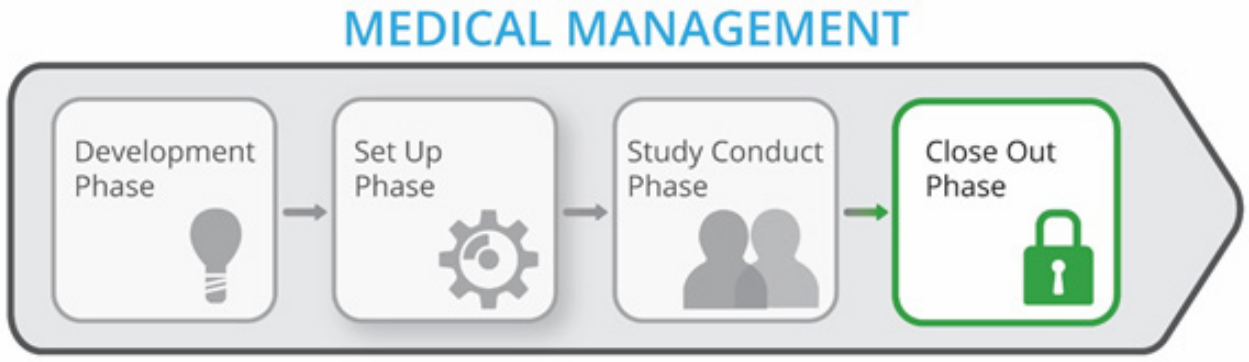
Medical Management in Clinical Trials: A Roadmap to Operational Excellence (Part 4 – Close-out Phase)

PEER REVIEWED

Being the final feature of this four-part series of medical management of clinical trials, this article will focus on the medical activities during the close-out phase of a clinical study. The close-out phase here refers to the period from last patient out (LPO) till the issuing of the final clinical study report (CSR). As the study conduct operations come towards a conclusion, the routine medical monitoring activities give way to the intense data cleaning, data review and reports development phase. This same set of activities will also be carried out in the event that interim analyses need to be performed at predefined time points of the study. This last phase holds major significance as patient data from the study will be extracted, organised, evaluated and formulated in the CSR, in order to provide a comprehensive presentation of the study results. Insight from the medical monitor (MM) is needed at this critical juncture to generate evaluable data, and to structure the data presentation in such a way as to support the assessment of study objectives. The role of the MM in the close-out phase therefore is pivotal, as medical management and guidance in this final stage is imperative in realising the desired goals of the study.

