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Preserving the Blind: Cross-Functional Solutions During Study Design Evolution from Blinded Parent to Open-Label Extension

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ABSTRACT

Addition of an open-label extension to a blinded parent study mid-study introduces significant risks to trial integrity and requires coordinated effort across multiple functions. This case study highlights how data management, statistical programming, and statistical teams collaborated to address complexities during study conduct, driven by evolving design requirements.

The transition posed an immediate risk of unintentional unblinding and potential treatment disruption, primarily due to complex randomization schema. In response, the cross-functional team rapidly implemented data masking, dummy randomization strategies, and strict access controls to preserve the blind while ensuring uninterrupted patient treatment.

The evolving trial design had far-reaching impacts on data operations. It necessitated updates to the electronic data capture system, edit checks, and data transfer specifications. Metadata, SDTM & ADaM data, and reporting logic were revised to support parallel streams of blinded and open-label data. Vendor contracts & data integration agreements were also updated to reflect changes in scope, timelines, & deliverables.

The result was a seamless continuation of the study without compromising scientific validity or regulatory compliance. This session provides a practical blueprint for how cross-functional teams can manage mid-study design changes with agility, ensuring data quality, treatment continuity, and operational consistency across the trial lifecycle.

INTRODUCTION

Modern clinical trials often evolve in response to emerging data, regulatory input, or long-term treatment goals. Transitioning from a double-blinded parent study to an open-label extension is increasingly common but fraught with operational and methodological challenges. Such transitions must preserve the scientific integrity of the trial, avoid unintentional unblinding, and ensure continuity of patient care.

This paper describes a real-world case study from a neurodegenerative disease trial, illustrating how cross-functional collaboration between data management, statistical programming, clinical operations, biostatistics, and external vendors was critical to successfully managing the transition. It outlines the data architecture and operational processes that enabled the team to maintain the blind, update infrastructure, and comply with evolving regulatory expectations.

EVOLUTION OF PARENT STUDY AND IMPACT ON RANDOMIZATION STRATEGY

It is a very common practice to amend the clinical trial protocol due to safety related reasons, trial conduct and design, administrative and regulatory factors, etc. The initial parent study design was assigning participants in Part A or Part B (two dose groups) in a 1:1 randomization ratio and assign 2:1 ratio of active treatment to placebo within each group. Example, if the trial population is 90 participants, then Part A & Part B will contain 45 participants each and within each part, 30 participants will be assigned to active treatment and 15 will be assigned to placebo.

The initial design also has a condition where Drug Safety Monitoring Board (DSMB) Charter will undertake an unblinded review of safety data in Part A and Part B and provide a recommendation on when Part C (additional active treatment arm) can be initiated. At that time, participants will be randomized to any study

Part that is currently open for enrollment, and then to either active treatment or placebo (in a 2:1 ratio) within that Part. Example, if the trial population is 90 participants, then Part A, Part B, and Part C will contain 30 participants each and within each part, 20 participants will be assigned to active treatment and 10 will be assigned to placebo.

The duration of initial trial was 12 weeks where participants will receive study medication once daily orally. As the study progressed, the protocol was amended and trial duration was increased from 12 weeks to 12 months. A further evolution of study design was addition of stratification criteria per disease staging which added additional parts (D and E) to the study design. Example, considering disease staging criteria classified into two categories – if trial population is 180 participants, then Part A, B, C, D, E, and F will contain 30 subjects each as the total population will be split into 1:1 ratio per disease staging criteria and then further split into three different dosing groups. Each of the part will be split into 2:1 ratio consisting of 20 subjects assigned to active treatment and 10 subjects to placebo.

As the study design evolved, it also impacted to randomization strategy. The initial randomization strategy was a block randomization followed by adaptive design. After the study design updates the randomization strategy updated multi-stage, stratified, adaptive, and block randomization as shown in figure 1.

