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Finding the Right Balance – Data Management Surveillance in a Fully Outsourced Partnership Model

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ABSTRACT

Merck Healthcare runs the majority of its global clinical studies in an end-to-end model with partner Contract Research Organizations (CROs), who independently conduct the operational part of the study according to a partnership manual, while the Sponsor role is primarily the oversight of the activities. Although our collaboration model is called 'a partnership', ICH-GCP clearly states that the Sponsor is ultimately responsible for the quality of the study and, therefore, also for the quality of the data collected. This paper illustrates how Merck Healthcare performs its oversight duties within the Clinical Data Sciences department (referred to in this paper as Data Management). It will highlight the tools and checks that have been developed, how they are used to continuously check the data for consistency and cleanliness and how findings are communicated to ensure that the trial is meeting, or exceeding, the defined cross-functional expectations with regards to data quality, timeliness and inspection-readiness.

INTRODUCTION

According to ICH-GCP, the Sponsor is responsible for the quality of the study, even if large parts of the study are handed over to a CRO. In Merck Healthcare's fully outsourced partnership model, the CRO is responsible for the operational execution of the clinical studies and Merck Healthcare is mainly responsible for oversight tasks. The oversight takes place during the full life cycle of a study – from Study Setup, through Study Conduct to Study Reporting & Closure. A high-level overview of the process is shown in Figure 1.

Based on a Partnership Manual, which describes the interface processes between the Sponsor and the CRO, different tools were developed to continuously check the data of the clinical trial for completeness and consistency. The tools are used both internally in the Data Management (DM) department for quality control and cross-functionally for joint data checks with interface departments such as Biostatistics or the Patient Safety department. On top of the internally developed quality checks and regular internal cross-functional meetings to detect and address trends in the conduct of the study and the collection of data, there are also additional tools in place that are provided by the CRO to help the study team and particularly the Sponsor Data Manager (SPDM) to perform their oversight duties.

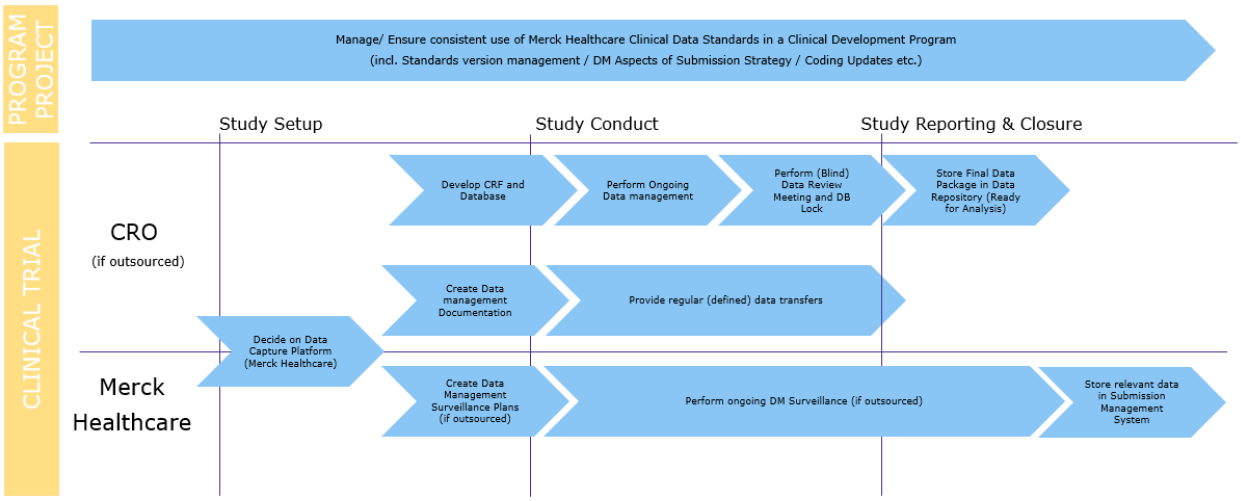

Figure 1: High-level process overview

The SPDMs need to perform several activities in order to fulfill their oversight duties at the different stages of the study lifecycle. Such activities include, but are not limited to, ensure that the electronic Case Report Form (eCRF) set-up follows Merck Healthcare's data collection standards, perform data quality and consistency checks, review Protocol Deviations (PDs) and the electronic Trial Master File (eTMF), check subject PDF files for submission readiness, as well as checking standard metrics to ensure that the DM milestones and deliverables are achieved in line with time, cost and quality expectations. This also includes alignment with different stakeholders internally, as well as with the CRO and external data providers, from the start of the study until the end of the project. To ease the work and support the SPDMs, a variety of tools have been developed internally, as well as by the CRO, that can be used at different stages during the study lifecycle.