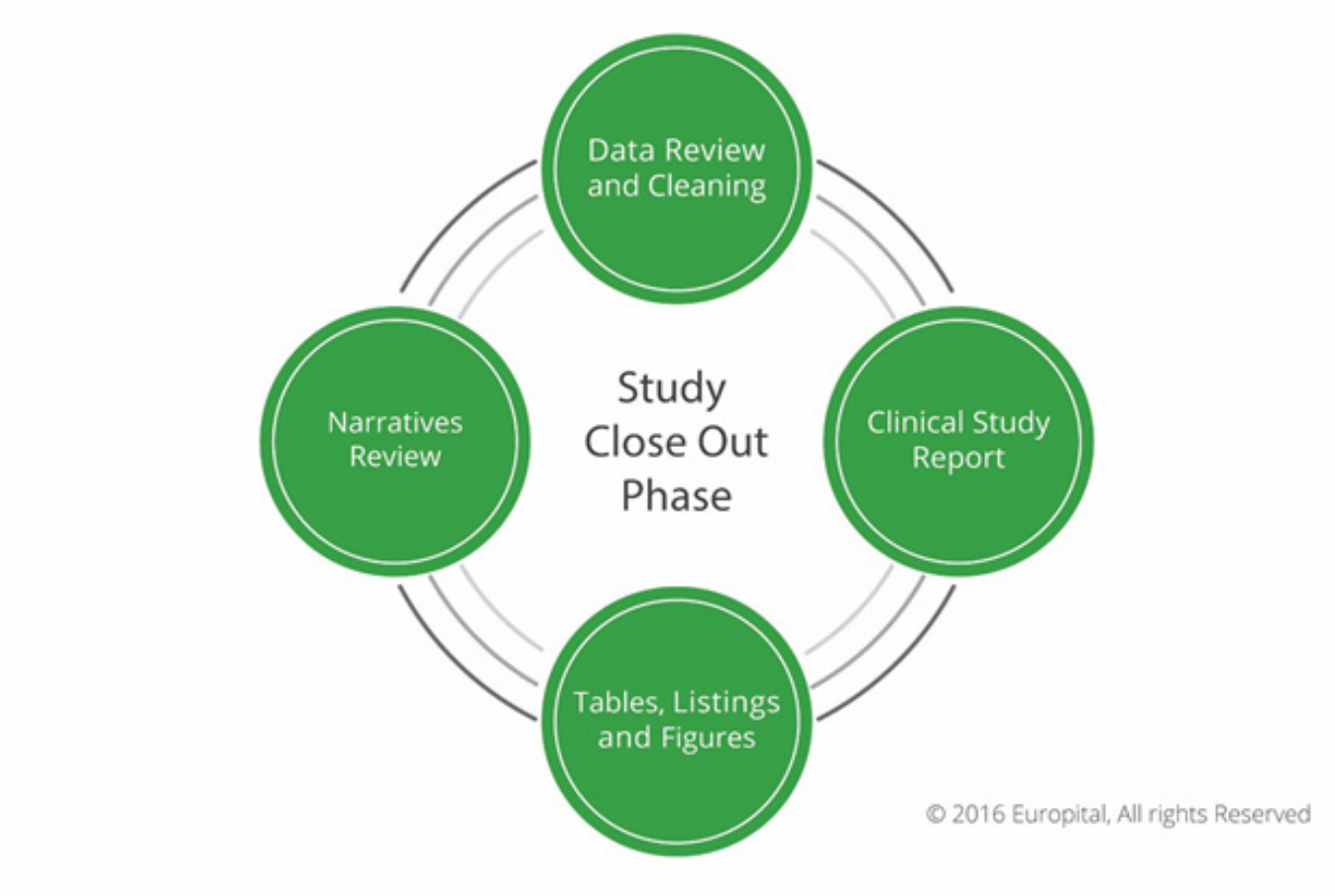
entry in case report form (CRF), last query answered, database lock (DBL), production of data output and, when applicable, closure of sites. The data review activities are intensified to meet the timelines and the methodology of data cleaning and review is followed per the data management plan (DMP) and medical management plan (MMP) established during the study set-up phase. The clinical operations members play an important role in supporting the sites to provide all required data within the CRF, conducting site visits to perform source data verification (SDV) and ensuring that data entry obligations are kept up by the sites. The agreed data listings and patient profiles are generated by data management at the planned data cut-off for clinical database output, generally after the last data entry. The medical review cycle is then started, marked by MM review and query generation by the use of a designated medical query tracker (MQT) that can be circulated within the study team. The number of review cycles depends on the volume and quality of data available at cut-off date. Besides the patient profiles used for in-depth review of individual subject data, aggregate data listings are also utilised. When applicable, the review can also be done



Data Review and Cleaning

After data entry cut-off for all subjects in the study, the MM holds the responsibility to review the presented study data for accuracy, consistency and medical logic. The MM plays a vital role in ensuring that all raised medical queries have been adequately addressed and answered satisfactorily by study sites, and that clarifications, where needed, have been provided.

The timelines for data cleaning and review are agreed between data management, medical and project management teams. This plan should include agreed dates, from the last patient last visit (LPLV) onwards, thereby bringing into line scheduled dates for last data using smart listings that are designed and programmed to capture critical parameters. The smart listing is a customised tool to review specific data sets representing information usually entered in various locations within the CRF such as relevant efficacy, safety or eligibility parameters. This could also be a useful tool to assess consistency and identify any discrepancy between data entered in different electronic platforms. A good example of that would be the randomisation/enrolment data or study drug assignment information entered both in various CRF pages and in the interactive web response system (IRS). Additionally, reconciliation between safety and clinical database is performed, usually by the data manager and the concerned pharmacovigilance (PV)



officer, with any needed medical support provided by the MM. The medical coding of the events and medications are also reviewed by the MM, with reference to the applicable coding conventions. The medical dictionary for regulatory activities (MedDRA) is commonly used for the coding of adverse events and medical history conditions; while the World Health Organization–Anatomical Therapeutic Chemical (WHO-ATC) classification is used for coding the medications. Ambiguous reporting of events or medications is queried and resolved at this stage so that right coding terms are assigned before the safety analyses. Wherever local laboratories are used for the study assessments, the MM provides inputs to harmonise the results across sites during the generation of conversion tables to aid the review. The finalised list of protocol deviations (PDs) is also reviewed by the MM to determine the effect of major deviations on data analysis based on pre-defined study population. When applicable, said deviations are also classified accordingly, to foresee the impact on planned intention-to-treat (ITT) or per-protocol analysis.

