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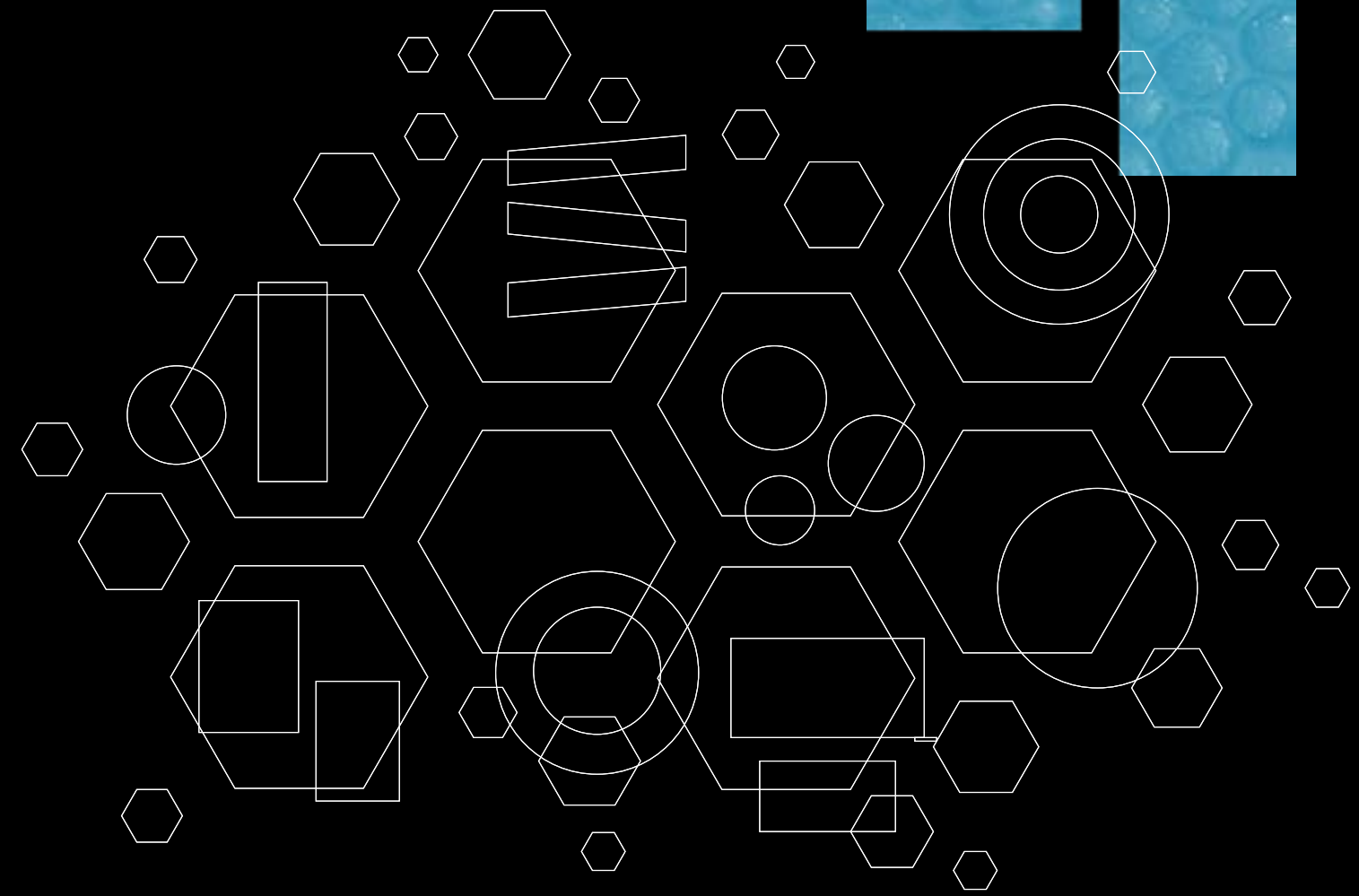
Central Data Monitoring in Clinical Trials



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Central Data Monitoring in Clinical Trials

Introduction and background

The complexity of clinical trials has increased significantly during the last two decades. This led to major challenges for quality assurance and control, in particular for multicentre trials. It became apparent that there is a need to complement conventional monitoring at the study sites (on-site monitoring) by new monitoring approaches.