The structure of this paper will follow the life cycle of a study and is divided into three sections. The first section will cover the Study Setup phase. The second section will combine the Study Conduct and Study Reporting & Closure phases as the activities during these phases are overlapping. The third section will highlight the challenges experienced and a few first ideas how to address some of them.

STUDY SETUP

TRIAL OVERSIGHT PLAN (TOP)

The beginning of a new study is also the beginning of the oversight activities. At this point, the Trial Oversight Plan (TOP) is developed. The TOP is the aligned oversight plan for the Sponsor and is created by the Sponsor Clinical Trial Lead (CTL) with input from all involved functions regarding their strategic oversight approach. The objective of the TOP is to ensure that the study related materials, data, products, equipment and services that comprise the trial consistently meet the company requirements, that these activities and deliverables are in compliance with ICH-GCP and applicable regulations; and achieve the defined levels of quality, timeliness and cost, as well as ensure inspection readiness.

DATA MANAGEMENT VENDOR SURVEILLANCE PLAN (DM-VSP)

Based on the TOP, the individual Sponsor functions create function specific surveillance plans, which for Data Management is called the Data Management Vendor Surveillance Plan (DM-VSP). The DM-VSP describes the planned surveillance activities to verify that the CRO is meeting the Sponsor expectations regarding quality and timeliness. It specifies the different CRO tasks (e.g. eCRF development), the surveillance owner (e.g. SPDM) and surveillance method (e.g. review), the activities that are performed by the surveillance owner (mainly the SPDM) (e.g. review eCRF and provide comments), the frequency/trigger of the different surveillance tasks (e.g. on initial version and all amended versions), as well as the associated expectations (e.g. eCRF must match protocol requirements and follow current Sponsor General Data Standards), and finally the documentation of the performed surveillance (e.g. eCRF review log stored in Sponsor Clinical Data Repository). The level of surveillance will be defined by the SPDM in collaboration with the Study Team and can be adjusted depending on different parameters (e.g. the type of study, the stage of the study (set-up, conduct, analysis/reporting), the previous experience with the CRO etc.).

INTEGRATED DATA REVIEW PLAN (IDRP)

The Integrated Data Review Plan (IDRP) is a result of a data quality risk assessment process (as mandated by ICH E6 (R2) Addendum "Section 5: Sponsor Responsibilities"). It is an overarching plan that references multiple operational plans from the involved functions and defines the cross-functional data review and cleaning (see Figure 2). It is intended to be used to identify, assess, control, communicate and review the risks associated with the clinical study during its lifecycle to provide quality data fit for purpose. The aim of the IDRP is threefold: (1) it defines the study specific Key Data Points and possible risks with these data; (2) it supports the detection of possible failures, i.e. defining the cleaning strategy for each Key Data Point in order to control the associated risks and (3) it reduces redundancies in the cleaning process and ensures team alignment on what is considered critical. The Key Data Points are defined by the Study Team and approved by the Biostatistician and the Medical Advisor and can be grouped in one of the following categories: (1) data that may impact the assessment of the primary and/or secondary objectives of the study; (2) data that can impact the assessment of patients' safety; (3) other data deemed of special relevance by the Study Team.

Figure 2: Cross-reference from IDRP to functional operational plans

The stakeholders involved in the setup and review process of the IDRP are representatives of the functions that are involved with the design, planning, execution, analysis, and reporting of clinical studies (e.g. Data Management, Biostatistics, Study Management, Clinical/Medical, Safety, Lab/Analytics etc.). The setup starts early in the study lifecycle with a first draft being produced soon after the final draft protocol. As well as the defined Key Data Points, the plan also specifies the associated failure/risk with a probability, severity and criticality rating for these failures/risks, as well as risk mitigation actions, the responsible team to mitigate the risk and a reference to the functional study plans which include more detailed risk mitigation actions (for an excerpt, see Figure 3). Once the protocol is final, the list of key items must be completed and the IDRP is released prior to First Subject First Visit (FSFV). The review of the IDRP is done on a regular basis in order to adapt it according to the study needs (e.g. in case of Protocol Amendments that have an impact on the Key Data Points).

