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In-house Data Monitoring Committee Report Programming

Lingjiao Qi, Alnylam Pharmaceuticals;
Amanda Plaisted, Alnylam Pharmaceuticals;
Sreedhar Bodepudi, Alnylam Pharmaceuticals;

ABSTRACT

A Data Monitoring Committee (DMC) is an independent group of experts tasked with overseeing the safety and/or efficacy of an ongoing double-blind clinical trial. The DMC periodically reviews accumulated data in unblinded study reports and provides recommendations on the study's conduct. While DMC report activities in pivotal trials are typically external to the sponsor, for non-registrational trials (e.g., Phase 2 trials), it is acceptable for an internal, independent group to manage DMC report activities. This internal approach can streamline processes and enhance efficiencies in both timelines and costs.

This paper shares the authors' experience in establishing the first in-house DMC, where an independent group of statisticians and programmers was formed within the organization. It discusses the processes and responsibilities established between the blinded and unblinded programming teams to maintain data integrity and ensure appropriate access for relevant stakeholders. The paper also highlights key planning activities involving data management teams, statisticians, and cross-functional teams. Additionally, it addresses the special handling required for unblinded IRT, PK, and PD files during the transfer of SDTM, ADaM, and TLF programs from the blinded to the unblinded team.

INTRODUCTION

In clinical research, Data Monitoring Committees (DMCs), also known as Data and Safety Monitoring Boards (DSMBs), play a pivotal role in ensuring participant safety and maintaining the integrity of study data in double-blind clinical trials. According to FDA guidance, these independent committees are essential in periodically assessing accumulated trial data to make recommendations regarding the continuation or modification of the study (FDA, 2006). Typically, pivotal trials utilize external vendors for DMC activities to minimize bias. However, non-registrational trials, such as Phase 2 studies, can effectively leverage internal resources to manage DMC activities (Clinical Trials Transformation Initiative, see reference). Implementing an internal DMC team can enhance operational efficiency and significantly reduce costs without compromising data integrity.

At our organization, the decision to create an in-house DMC was driven by the objective of streamlining processes while ensuring regulatory compliance. A comprehensive understanding of DMC programming considerations is critical, particularly the establishment of robust processes and safeguards to prevent inadvertent unblinding (PharmaSUG, 2024). By establishing an Independent Data Analysis Group (IDAG), consisting of unblinded statisticians and programmers, we achieved a clear separation between the teams handling blinded data and those performing unblinded analyses. This separation is aligned with the best practices described by industry experts from both statistical and programming perspectives, emphasizing clarity in roles, responsibilities, and careful handling of sensitive data (Phastar; Exploristics, see references). This paper outlines our journey, emphasizing detailed planning, interdepartmental collaboration, and programming best practices.

ESTABLISHING AN IN-HOUSE DMC PROCESS

The process began with developing a comprehensive DMC charter, clearly defining the purpose of the DMC, specifying responsibilities of each party (DMC members, CRO vendors, Data Management, Clinical team, Safety team, Study statistician, Programmers, IDAG, etc), identifying the scope of safety data, and establishing the frequency of data transfers for DMC reporting. The charter also clearly outlined the meeting schedules and format, differentiating between open sessions, where blinded data was used to review overall study progress, and closed sessions, dedicated to detailed unblinded analyses.

Once DMC charter was finalized, Clinical Operations team organized an orientation meeting involving key stakeholders such as DMC members, clinical research staff, safety teams, blinded statisticians,

programmers, data managers, and the IDAG to review the study overview and DMC scope. Following this, a kickoff meeting led by the study lead statistician clarified the scope, timelines, and defined the responsibilities for the blinded and unblinded teams.

A dual-track programming workflow was established:

- Blinded programming team to develop SDTM, ADaM, and TLF programs using blinded data, and produce open session reports.
- IDAG team to incorporate unblinded data into developed programs and generate closed session outputs.

These early and comprehensive plannings ensured clear communication of responsibilities and timelines across all stakeholders. An example of DMC timeline in our organization is shown in Figure 1 for reference.