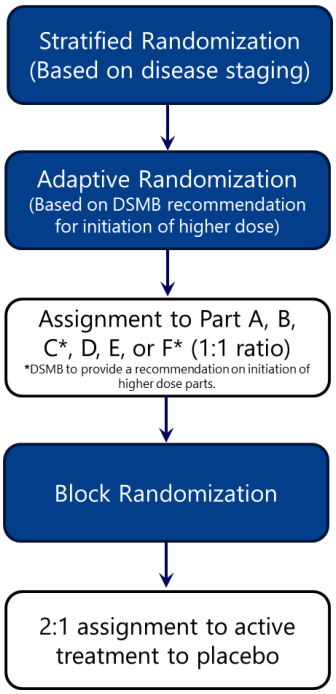

Figure 1: Multi-stage, stratified, adaptive, and block randomization

Table 1: Summary of Randomization Types Used

Randomization Step	**Type**
Assignment to Part A/B/D/E based on disease staging	Stratified Randomization
2:1 assignment within each part	Forced / Block Randomization
DSMB-triggered inclusion of new parts (C and F)	Adaptive Randomization
Randomization to available parts after expansion	Dynamic / Multi-stage Randomization

ADDITION OF OPEN LABEL EXTENSION AND ITS IMPLICATIONS ON BLINDING

Due to competitive landscape and to monitor safety of participants and open label extension (OLE) study was added where participants from parent study had an option to enroll in OLE and it was designed in such a way where participants in original part would continue in the same cohort (or treatment dose level) and placebo subjects would be treated with active treatment at the same dose-level. As the OLE wasn't planned when the parent study was initiated the data collection strategy in electronic data capture (EDC) system had randomization numbers as open/visible to all who had access to EDC, such as site staff, internal team members – clin-ops, data management, medical monitors, statisticians, and statistical programmers. The randomization numbers were not considered un-blinding during the parent study initiation, but as the study evolved (as shown in figure 2) and participants assigned to parts A-F, OLE introduced several unblinding risks because participants and investigators could deduce prior treatment assignments based on the randomization number or dose group continuity.

The parent study used block randomization within each treatment part (A-F) to maintain a 2:1 ratio of active drug to placebo. However, this design created an unexpected unblinding risk when the OLE was introduced. In the OLE, all subjects received active treatment, continuing at the same dose if they had previously received active treatment in parent study.

This created a critical integrity issue: if even one subject from a given part (e.g., Part A) transitioned into the OLE and continued at a specific dose, site staff or other blinded study personnel could infer not only that subject's prior assignment, but also deduce the assignments of other participants within the same block, effectively unblinding the entire cohort for that treatment part. Example: If Subject number 100-001 with randomization number 50001 from Part B transitions to OLE, it could have potentially unblinded the dose group of other subjects within the 5000x randomization number series.

Given the progressive nature of neurodegenerative disease, any delay in resolving potential unblinding could lead to treatment interruptions, worsening patient outcomes and compromising the scientific validity of the trial. Preserving the blind and maintaining continuous treatment access were at risk due to addition of OLE.