ID. No.	Data Point	eCRF form/ External vendor	Description of the failure/risk	Probability of Failure (1-3)	Severity of Failure (1-3)	Risk Criticality	Risk Mitigation Actions	DM	Medical	Safety	CRA	Stats	Vendor	Tool / Source of data	Study Plan
1	Assessment of Response to Treatment (based on RECIST 1.1)	SOLD/EOR/ IRRC	Wrong EOR or target lesions calculation (sum of longest diameters for RECIST, modified irRC)	3	3	9	Queries raised by DM to capture wrong assessments Assessments reviewed by Medical	X	X					eCRF	Validation Specifications (e.g. Edit Checks) Medical Review & Supervision plan
2	Assessment of Response to Treatment (based on RECIST 1.1)	TMTL	Error when entering measures in eCRF (entry of longest diameters/short axis)	1	3	3	Queries raised by DM to capture wrong assessments Assessments reviewed by Medical	X	X					eCRF	Validation Specifications (e.g. Edit Checks) Medical Review & Supervision plan

Figure 3: Excerpt of IDRP

The benefits of the IDRP include a common understanding of quality expectations at different study milestones, using only one central document referencing all cross functional cleaning steps that are aligned between the different stakeholders to avoid double reviews. It focusses on critical variables impacting study endpoints and is also used as the basis to define the monitoring strategy. In case a risk-based monitoring approach is used, the IDRP also helps to identify the sites with the highest associated risks and to evaluate the frequency of the monitoring visits to be performed for these sites.

STUDY CONDUCT / REPORTING & CLOSURE

QUALITY EXPECTATIONS

Once the eCRF is live and subject enrollment starts, the ongoing DM surveillance focusses on continuously checking the data of the study for completeness and consistency, as well as detecting trends in the conduct of the study and the collection of the data. During the course of the study there will be different deliveries of data for different purposes. In general, ongoing data cleaning of the data is expected to be in place to provide data fit for the purpose of the respective study milestones. However, depending on the exact purpose of the data, the minimum level of cleaning required has been defined differently (e.g. for a Safety Monitoring Committee (SMC) etc.). For partial locks intended for primary analysis and for final locks, the quality should be ready for submission, i.e. the submission of the data and supporting documentation should not lead to a rejection by the competent authorities (e.g. FDA). Quality metrics should be in place to measure the level of data quality and completeness on an ongoing basis from the start of the study.

DM STATUS REPORTS/METRICS – CLEAN PATIENT TRACKER (CPT) – DATA HEALTH REPORT (DHR)

A standard set of reports and metrics has been developed to ensure consistent reporting across studies, with each individual report tracking the status at the individual study level.

The standardized DM status report is a template that is applicable for all Merck Healthcare studies and includes high level metrics on the most critical items to enable ongoing study status surveillance for items impacting the trial and the trial quality. In order to ensure consistency across all studies and to keep manual work to a minimum, the metrics reports are programmed by the CRO. The standard metrics support a common understanding of trends and potential issues between Merck Healthcare and the CRO and, as tracking is done over time, they allow an early detection of trends or issues in data collection / cleaning, including any underlying processes. Standards metrics are divided into the following categories:

- Enrollment status
- Data completeness
- Laboratory Normal Ranges (e.g. missing/clean LNRs)
- Data cleaning
- Source Data Verification (SDV) status
- Medical review
- Coding
- Serious Adverse Events (SAE) reconciliation

The DM status report cumulatively captures the updated figures from each run, in order to track progress over time. It is also used as a communication tool between the SPDM and the CRO DM counterpart for their regular calls.

The CPT provides a full set of information per patient, enabling the monitoring of cross-functional data collection and cleaning activities. It also allows to determine if a subject is clean or not (based on eCRF and non-eCRF issues). The CPT is used internally by the CRO to define actions about cleaning across functions/third party vendors and is shared with the SPDM at a pre-defined frequency, as agreed on during the set-up of the study.

The DHR provides general information about the operational performance of the study in order to identify potential risks that may lead to insufficient quality at certain milestones within the study. It is a standardized set of slides prepared by the CRO, incorporating status reports on DM related critical items, including historical data, that allow projections to estimate data base lock readiness at a given timepoint. The DHR is based on the CPT to allow the tracking and surveillance of the cleaning status at a site, country and study level and is used as a source for regular functional and cross-functional reviews and follow-up. It comprises of an extensive set of different items, such as study milestones, patient status, risk and mitigations, overall cleaning including database cleanliness, missing pages,

SDV status, outstanding queries including breakdown by function, external data reconciliation and completeness status, QOL completion rates, SAE reconciliation and Medical review status as well as cleaning status of completed subjects and casebook signature status that should be presented as regular DM status update during study team meeting calls. Due to the comprehensive number of metrics the SPDM and the CRO DM counterpart perform a functional review of the DHR and align on key issues that need to be flagged and presented in depth during the study team meeting calls. In addition to the DHR slide deck provided by the CRO, Merck Healthcare also runs their own DHR internally in a data visualization tool (Spotfire ®), which cover multiple areas of interest, such as the verification of the monitoring strategy.