Activities	Details	EAs	Duration (day)*
Dry-run (purpose: mimic DMC blinded and unblinded TLFs generation process)	Blinding/unblinding data transfer from DM vendor	DM, DM vendor	1
	Generates blinded TLFs as open session report (including stat review, comments incorporated, output updated)	Study Statistical Programming, Study Statistician	3
	Study team review (including comments incorporated and blinded output finalized)	Clinical Research, Safety team	3
	Transfer all programmings to IDAG; IDAG generates unblinded output as close session report;	IDAG (supported by study SP and stat)	3
DMC true-dry (data cut: at least 4 weeks prior to DMC1)	'Clean' data transfer from DM vendor	DM, DM vendor	1
	Generates blinded TLFs (including stat review) as open session report	Study Statistical Programming, Study Statistician	5
	Generates unblinded TLFs as close session reports	IDAG	3
	Send out open/close session reports to DMC Members (at least 5 business days prior to the meeting)	IDAG	1

* Duration may vary study to study, depending on alignment with study team.

Figure 1: example of an in-house DMC timeline

ROLES AND RESPONSIBILITIES WITHIN DMC REPORTING

After the study lead statistician scheduled the kick-off meeting with key stakeholders to confirm the scope and timelines for DMC reports, the study lead data manager began facilitating the cleaning and transfer of the clinical database and required external vendor data as specified by the DMC charter. Concurrently, the blinded programming team initiated the setup process to write statistical programs to generate blinded datasets and outputs. This team developed robust, defensively programmed code to produce SDTM, ADaM, and TLF outputs. Additionally, they created a comprehensive hand-off documentation detailing necessary modifications for subsequent unblinded analysis for IDAG.

Once blinded outputs were generated and reviewed by the study lead statistician, the process transitioned into the unblinded phase. The IDAG team then copied all relevant SDTM, ADaM, TLF programs, and associated data files from the blinded folder into an access-restricted unblinded folder, where the IDAG team updated these programs with actual treatment assignments, replaced any placeholder values, integrated unblinded files (ie, pharmacokinetic (PK) and pharmacodynamic (PD) data), and followed the hand-off documentation to produce accurate unblinded DMC reports. These reports underwent thorough review before secure delivery to the DMC. Additionally, the IDAG managed meeting logistics, recorded closed session meeting minutes, documented DMC recommendations, and securely stored final documentation. Detailed roles and responsibilities during in-house DMC programming and reporting at our organization are listed below:

Blinded Statistical Programming

- **SAS System Owner** grants Study Lead Programmer, blinded programming team, and Study Lead Biostatistician access to the blinded data folders on the SAS system.
- **Study Lead Programmer** and blinded programming team, in collaboration with the Study Lead Biostatistician define the structure and format of the analysis datasets based on the requirements outlined in the SAP, if available, and DMC TLF shells.
- **Study Lead Programmer** coordinates with the blinded programming team to develop SAS or R code to generate the required datasets and statistical outputs. Ensures that all code is thoroughly documented and adheres to internal coding standards.
- **Study Lead Programmer** ensures a robust validation process, consulting Study Lead Biostatistician as needed, to ensure that the code is accurate.
- **Study Lead Programmer** coordinates with blinded programming team preparing all codes for open and closed sessions.
- **Study Lead Biostatistician** reviews open session outputs to ensure they are clear, accurate, and aligned with the DMC charter.

IDAG Reporting

- **SAS System Owner** grants IDAG Programmer(s) and IDAG Biostatistician(s) access to the blinded and unblinded data folders on the SAS system.
- **IDAG Programmer**(s) generate the closed session outputs for review utilizing programming codes written by the blinded team.
- **IDAG Biostatistician** reviews closed session and open session outputs to ensure they are clear, accurate, and aligned with DMC charter, and delivers outputs to the DMC.
- **IDAG Biostatistician is also responsible for the following**:
    - Records DMC Closed Session meeting minutes and DMC recommendations
    - Shares the DMC Recommendation Report with the medical monitor, as governed by the charter
    - After the DMC is disbanded, shares the DMC closed session meeting minutes, DMC recommendations, and any other relevant communication between the DMC and IDAG with the study team
- **IDAG Programmers are also responsible for the following**:
    - After the DMC is disbanded, shares any programming codes maintained by IDAG Programmer(s) with Study Lead programmer