In 2011, the U.S. Food and Drug Administration (FDA) released a draft guidance (see references for the link to the current version 2013) addressing Risk-Based Monitoring (RBM) and the use of alternative monitoring methods, such as centralised monitoring, which, in combination with conventional on-site monitoring, should enhance quality in clinical trials. To a great part, it is the development and implementation of internet-based databases that led to centralised monitoring gaining more and more importance, also within the realm of RBM approaches. In the revised ICH-GCP guideline E6 (R2), published in 2016, the principle of centralised monitoring was further elaborated on by stating that "*Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data*".

Terminology

According to the FDA guidance, centralised monitoring is "*a remote evaluation carried out by sponsor personnel or representatives (e.g. clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted*". This not only includes reviewing the data accumulating in the study database over the course of the trial but also activities such as (regular or unregular) phone calls with sites to discuss study procedures and enrolment progress, or follow-up on action items of previously conducted on-site visits, as well as reviews of documents received from the study sites (e.g. site delegation logs, investigational product accountability logs, temperature logs, etc.).

ICH-GCP too uses the term centralised monitoring, but, in contrast to the FDA guidance where centralised monitoring includes *all* monitoring not done directly at the study sites, ICH-GCP uses the term to describe monitoring of the data in the study database only: "*Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).*"

These two different uses of the same term may lead to confusion. To make it worse, several other terms, such as remote monitoring, off-site monitoring, or central monitoring, are used inconsistently to describe either all monitoring not done at the study site or parts of that, such as monitoring of the data in the study database or specifically only telephone calls with the study sites to address monitoring issues. Since no official definition exists for any of these additional terms, **we recommend using the term centralised monitoring according to the definition in the FDA guidance to describe all monitoring that is not done at the study site**.

Centralised monitoring, when used according to the definition of ICH-GCP, is the central review of the accumulating data in the study database. We recommend calling this Central Data Monitoring (CDM) to distinguish it from the other centralised monitoring tasks. Of note, when statistical analyses are performed to look for data abnormalities or incongruities (e.g., statistical search for outliers, data trends, or evaluating site performance based on accumulating data), the term central statistical monitoring is often used. Central statistical monitoring is, however, considered an integral part of (properly conducted) central data monitoring. See figure 1 for the terms we recommend using when describing the different monitoring activities.

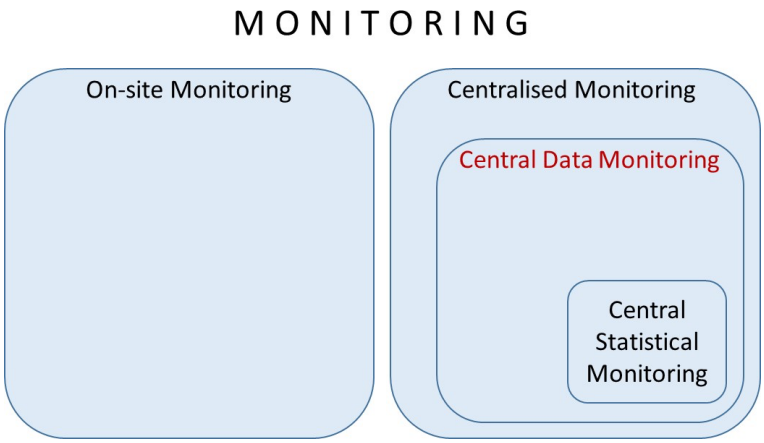

***Figure 1**: Recommended terms to describe monitoring activities*

Central data monitoring is more than just data cleaning

Even though CDM is meanwhile well established in clinical research, the scope and extent of it is not clear among researchers, particularly in the academic setting. CDM is often seen or understood as a mere process of data *cleaning*, i.e., identifying and, if possible, correcting incomplete, inconsistent, and inaccurate data in the database. However, this is not all CDM entails. This data cleaning is certainly an essential and inevitable step in ensuring data quality in preparation for statistical analyses, but an important goal of CDM is to also allow (early) identification of problems and risks which are not directly related to single data entries per se. This may include the monitoring of (Serious) Adverse Event ([S]AE) reporting or trends in data that might affect the safety of the study participants and integrity of the trial. Importantly, CDM does not generally comprise any form of source data verification which would require sites to provide the monitor with copies of medical records, either by allowing the monitor to remotely access the electronic medical record systems, or by sharing computer screens displaying items of the electronic participant file via Skype or other communication software. At least in Switzerland, for data protection reasons, regulators do not allow access to source data for monitors when not at the site, albeit, in light of the COVID-19 public health crisis, this regulatory ban was relaxed at least temporarily.