SDTM REVIEW

It is expected that all Study Data Tabulation Model (SDTM) annotated Case Record Forms (aCRFs) and SDTM data sets provided for a clinical trial will follow the Sponsor data model as well as the Sponsor SDTM Standards, which are both based on the Clinical Data Interchange Standards Consortium (CDISC). In order to assist the SPDMs in carrying out some of their review tasks, different tools have been developed internally, e.g. a Pinnacle 21 review template, that assesses the criticality of issues found and provides instructions how to best address those issues. For structural SDTM issues that are not detected by the standard Pinnacle 21 checks, a set of Structure Quality Checks (SQSP) have been developed internally and are being currently rolled out on the first studies. All findings are shared with the CRO SDTM team in a consolidated issue log that is centrally stored on a Microsoft SharePoint ® folder. This allows all involved functions to add and respond to SDTM findings. Any uncertainties regarding comments are addressed in a meeting between the SPDM and the CRO SDTM team with the help of the Sponsor SDTM expert, if needed.

DATA QUALITY SURVEILLANCE PLAN (DQSP) – CENTRALIZED QUALITY REPORTS (CQR)

The delivered SDTM packages are used by the SPDM to continuously review the data of the clinical studies for meaningfulness and consistency by running the checks contained in a study-specific Data Quality Surveillance Plan. The DQSP is a document that defines what kind of independently developed and programmed standard and study-specific checks will be performed on the delivered pre-cleaned SDTM data in order to check the level of data quality that has been achieved. It is developed and applied by the SPDM with input from the Sponsor Medical Responsible and other functions as applicable (e.g. Biostatistics, PK/Biomarker representatives etc.). The DQSP focuses on overseeing the quality of key data items and is not intended to repeat the edit checks applied by the CRO for data cleaning.

The DQSP-Checks (running in the Sponsor Clinical Data Repository) are conducted on a regular basis and can be grouped into three categories:

- checks to identify general issues in the data
  - e.g. ‘End date is before Start date’, ‘Adverse Event is indicated as serious adverse event but none of the serious criteria have been ticked’
- checks that need manual review of the SPDM to assess if the detected issue is confirmed
  - e.g. date of collection of archived tumor samples can be before Informed Consent vs. Treatment administration date is before Informed Consent
- checks that should be forwarded to the Sponsor Medical Responsible
  - e.g. ‘Tumor size measurements to check they are physiologically possible’

The SPDM aligns with the Sponsor Medical Responsible and other functions as needed on the detected deficiencies and summarizes the findings that need to be clarified. The consolidated comments are sent to the CRO DM counterpart or to the CRO SDTM team (in case of an SDTM mapping error in the datasets). The process is displayed in Figure 4.

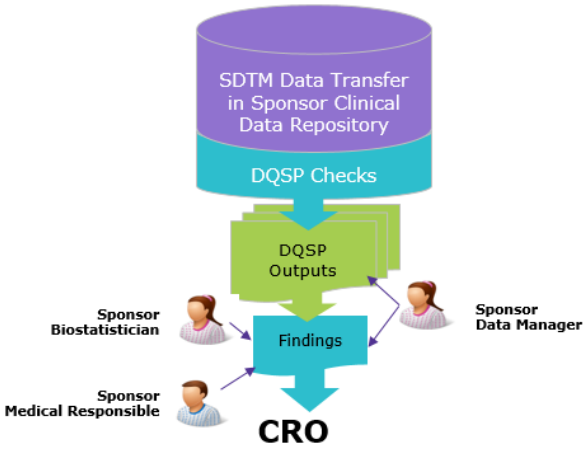

Figure 4: DQSP process

As part of the comments process, the SPDM always requests the CRO to provide an action plan with appropriate corrective measures to ensure the problems do not re-occur. This also includes associated timelines for implementation of the corrective measure(s) (e.g. to add an Edit check and not just raising a manual query). Together with the output files an error rate is calculated that is based on the standard checks only. The expectation is that the error rate will go down over the course of the study, as the CRO resolves the underlying issues. However, the error rate could increase again if some new type of data will become available. Close to the final database lock, the error rate should go down to almost zero (only truly unresolvable issues are left). An example of how the error rate can change over time is displayed in Figure 5.

