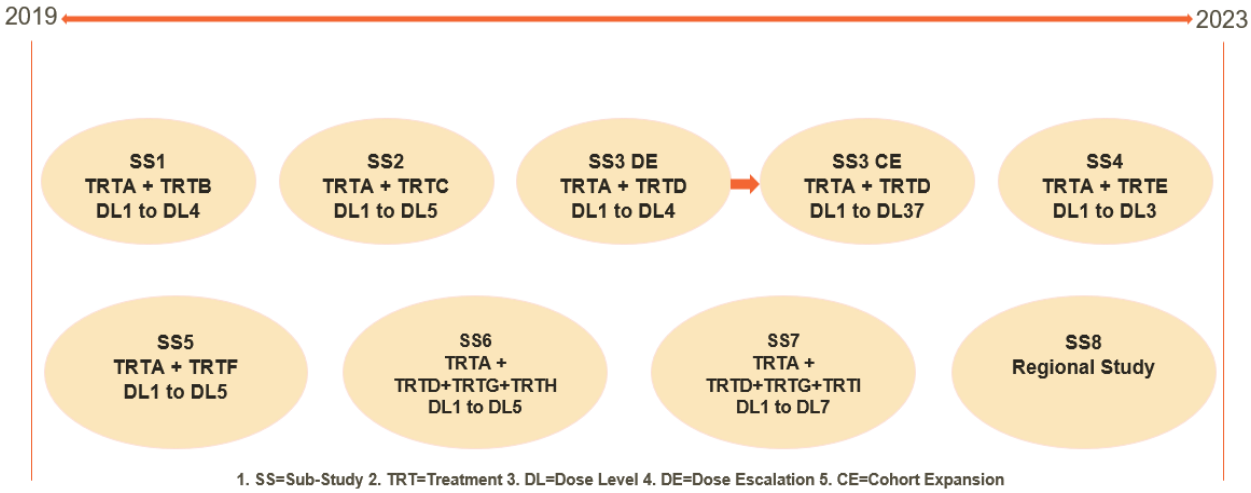


3. **Platform Trials**[2][3]**:** Platform trial design integrates key elements from both basket trials and umbrella trials. Like basket trials, platform trials can explore treatments across different diseases that share common characteristics. At the same time, they adopt umbrella trials' approach by testing multiple therapies within a single disease, targeting various subgroups or genetic profiles. This flexible framework allows platform trials to dynamically add or remove treatments based on real-time results, making them adaptable and efficient in assessing a wide range of therapeutic options.



Navigating Study Design: Challenges Faced and Solutions Found:

The trial is a Phase I/II, randomized, open-label platform study that utilizes a master protocol. It involves evaluating multiple treatment combinations across distinct sub-studies. Each sub-study consists of data collected in both the dose escalation (DE) and controlled expansion (CE) stages for each treatment combination arm, along with its associated shared control arm (in CE only) within the study.



1. SS=Sub-Study 2. TRT=Treatment 3. DL=Dose Level 4. DE=Dose Escalation 5. CE=Cohort Expansion

**The diagram above shows the number of sub-studies initiated from 2019 to 2023 and the planned dose level for each sub-study.

***At the start of the DE phase, a few participants will be recruited at the initial dose level within a sub-study. If this dose is safe, additional participants can be enrolled, and the dose could be increased. If it's unsafe, participants will try a lower dose, or the dose level may end

As illustrated in the figure above, the platform trial structure enabled the team to make numerous enhancements to the original study design over time, with each improvement offering distinct benefits and obstacles.

Key Benefits of Platform Trials:

1) Efficiency and Simplification:

Streamlining setup activities with unified case report forms and maximizing efficiency are key benefits of platform trials. Using the same form across different trials reduces setup tasks, saving time and administrative effort, allowing teams to focus more on research than logistics. Additionally, if a company wants to test various dosing regimens, platform trials let them conduct different tests simultaneously without starting new studies each time, thereby conserving resources, time, and money.

2) Enhanced Patient Recruitment Through Established PI Networks:

A potential advantage of utilizing the same principal investigator (PI) is that it facilitates easier patient recruitment for different sub-studies. Having the same PI helps tap into existing relationships and networks, making patients more likely to join because they trust the PI. This familiarity speeds up recruitment and keeps more patients engaged, making the research process more efficient overall.

3) Streamlining Trials:

Proactive data management and stakeholder engagement are key for smooth trials. In-stream data cleaning means fixing data errors as they happen instead of waiting until the studies end, ensuring accurate results and easier analysis. Keeping stakeholders like researchers, sponsors, and regulators informed helps solve problems quickly before they grow. This approach keeps everyone working together towards common goals, making the study more efficient and effective.