DMC DATA FLOW

A clear understanding of the data flow in DMC reporting is essential, particularly when handling unblinded data. It is critical to manage unblinded data securely to minimize any potential risks associated with inadvertent unblinding. Figure 2 illustrates the detailed data flow process used within our organization for DMC reporting. Initially, the data management team (including the DM vendor) extracted data from Electronic Data Capture (EDC) systems and collected data from external vendors, including blinded and unblinded sources. The data collected was then separated into two distinct streams: one directed to the blinded programming team and the other securely transferred to the IDAG.

The blinded team began preparing programming code with blinded data to generate DMC outputs for open sessions. Once these initial codes and outputs were developed, reviewed, and finalized, the IDAG team assumed control of these programs. IDAG incorporated unblinded data to create outputs for the closed DMC sessions. This dual-stream approach effectively supported both open and closed sessions

by providing accurate and timely data, while preserving the critical separation between blinded and unblinded processes.

Given the initial DMC review was scheduled three months right after post-enrollment of the first patient, and the workload of creating and validation SDTM, ADAM, and TLF programs for a brand new study, the blinded team proactively began programming once test data from the EDC and external vendors became available. Furthermore, considering the quick turnaround required during actual DMC reporting (usually within three days for SDTM/ADAM/TLF refreshing with new data transfer, as illustrated in Figure 1), programs were robustly developed using defensive programming techniques. These techniques allowed the blinded programming team to rapidly adjust for inconsistencies between data transfers and dynamically managed folder paths and filenames, facilitating seamless transition to the IDAG team, who had limited direct study involvement.

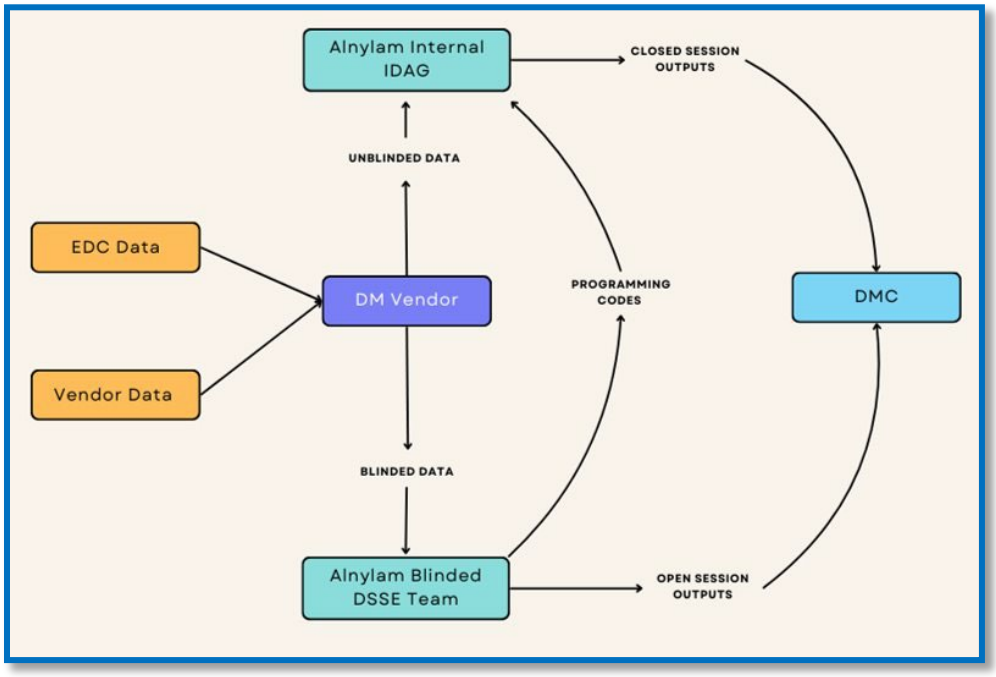

Figure 2. DMC Data flow

SPECIAL HANDLING OF DATA WITHIN PROGRAMMING AND REPORTING

A challenge in the DMC programming process involves properly managing sensitive, unblinded data. Since the blinded team does not have access to actual unblinded data, careful and robust setup of blinded programs is necessary to ensure seamless execution when transferred to IDAG.