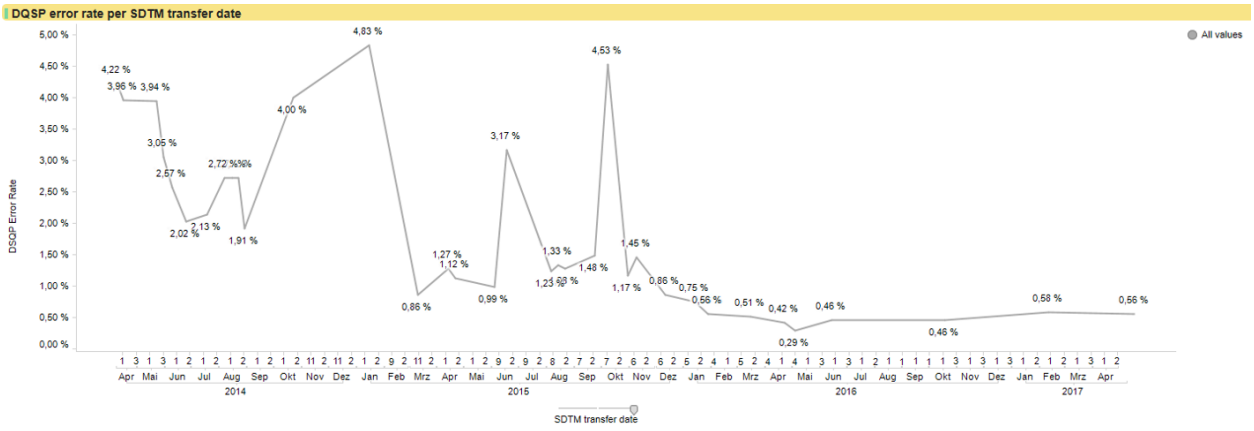

Figure 5: Example of DQSP error rate over time

Centralized Quality Reports (CQRs) – visual reports to detect site quality and other signals/trends – can be run in conjunction with the DQSP. These reports are mainly bar charts that are used by the SPDMs to check, on a cross-site basis, such things as subject disposition, primary discontinuation reasons, average number of Adverse Events per Month per Subject, Laboratory, Vital Signs and ECG Parameters in SI units. The different outputs are used as a basis for discussions with the Trial Team (an example is displayed in Figure 6).

Figure 6: Example of CQR outputs

DATA DRIVEN OVERSIGHT (DDO)

The Data Driven Oversight (DDO) meeting is a Sponsor internal monthly meeting between the CTL, the Clinical Site Lead (CSL) and the SPDM to ensure appropriate conduct of the outsourced studies and the quality of the data. In preparation for the meeting, a joint review of site performance and quality for certain key parameters is performed by utilizing standardized reports and visualizations. Any sites that are identified as outliers, according to pre-specified thresholds (signaled by traffic lights), are discussed during the meeting and all stakeholders mutually agree upon a strategic and targeted oversight action plan (e.g. recommend targeted CSL visit for specific sites). Depending on the status of the study, the following data will be reviewed:

- site start up information (e.g. sites delayed in startup)
- enrollment information (e.g. outliers - low/high enrollers)
- protocol deviations (e.g. outliers - high/low number of PDs)
- data entry lag
- query resolution lag
- safety data (e.g. number and type of reported events)
- issue management information (e.g. open action items)

The DDO can help to identify possible systematic errors and to implement “proactive” corrective actions, as well as to identify trends that might be useful to share with the whole drug development program. An example of a visualization to check for missing pages which are outstanding for more than 10 days, is displayed in Figure 7.