Unique Challenges & Solutions:

Starting a new sub-study and closing one sub-study while others are still enrolling creates logistical and procedural challenges. Closing all sub-studies also requires careful planning to ensure everything finishes smoothly and accurately. Here are the main issues and strategies to address them.

Challenge 1: Introducing Additional Sub-Studies

1) Creating Statistical Analysis Plan (SAP) and Output and Programming Specification (OPS):

Description: Master vs Individual SAP and OPS. OPS refers to GSK's standard documents that include a table of contents (TOC) listing the tables, listings, and figures needed for each key deliverable of the study, along with their mockups.

Solution: There are several ways to address this situation.

Option A: Create SAP and add appendix for each sub-study: This approach creates a detailed SAP for the whole trial and adds appendices for each sub-study. Each appendix includes methods or changes specific to that sub-study. This way, everything is in one main document, making it easy to find and use specific information for each sub-study, keeping things consistent while addressing different needs.

Option B: Create Individual SAP for each sub-study: This option creates a separate SAP for each sub-study in the trial. Each SAP focuses entirely on that sub-study's goals, methods, and analyses, allowing for complete customization. This is useful when sub-studies have very different needs and purposes, providing specific and detailed plans for each one.

Option C: Create Master SAP and produce individual study SAPs only when necessary: This strategy involves making one main SAP for the whole trial. Separate SAPs are made only if a sub-study has special needs that are very different from the main SAP. This way, everything stays consistent but can change as needed. It avoids repeat work and keeps organizing documents simple and efficient.

We opted for Option C because it fits our study needs well. At first, our sub-studies didn’t need many changes, so having a Master SAP helped keep everything consistent and simple. Separate SAPs were made only when changes were needed for specific sub-studies, like the method for cumulative doses or different assessments between investigators and sponsors etc. This saved us from repeating work and allowed us to focus on unique needs efficiently.

For the **OPS**, we considered the same three options, but decided on Option B. Each sub-study had different phases and milestones, so creating individual OPS for each sub-study was the best choice. This setup permitted adjustments within a sub-study's OPS without impacting the others.

2) Adjusting Existing or Adding New Case Report Form (CRF):

Description: Adding new sub-studies lead to add/update existing forms may not cover new data points required previous the sub-studies, leading to potential gaps in data capture and analysis.

Solution: As CRF pages were updated or new pages were added that were specific to one sub-study, we couldn't use methods from previous sub-studies. This led us to review and modify our analysis plan. We adjusted the SAP to include new statistical methods and revised the OPS to account for changes in data and output generation. Additionally, we revisited the SDTM datasets to ensure the updated CRF data was properly integrated, and we checked that any necessary new codelists were created and implemented.

Example:
Sub-study 3 has introduced a specific requirement for capturing flow cytometry data, which is critical for its research objectives. This data type was not required for previous sub-studies within the trial, necessitating adding new CRF.

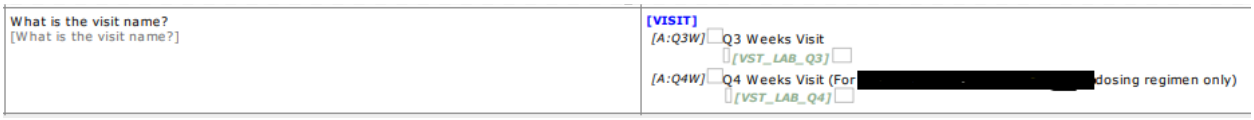
3) Adding New Visit Cycle / Follow-Up:

Description: Adding a new sub-study required alterations to the visit cycle and follow-up schedules, affecting resources, staffing, and participant management processes already in place.

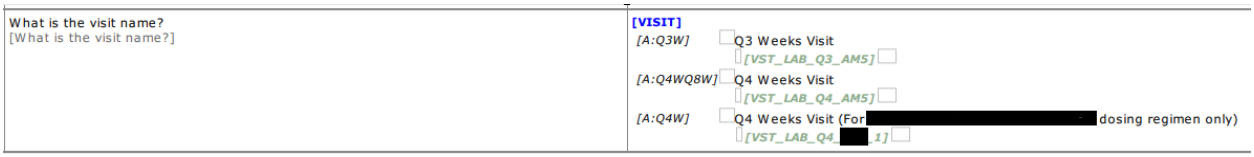
Solution: We originally had a 21-day cycle, but some new sub-studies adopted to a 28-day cycle, which changed how we numbered visits. Also, one study only used one treatment from a combination until the next cycle. Because of these changes, we couldn't use our old programs and had to create new ones that could handle different situations. The programming team created macros to make it easier to manage these differences across studies. We also established unique visits naming conventions tailored to study when the design was specific to that study.