For instance, in our in-house DMC process, the blinded team received empty IRT files containing only variable headers and no actual treatment assignments. To enable development and testing of programs, the blinded team populated these IRT files with dummy treatment information, and clearly marked ARM and related variable with "DUMMY" when developing SDTM.DM datasets. These "DUMMY" treatment values were also consistently applied across analysis datasets (ADaM), and TLF outputs, clearly signaling to reviewers that these were not actual treatments (Figures 3 and 4). During IDAG programming, IDAG replaced the dummy data with actual treatment assignments from real unblinded IRT files, ensuring accurate unblind outputs for the DMC closed session.

STUDYID	DOMAIN	SUBJID	SEX	RACE	ETHNIC	ARM	ACTARM
STUDY-001	DM	1000-0001	F	WHITE	NOT HISPANIC OR LATINO	DUMMY PLACEBO COHORT 1	DUMMY PLACEBO COHORT 1
STUDY-001	DM	1000-0002	M	WHITE	NOT HISPANIC OR LATINO	DUMMY PLACEBO COHORT 1	DUMMY PLACEBO COHORT 1
STUDY-001	DM	1000-0007	M	WHITE	NOT HISPANIC OR LATINO	DUMMY TRT COHORT 1	DUMMY TRT COHORT 1

Figure 3: Blinded SDTM.DM dataset showing Dummy treatment

Listing 16.2.5.1
Study Drug Administration

Cohort	Treatment Group	Participant	Period	Visit	Study drug administered?/ If not, specify the reason	Dosing Admin. Date: Time/Day[1]
Cohort 1	Dummy - Group A	1000-0007	DB	DAY 1	Yes	2024-09-27:10:52/1
	Dummy - Group B	1000-0002	DB	DAY 1	Yes	2024-08-15:10:03/1
		1000-0009	DB	DAY 1	Yes	2024-12-09:11:35/1
		1000-0011	DB	DAY 1	Yes	2025-01-10:11:42/1

Admin=administrated/administration; Conc=concentration
[1] Study day relative to the first dose of study medication in the double-blind (DB) period.

Figure 4: Blinded TLF output showing dummy treatment

Similarly, pharmacokinetic (PK) and pharmacodynamic (PD) files are sensitive due to their potential to indirectly reveal treatment assignments. In our in-house DMC process, PK/PD files delivered to the blinded team contained sensitive fields left intentionally blank by vendors (e.g., PCORRES, COVAL variables in Figure 5). The blinded team filled in these blanks with realistic dummy values to set up SDTM, ADAM and TLF programs, reducing the effort and risk of error for the IDAG when integrating the authentic PK/PD data with programs to generate final unblind analysis.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
STUDY	SUBJID	PCSPEC	VISIT	PCREFID	PCNAM	PCMETHO	PCTPT	PCDTC	PCCAT	PCTEST	PCTESTCD	PCORRES	PCORRESU	PCSTAT	PCREASND	COVAL
ALN-STUDY-001	10010001	Serum	Day 1	AP806670I06	Vendor	METHOD	Predose	2024-07-0	Analyte	DRUG1	DRUG					
ALN-STUDY-001	10010002	Serum	Day 1	AP806668I06	vendor	METHOD	Predose	2024-08-1	Analyte	DRUG2	DRUG					
ALN-STUDY-001	10010003	Serum	Day 1	AP806671I06	vendor	METHOD	Predose	2024-09-2	Analyte	DRUG3	DRUG					

Figure 5: Blinded PK data from vendor where values are left as blank

Contents in exposure listings also require additional careful handling due to their unblinding potential. Since treatments were dummy data in open session reports, in our case, the blinded team uniformly presented planned dosing details for all participants, regardless of treatment. Conversely, IDAG modified these dosing columns in closed session reports to accurately represent actual dosing—specifically setting placebo patient doses to zero—clearly reflecting true dosing information (Figure 6).