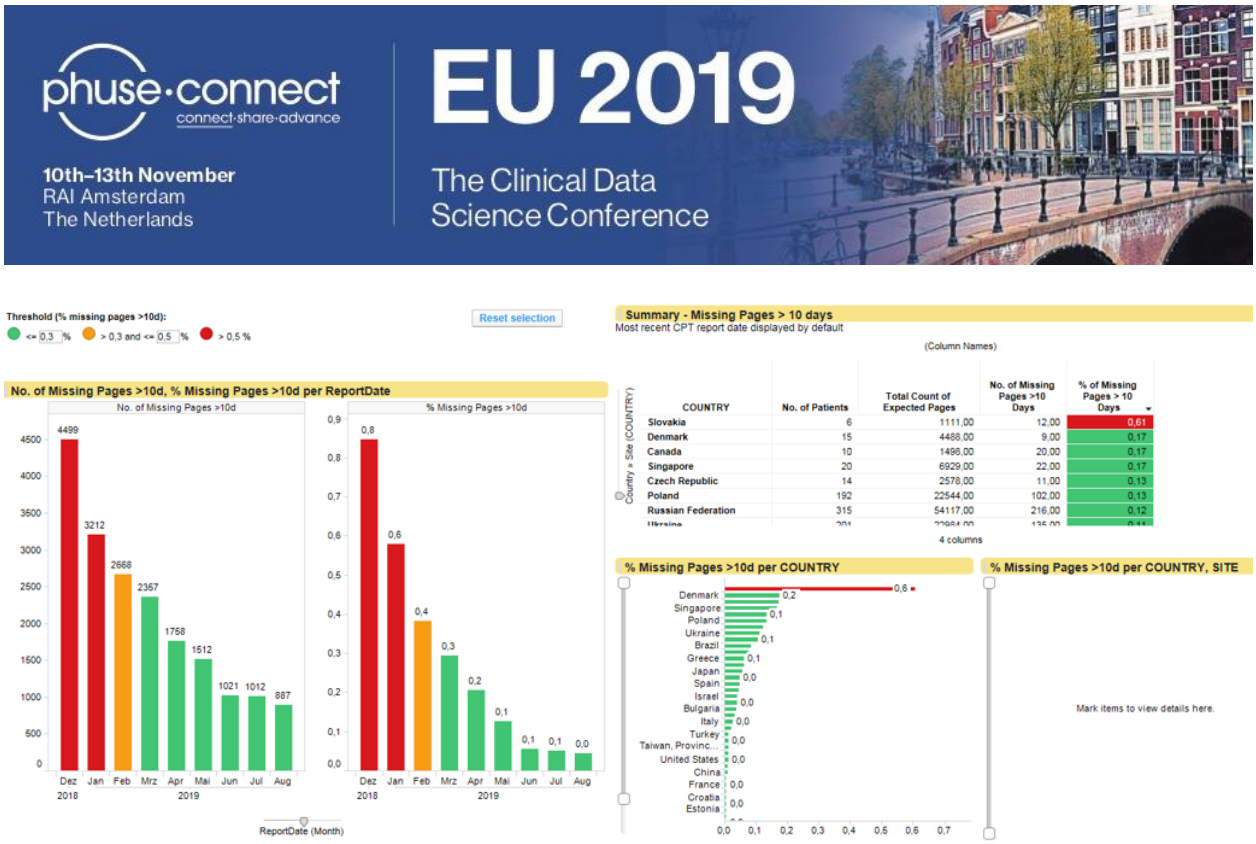

Figure 7: Example of visualization to check for missing pages outstanding >10 days

PERIODIC DATA REVIEW MEETING (PDRM)

Throughout the conduct of the study and up to the final database lock, regular Periodic Data Review Meetings (PDRMs) are conducted (see Figure 8). The PDRM is a joint cross-functional meeting between the Sponsor and the CRO to assess the completeness and quality of all study related data, as defined in the IDRP, including the data status of discontinued subjects, and if applicable, trigger corresponding actions regarding timely resolution of the identified issues. A detailed PDRM Report is prepared by the CRO DM counterpart with support of other functions and distributed to the study team before the PDRM. This report will contain information on:

- baseline characteristics (e.g. number of subjects included; subject disposition)
- safety and protocol compliance (e.g. SAE reconciliation; status of protocol deviation review)
- quality and compliance (e.g. all data entered and sufficiently clean – missing/incomplete pages; SDV status; outstanding queries; external data reconciliation status)

At the end of the meeting, the joint team will decide if the quality expectations have been met (or not), an action log will be set-up and agreed on and subsequent timelines will be discussed. The benefits of the PDRM include:

- joint team review, quality and risk assessment with one action plan with further follow-up until resolution
- verification that all cleaning activities are conducted as planned (external data, medical review, PD handling, coding review/surveillance, SAE review/Surveillance)
- database lock timelines reduced for critical database locks (reduced data entry, data cleaning and SDV backlog; ongoing external data reconciliation; majority of discontinued subjects already locked)