Example:
Adjustments were made to the visit cycle and follow-up schedules for Sub-study 5. Specifically, since Treatment A was not administered while Treatment B was, a new visit was added to the schedule between the Day 1 visits for the next cycle. This helped in better accommodating the requirements without disrupting the existing processes.

Before:



After:



Cycle 1 Day 1	101	VISIT_C1D1
Cycle 1 Day 4	104	VISIT_C1D4
Cycle 1 Day 8	108	VISIT_C1D8
Cycle 1 Day 15	115	VISIT_C1D15
Cycle 1 Day 22	122	VISIT_C1D22
Cycle 1 Day 29 TRTB	129	VISIT_C1D29
Cycle 1 Day 43 TRTB	143	VISIT_C1D43
Cycle 1 Day 57 TRTB	157	VISIT_C1D57
Cycle 2 Day 1	201	VISIT_C2D1
Cycle 2 Day 15	215	VISIT_C2D15

→ Newly Added Visit for Sub-study 5

Challenge 2: Closing Out the Study While Other Studies Are Still Actively Enrolling

1) Unblinding Process:

Description: It was crucial to carry out the unblinding process carefully to prevent bias, protect data integrity, follow ethical standards, and ensure that other ongoing studies weren't affected.

Solution: Since our study included a CE phase, we had to follow GSK's standard randomization process, which added complexity to our platform trial compared to regular studies. To address this, we assembled a specialized unblinding team to oversee the process, using secure data systems to protect sensitive information. We established clear guidelines for those who can access unblinded data under specific conditions, utilized secure platforms to control access, and provided training to staff accordingly.

2) One Randomization Schedule for Full Study:

Description: At the close of first sub-study, maintaining a single randomization schedule across all sub-studies in a platform trial did lead to difficulties, especially with varying participant timelines and criteria across different sub-studies.

Solution: The randomization team created a flexible plan that adjusts participant allocation smoothly as one sub-study ends and others continue. The programming team collaborated with the statistical teams to check the model's integrity and keep changes in line with the trial's goals. They also improved the process by adding specific numbers to each schedule, making sure only the correct schedule is used.

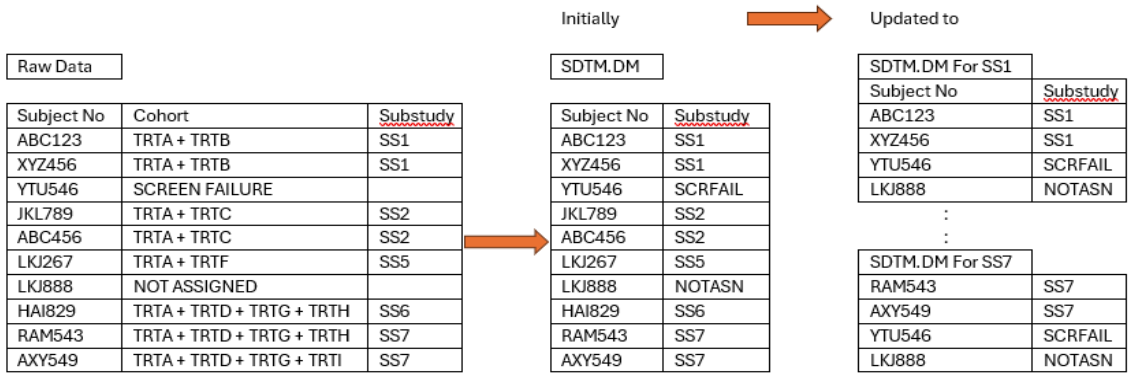
Example:

Schedule Number	Schedule Description
10	Randomization to combination treatment in DE
20	Randomization with SS3 combo – DE
21	Randomization with SS3 combo - DE Re-randomize with fewer dose levels
22	Re-randomisation to SS3 DE
23	Randomization for PA5 sub-study 3 new DE cohorts
30	Randomisation to SS4 combo – DE
40	Randomisation to combo DE SS5
41	Randomisation PA5 SS5 DE
50	Randomisation PA5 SS6 DE
60	Randomisation PA5 SS7 DE
70	Randomisation to SS8, DE phase as per protocol amendment 6

3) Creating Define Package:

Description: Since all the sub-study data was combined in a single database, we encountered a challenge while creating the SDTM define package: we couldn't use the unrandomized data because it contained information from all the sub-studies.