Listing 16.2.5.1
Study Drug Administration

Cohort	Treatment Group	Participant	Period	Visit	Study drug administered?/ If not, specify the reason	Dosing Admin. Date: Time/Day[1]	Planned Dose Level (mg)[2]	Dose Conc. (mg/mL)[2]	Total Volume Admin. (mL)/ Reason for Partial Volume	Dose Admin. (mg)[2]
Cohort 1	Dummy - Group A	1000-0007	DB	DAY 1	Yes	2024-09-27:10:52/1	45	30	10	45
	Dummy - Group B	1000-0002	DB	DAY 1	Yes	2024-08-15:10:03/1	45	30	10	45
		1000-0009	DB	DAY 1	Yes	2024-12-09:11:35/1	45	30	10	45
		1000-0011	DB	DAY 1	Yes	2025-01-10:11:42/1	45	30	10	45

Admin=administrated/administration; Conc=concentration
[1] Study day relative to the first dose of study medication in the double-blind (DB) period.
[2] Planned Dose Level, Dose Concentration, and Dose Administered are assumed as listed (45 mg, 30 mg/mL, 45 mg) to maintain blind.

Figure 6: Blinded exposure listing where 'Planned Dose Level', 'Dose Concentration', and 'Dose Administered' are displayed as planned for all patients. regardless of treatment.

Furthermore, in our DMC process, distinctive headers or cover pages explicitly identifying open session reports (blinded) and closed session reports (unblinded) were utilized to prevent confusion (Figure 7).

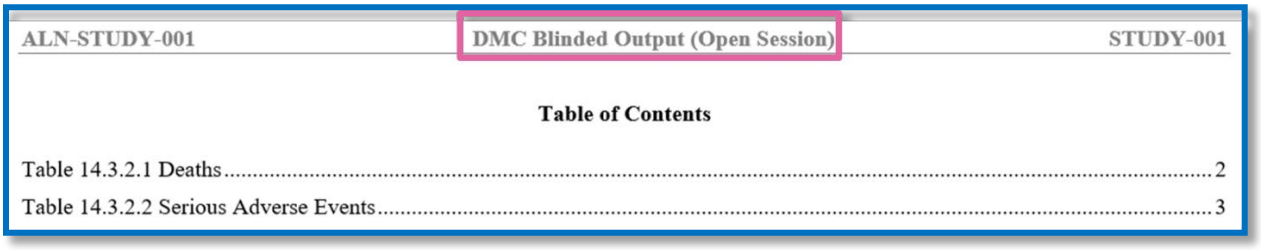

Figure 7: Blind final output indicating this document is for DMC open session

CONCLUSION

Implementing an in-house DMC at our organization required navigating some challenges, notably maintaining a robust separation between blinded and unblinded processes while ensuring efficient communication and seamless collaboration between teams. To overcome these challenges, we established regular cross-functional meetings and utilized dry runs to refine programming and reporting processes.

Throughout the establishment of our internal DMC, several best practices were identified and implemented successfully. Utilizing dynamic, defensively programmed code significantly enhanced our capability to rapidly adapt to changes and detect potential issues early in the process. Comprehensive and clear documentation ensured transparency and reproducibility at each step, facilitating smoother transitions between the blinded and IDAG teams.

Our experience underscores the effectiveness of integrating blinded and unblinded programming within a clearly defined internal structure. This integrated approach has not only met regulatory expectations but has also improved operational efficiency, reduced timelines, and streamlined resource allocation. Ultimately, the in-house DMC model established demonstrates a viable, effective strategy for managing non-registrational clinical trials, reinforcing data integrity, enhancing productivity, and providing a scalable framework for future clinical trial activities.

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CONTACT INFORMATION

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

Lingjiao Qi,
Alnylam Pharmaceuticals,
9193603585
lqi@alnylam.com

Amanda Plaisted,
Alnylam Pharmaceuticals,
6176824160
aplaisted@alnylam.com

Sreedhar Bodepudi,
Alnylam Pharmaceuticals,
6177044749
sbodepudi@alnylam.com