Narratives Review

The date of last data entry is approximately a couple of weeks post-LPLV and the process of narrative writing commences parallel to the data cleaning activities, while the finalisation of case narratives is planned so that they can be included in the CSR. The narrative categories required for the study are first established and then all the cases that fall into the selected criteria are extracted in the narrative listings. The narrative listings, along with clinical and safety databases, serve as the reference source for the writers to draft the initial narratives. The MM reviews the narratives and provides comments or queries based on the review outcome. The queries are handled by the DM and operations in a similar pathway as the medical queries issued following data review. When all the narrative queries have been answered by sites and considered closed, the new or changed information is imbibed into the narratives, thereby generating revised narratives, which can then be finalised after a second medical review. Our recommended approach for narratives review is to establish a three-step process of verification, medical review and quality control (QC). The verification step is to ensure the completeness and correctness by cross-checking narratives contents with the source of information in the clinical and/or safety DB. Medical review is performed to confirm the plausibility and medical logic within the narrative content. Finally, a QC by a second medical reviewer stamps the narrative content for finalisation. In a Phase III study where the volume of case narratives can be high, the workflow needs to be planned in advance so that different sets of narratives are phased out to coincide with the data cleaning timelines and the finalised narratives are delivered before CSR drafting. During these reviews, the scientific integrity of the study data should be the underlying objective to govern the actions to be taken for any observation or discrepancy identified by the MM.

Tables, Listings and Figures (TLFs)

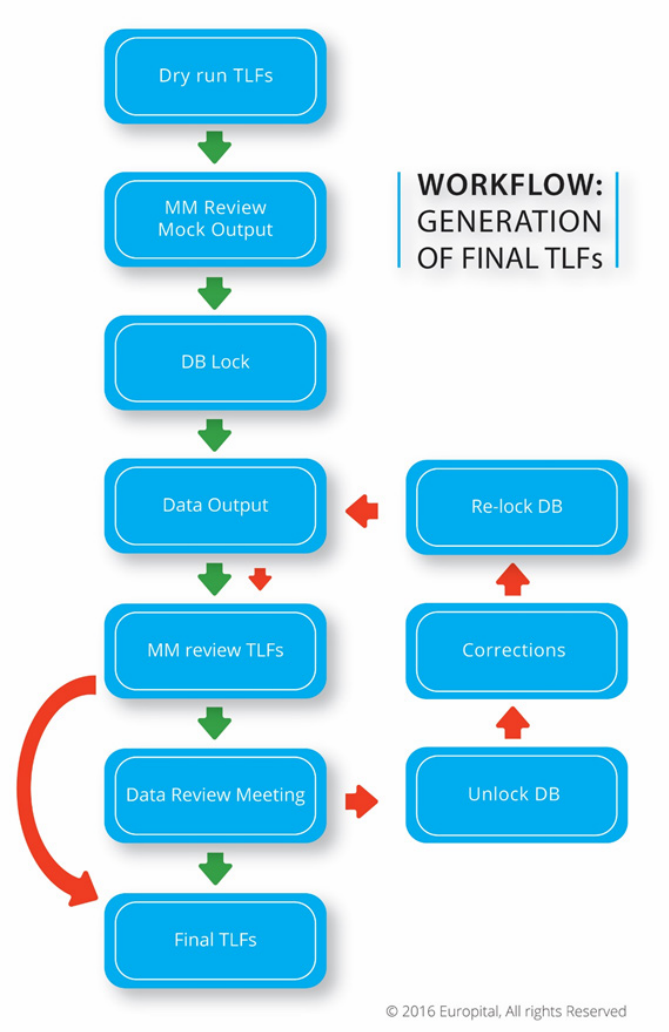
Once the data cleaning measures have been completed,

the DBL takes place and data is transferred to the statistics team in order to generate TLFs as detailed in the statistical analysis plan (SAP). More often than not, the SAP provides drafts for the TLF shells, which are essential for presenting the study findings in a clear and concise manner, and to best interpret study results. Where available therefore, pre-planned TLF shells will be employed for dry runs by the statistical team. Together with the statisticians, a review of the mock output by MM is thereafter conducted to guarantee its conformity to study objectives and endpoints, and, where required, adapt or create additional TLFs, leading to subsequent approval of the TLF shells.