Solution: Programing team setup new process to summarize each study individually by creating detailed documentation for each sub-study's data requirements, including specific fields needed for the SDTM define package. We applied sub-study cutoffs to the SDTM data, ensuring that only relevant information is processed in the SDTM package, including details on subjects marked as Screen Failure, Not Applicable, and Not Assigned. Additionally, we performed verification checks to confirm that the cutoff process accurately excludes only irrelevant data. This step was crucial to maintaining the integrity of the dataset and ensure compliance with study protocols.



Challenge 3: Closing Out All Sub-Studies

1) One Database:

Description: Managing a single database for multiple sub-studies creates complexity in data handling, especially during the closeout phase. Ensuring data accuracy,

consistency, and integrity across all sub-studies while preparing final analyses can be challenging.

Solution: Created detailed documentation for each sub-study's data needs, ensured strong data management with validation and audits, and regularly checked and updated data to resolve issues and keep it compatible with studies.

Example:

Various systems, like SMS2000 and WATSON, were used for pharmacokinetics data, each employing different variable naming conventions. This disparity caused challenges when merging data back into the crf data also we faced truncation issues.

2) Standardizing Tables, Listings, and Figures (TLFs):

Description: Ensuring consistency in TLF presentations across multiple sub-studies is essential for clarity and uniformity in final reports. Variability in formats or numbering can hinder comprehensiveness and accuracy during the final analysis phase.

Solution: We outlined the requirements for the final Case Study Report (CSR) by concentrating on primary, secondary, and exploratory endpoints. Additionally, discussions were held with study stakeholders to uncover any extra needs. Also develop a comprehensive TLF standardization guide that defines formats and numbering for each section.

Section	Tables	Figures
Study Population	1.01 to 1.nn	1.01 to 1.nn
Efficacy	2.01 to 2.nn	2.01 to 2.nn
Safety	3.01 to 3.nn	3.01 to 3.nn
Pharmacokinetic	4.01 to 4.nn	4.01 to 4.nn
Pharmacodynamic/Biomarker	5.01 to 5.nn	5.01 to 5.nn
Patient Reported Outcome	6.01 to 6.nn	6.01 to 6.nn
Section	**Listings**	
ICH Listings	1.01 to x	
Other Listings	x+1 to z	

We ensured that table numbers remained consistent across all sub-studies, despite variations in mockups for similar outputs, like “Summary of Exposure.” Due to differences in design, we developed separate analysis plans for each study. We also provided notes to help the programmer clearly understand these variations.

Maintaining consistent numbering simplified downstream applications for CSRs, saving time and ensuring uniform report replication. We also facilitated communication between active study teams and closeout teams to avoid information gaps and keep everyone aligned.

Conclusions

Platform trials have changed clinical research by making it more efficient and speeding up drug development. Despite the challenges with these types of studies, we have successfully completed the closure of two sub-studies using the innovative solutions outlined.

We expect more master protocols to be used in the future, and it's important to raise awareness and provide training to apply these methods beyond oncology so we do need collaboration at industry level to improve guidelines and standardized reporting become essential. Addressing these areas will enhance consistency and transparency, ultimately supporting wider acceptance within the clinical research community.

References

[1] Basket and Umbrella Clinical Trial Design | BioRender Science Templates, *Gaia Lugano*

[2] *Basket, Umbrella, and Platform Trials: The Potential for Master Protocol–Based Trials in Inflammatory Bowel Disease - ScienceDirect*, *Sailish Honap, BruceE. Sands, Vipul Jairath, Silvio Danese, Eric Vicaut, Laurent Peyrin-Biroulet*

[3] *Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols | Trials | Full Text*, *Jay J. H Park, Ellie Siden, Michael J. Zoratti, Louis Dron, Ofir Harari, Joel Singer, Richard T. Lester, Kristian Thorlund & Edward J. Mills*

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Recommended Reading

Practical Considerations and Recommendations for Master Protocol Framework: Basket, Umbrella and Platform Trials, *Chengxing (Cindy) Lu, Xiaoyun (Nicole) Li, Kristine Broglio, Paul Bycott, Qi Jiang, Xiaoming Li, Anna McGlothlin, Hong Tian, Jingjing Ye*

Master Protocols for Drug and Biological Product Development | FDA, *Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research*

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