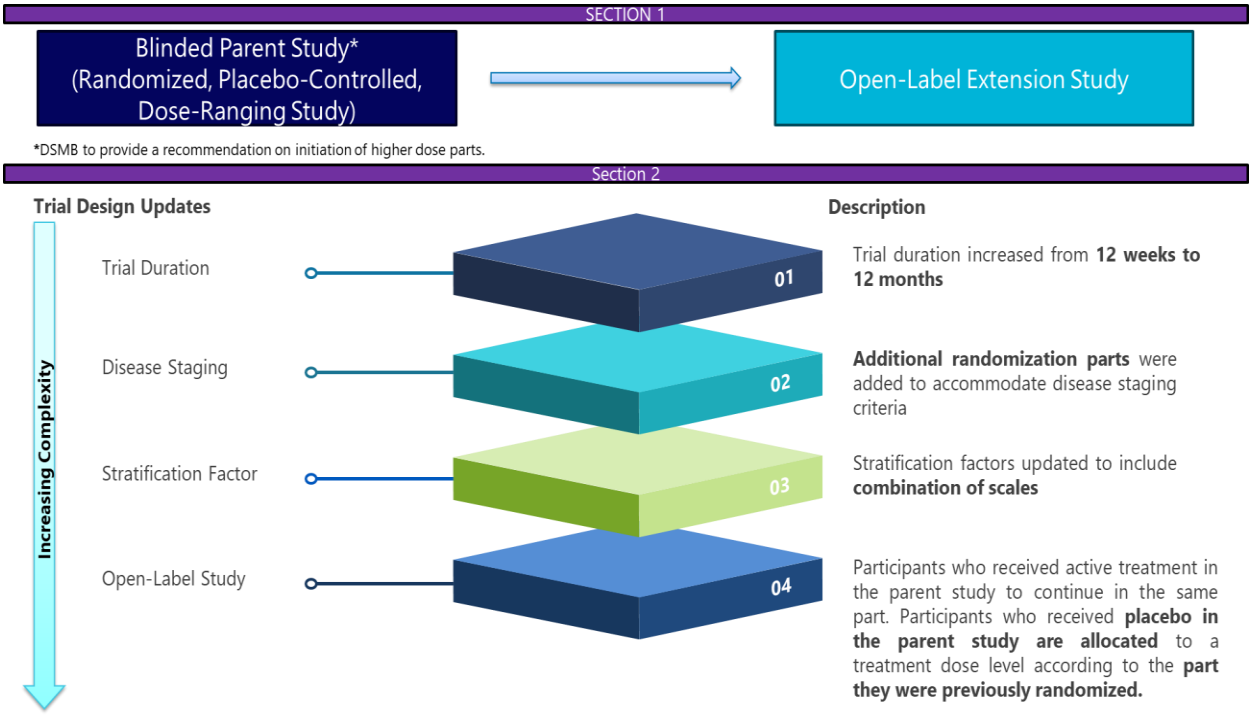

Figure 2: Study Design Evolution: Blinded Parent to Open-Label Extension

CHALLENGES DURING STUDY DESIGN TRANSITION

Unblinding Risk from Randomization Schema: The existing randomization schema created risk for retroactive unblinding during the OLE transition. The randomization files contained randomization numbers in sequential format and treatment assignments. These files were categorized by the parts A-F for disease staging and dose groups. The randomization numbers were visible in EDC system which caused a risk that if a subject from particular part transitioned to OLE, it could potentially unblind the participants dose-group in parent study. Without mitigation, dosing-groups could inadvertently be exposed.

Patient Continuity and Operational Risk: Transitioning subjects required rapid solutions to ensure uninterrupted treatment while maintaining the blind. The traditional process would be to create new randomization numbers for OLE instead of re-using form parent study, getting informed consents forms (ICF) re-signed form participants, collaborating with internal team and Randomization and Trial Supply Management (RTSM) team to implement the solution to potential un-blinding risk. However, this process would be time-consuming, ranging from few weeks, to get the ICFs reconsent and update the RTSM systems. As there were several subjects who were about to transition to OLE and this process could have caused transition delays and treatment interruption.

Risk to Trial Integrity: This posed a critical threat to trial integrity, with potential consequences for regulatory approval, data interpretability, and ethical treatment access. Delays in resolving this issue risked participants staying off therapy, which could accelerate neurodegeneration in this vulnerable population.

SOLUTION TO PRESERVE BLIND AND TREATMENT CONTINUITY

Cross-Functional Collaboration: a cross-functional crisis response, collaborating closely with biostatistics, clinical operations, data management, and RTSM vendors to develop and implement a layered mitigation strategy.

- Roles of internal team members such as statisticians, statistical programming, data management, clinical ops who had access to RTSM were updated
- Coordination across systems, data workflows, and team disciplines to provide transparency in process updates
- Removal of live randomization data from the EDC
- Implementation of dummy randomization numbers
- Edit checks, role-based access controls, and query restrictions
- Parallel handling of blinded and open-label data streams
- Updates to DTS, SAS® programs generating SDTM, ADaM, and reporting logic to integrate the dummy randomization numbers
- Study design changes cascaded through the data pipeline, impacting EDC configuration, data transfers, and metadata
- Locking legacy systems which stored randomization files and EDC data extracts

CONCLUSION

Adaptation to mid-study design evolution requires collaboration across all functional areas. In this case study, proactive cross-functional problem-solving enabled the team to preserve study blind, ensure treatment continuity, and maintain regulatory credibility. The lessons learned underscore the importance of forward-compatible data strategies, vendor alignment, and rapid implementation of technical safeguards. By executing rapid and strategic mitigation measures, the cross-functional team preserved the trial blind, ensured treatment continuity, and upheld scientific and regulatory integrity. This case study reinforces the critical need for forward-compatible randomization frameworks in adaptive trial design. The experience highlights the importance of proactive planning, flexible systems architecture, and seamless communication across domains. These learnings provide a scalable blueprint for future trials navigating similar transitions.

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