Following the production of the actual data output and its validation by the responsible statistician, the produced TLFs will once again be closely reviewed by the MM. A statistical output comments document may be used by the involved team members to list the review findings by the MM, and the relevant actions taken by the responsible statistician or data manager. A data review meeting (DRM) can be scheduled after review of TLFs to discuss the findings. Where applicable, discrepancies identified will be addressed and the most appropriate course of action will be agreed upon. For minor errors or inconsistencies in the generated output, footnotes might be used in the presentation of the TLFs. It is important to bear in mind, however, that said notes should provide adequate clarifications concerning the issue at hand. Additionally, wherever required, a note to file (NTF) can be documented and referenced to clarify any unclear situations, discrepancies and missing data, among others. Major inconsistencies, on the other hand, present a considerably bigger problem and relevant standard operating procedures (SOPs) or guidelines, when available, should be followed while handling these cases. Major issues will, inevitably, require unlocking of the database for necessary corrections to be made. This is a very crucial step, and needs to be adequately implemented, following laid-down specifications and guidelines in order to maintain data integrity. For the specific issue in question, and when required, the site is responsible for providing needed clarifications or making any necessary corrections. These changes are all tracked and reviewed again by MM to guarantee consistency. Subsequently, the database is locked up again and the TLFs are re-run and analysed if the desired consistency and structure of data sets have been achieved. The MM works closely with the statistician, besides the core team, to finalise the TLFs to allow drafting of the CSR. When applicable, a top line results meeting is scheduled to share available results with the core study and programme management teams to gather inputs on how best the data can be presented within the CSR and/or utilised in subsequent steps of the development programme.

Clinical Study Report (CSR)

The CSR represents a major milestone in the clinical development programme and is a crucial document for any investigational drug or device. The structure and content of the CSR are dictated by the ICH E3 guideline[1], where it is defined as "an integrated report of a study of any therapeutic, prophylactic or diagnostic agent in which the clinical and statistical description, presentations and analyses are provided in a single report, incorporating tables and figures into the main text of the report and in appendices". Once the TLFs and narratives have been finalised, the multidisciplinary team comprising, among others, the medical writer, project manager, MM and responsible statistician, follow the established plan with the associated timelines for the development of the CSR. An established CSR template, where available, would be



used by the medical writer to prepare an initial draft of the CSR that is subsequently distributed for review by the various team members. The MM review should take into consideration the objectives of the study while focusing on the efficacy and safety analyses and the conclusions drawn from the respective data. During review, the MM should pay considerable attention to the various sections of the CSR, including the synopsis, that should ideally provide a concise and comprehensive summary of the study and its results. Additionally, all observations and analyses need to be explained in the discussion section, along with the arguments that justify the conclusions derived from the study data. Background information and relevant literature on competitive products should be incorporated to provide a comparative analysis in the discussion, followed by a brief summary of the efficacy and safety findings outlined in the concluding section. In applicable cases, the MM should keep in mind during the review the position of the current study with respect to the study drug development plan so that the study observations are evaluated as per the overall strategy of the programme. When required, a comments review meeting (CRM) is scheduled where the core study team, including the MM, discuss the review findings, agree on resolutions for conflicting review comments and provide guidance to the writer on the final contents of the CSR. Following the availability of the study results, additional contribution of the responsible MM might be required with regard to the publication plan; this may include review for study abstracts, poster presentations for scientific conventions, or a full manuscript for publication in a scientific journal.

Closing Remarks

Critical inputs are required from the MM during this close-out phase and is demonstrated by the significance of the activities detailed here. Clinical data is the single most pertinent product of a study that serves as the base for the analysis and results interpretation; due diligence therefore is expected during final data review process. Understanding of the design concept, strategic positioning and study objectives and endpoints are essential for performing the MM tasks during this phase. The complexity of clinical trials during drug development is steadily increasing and the MM plays a challenging part in steering the team and the study towards the finish line.

Reference

1. ICH E3: Structure and content of Clinical Study Reports http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

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