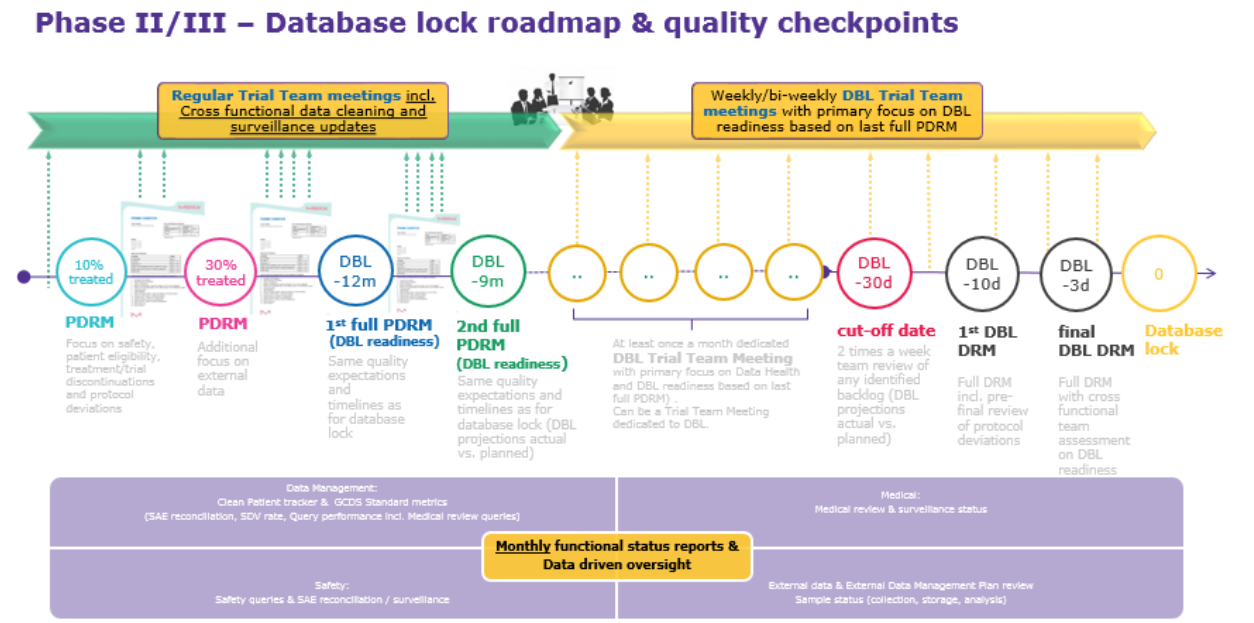

Figure 8: Example Database lock roadmap & quality checkpoints

FINAL (BLINDED) DATA REVIEW MEETING (BDRM)

The purpose of this meeting is to discuss and resolve any outstanding issues and to document any agreed irresolvable issues in the Data Handling Report, as well as to provide the green light for the (partial) database lock. The (B)DRM should include representatives from DM, Medical, Safety, Biostatistics, Clinical and the Project Lead and the respective counterparts from the CRO. During the meeting, at least the following topics are discussed: remaining outstanding queries review, remaining missing data, non-eCRF data reconciliation status, protocol deviations summary, SAE reconciliation status, medical review status and coding status.

CHALLENGES

FINDING THE RIGHT BALANCE

From a SPDMs point of view, a definitive challenge is to find the right balance between micro-management and functional surveillance of the CRO. An example would be the review of the DQSP. Some SPDMs check every single line in the output and provide comments accordingly, whereas other SPDMs only perform some high-level spot checks to address the underlying issue without getting into too much detail. But where does micro-management start and what does a term like “spot checks only” really mean? There is currently no clear definition to follow. In fact, how this is handled varies significantly from SPDM to SPDM and mainly depends on:

- the experience of the SPDM and the CRO DM counterpart
- the duration of the collaboration and amount of turn-over in study team members
- the point in time within the study (e.g. ongoing surveillance or checking for a specific milestone delivery)
- the quality of the previous deliveries

Having no clear guidance in place also makes it harder to onboard new colleagues. They will need to find their own ‘comfort level’ of how detailed they perform their reviews and oversight. New colleagues can be supported by performing the activity (e.g. eTMF review, DQSP outputs review) together with an experienced SPDM in the beginning or by asking for their support in providing suggestions, based on experience, on what to focus on during what phase in the study. Within the DM department, regular short cross-site calls are offered, where colleagues can raise questions, discuss problems or provide tips and tricks to each other. As already mentioned above, finding the right balance also depends on the previously delivered quality. The challenge is to find the specific points that trigger more in-depth reviews and activities. A possibility might be the definition of fixed quality gates regarding data content (e.g. for the DQSP error rate), SDTM structure (e.g. Pinnacle 21 and SQSP findings) as well as operational data (e.g.

reconciliation rates). Not meeting these quality gates could trigger the request to setup a definite action plan on the CRO side and additional review activities on Sponsor side or even an escalation to a higher Management Committee, if the issues do not decrease or occur repeatedly.

ALIGNMENT

As the CRO is performing their tasks according to their own Standard Operating Procedures (SOPs) and at the same time according to the earlier mentioned Partnership Manual, this sometimes leads to different approaches on how to handle certain tasks, either operationally or from a time perspective. For example, the CRO SOP may dictate that a certain review step can only start once the preceding activity is finalized, whereas the Partnership Manual plans for a parallel review. There could also be a mismatch of responsibilities, where the CRO working instruction only foresees an internal review whereas the Partnership Manual requests that the Sponsor reviews as well. In addition, work is not always done according to the shared concept. For example, the DQSP is not intended to be a part of the CRO data cleaning process. Instead the CRO should use the feedback provided by the SPDM to work on the root cause and to take appropriate corrective measures to ensure the problems do not re-occur. However, in reality the DQSP listings / sponsor identified errors are part of the CRO's manual data cleaning process. Therefore, it is currently being discussed to implement a new process, where instead of providing full DQSP listings, the SPDMs will select a limited number of identified issues per listing and only send these to the CRO, along with an action plan. Surveillance by the SPDM would then only be performed on error rates and the review of the action plan on all issues addressed to the CRO. In subsequent runs, any DQSP listing that had not been reviewed before (i.e. no data available in previous runs and/or 0 issues identified before and therefore no listing produced) would still need to be checked by the SPDM.

These are only a few examples which highlight another important challenge of finding the right balance of surveillance - the alignment of the processes. This needs to take place within the CRO (with all involved functions) and at the same time on the Sponsor side, and finally also between both companies. In order to address these challenges for the Data Management department, there are half-yearly face-to-face cross-company alignment meetings at the DM Management level (also in close cooperation with interface departments like Biostatistics) to co-develop and implement unique partnership processes.

COMMUNICATION

Once an alignment across companies is reached, there is the next challenge - how can these decisions be spread into the respective teams, on the CRO side as well as the Sponsor side? Decisions are taken at different levels in the Partnership – strategic decisions on a Partnership level, process decisions on a functional level and operational decisions on a study level – so there are different target audiences that need to be informed individually. Therefore, it needs to be ensured that decisions that are, for example, taken during the face-to-face alignment meetings are shared down the line with the respective functions and with the individual team members in a consistent and timely manner.

On a study level, an essential part of the oversight activities and daily work is ongoing communication and an open exchange with different stakeholders internally, as well as with the CRO representatives and external vendors. Most of the communication is conducted via email, but there are also regular meetings, either virtual or face-to-face. There are different levels of meetings, such as solely internal meetings, e.g. the DDO calls, to check for any trends on site/country level and for overall alignment. There are also regular calls between the SPDM and the CRO DM counterpart and there are regular cross-functional and cross-company team meetings with all involved stakeholders in the study. Of course, there are plenty of other meetings with different compositions of participants depending on the topics to be discussed and to be agreed on. While there is an abundance of possibilities for exchange between the different stakeholders, this also proves a challenge in terms of how to spread decisions and information to the intended audience, both at the CRO/vendors as well as internally.

RESOURCES

Finally, the retention of dedicated resources proves a challenge. Intensive training is needed on the Merck Healthcare processes and the Partnership Manual, as the tasks and steps for conducting a study, according to Merck Healthcare standards, are very specific. In order to profit from synergies across studies, it is important to increase team stability at a program level. Having well trained staff in place, who are dedicated to the partnership, will allow to cover for unforeseen shortages (e.g. long-term sick leave) or for flexible assignment of resources to projects (e.g. in case of urgent time-critical activities for submissions or other important milestones).

CONCLUSION

A key principle of the fully outsourced partnership model is that the CRO will, with limited exceptions, use its own systems, processes, and procedures and qualified vendors in providing services. This promotes efficiency and quality of delivery by allowing the CRO to operate in the ways in which they are most familiar, and on which they have established training and oversight programs. For this partnership to work efficiently, an excellent cross-functional and cross-company collaboration is key and expectations need to be clarified upfront. This model allows Merck Healthcare and its preferred partner CROs to work hand-in-hand and to continue to grow together and to be prepared for the challenges of the future regarding data collection and handling in a fast-evolving market. Finally, it needs to be emphasized again that, although this partnership is based on trust and long-term experience, there still needs to be a certain level of control, because Merck Healthcare as the Sponsor retains overall ownership and accountability and is ultimately responsible for the quality of the study and, therefore from a Data Management perspective, also for the quality of the data collected.

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RECOMMENDED READING

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