To allow for efficient CDM, the availability of a GCP compliant, electronic study database must be ensured. Furthermore, CDM can only be done efficiently if the individual study site personnel complete the database in a timely manner. It is the central data monitor's task to oversee the accumulating study data of all sites, especially in multicentre trials. This oversight allows early identification and resolution of potential issues that may not be easily recognised through the conventional method of on-site monitoring.

Implementation of central data monitoring

Similar to on-site monitoring, the scope and extent of CDM is defined in a (central data) monitoring plan. The set-up of this CDM plan is the responsibility of the sponsor. The monitor may draft the CDM plan, but its content must be approved and confirmed by the sponsor. The CDM plan should take into consideration the complexity and expected risks of the study, the planned number of study participants and study sites to be involved, and the total duration of the study. The data fields to be reviewed and the type of checks should be clearly defined. Other aspects that should be defined in the CDM plan include the time points of the data checks to be performed (in case CDM is not meant to proceed continuously during the study) and the frequency of reporting the progress of CDM to the sponsor. Despite all pre-settings, the plan should still allow sufficient flexibility for adaptations following findings during study conduct.

The process of CDM can start as soon as the database is productive and site personnel starts entering data into the database. Typically, the following issues are checked:

1. **Protocol compliance**: Are the required lab values recorded and do they fulfil the eligibility criteria; are study-specific visits performed in the correct time window, etc.?
2. **Participant safety**: Are (S)AEs recorded (by comparing site event rates) and reported in time to the sponsor? Are withdrawal criteria adhered to, etc.?

3. **Primary and secondary outcomes**: Is data required for the outcomes collected and properly recorded in the database? Are there any differences in the outcomes between study sites?
4. **Data completeness**: Are all study visits conducted; are all required assessments and questionings done and is the corresponding data properly recorded in the database? Are there differences in data collection between study sites?
5. **Data consistency**: Are there any inconsistencies or errors in data entry? E.g.: if the question "did any new adverse event occur since the last visit?" is answered with "yes", is there a corresponding event recorded in the database?
6. **Data plausibility**: Is the entered data plausible? E.g.: is the question whether a pregnancy test was performed answered with "yes" for a male participant?

In case of inconsistencies in the recorded data, the central data monitor can pose a question ("Query") within the database, which the site personnel can answer directly within the database. CDM involves intensive communication between the monitor and the study site.

Significance of central data monitoring for risk-based monitoring

As mentioned above, RBM, in terms of continuously assessing risks during trial conduct, relies on CDM to identify potential issues regarding participant safety, data quality, and/or study progress. Therefore, it is essential that the central data monitors oversee the data of all trial participants and study sites in order to identify trends as well as inconsistencies and differences between study sites. Major findings can then trigger targeted measures, such as a visit of the monitor on-site.

Examples of signals and their identifying features:

1. Possible **data fabrication**: Suspected due to the lack of variability or preference of digits[1] in the recorded data across visits of a single subject or across multiple subjects.
2. Problems regarding **site performance**: Sites with a high number of screening failures, withdrawals, or discontinuations; many protocol deviations; a large amount of missing data; a high number of queries or queries remaining unanswered for a long time, or answers are unclear.
3. Warning notice regarding **participant safety**: A site reports an unusual number of (S)AEs (i.e. considerably more or fewer [S]AEs than the average site); subjects are enrolled albeit not meeting all eligibility criteria.
4. Problems regarding **adherence to ethical principles and participant rights**: Study-specific examinations or interventions are performed before informed consent was obtained.

In most cases, such reviews can be performed by exporting the trial data into simple tools like Microsoft Excel. However, for the assessment of more complex issues, it might be necessary to apply statistical methods. Ideally, such complex issues are already identified during the planning of CDM, and the involvement of a trial statistician in the planning and conduct of CDM is thus recommended.

Reporting of central data monitoring findings and progress

While reporting of on-site monitoring findings is a common and established practice in clinical research, the communication of CDM findings is not yet clearly defined. A draft guidance addressing this topic was released by the FDA in March 2019. The guidance recommends that CDM reports contain, among others, "*a summary of the data or activities reviewed, a description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified; a description of any actions taken, to be taken, or recommended*". Such reports should be sent to the sponsor and/or the responsible sponsor staff on a regular basis.

Also, if, in the sense of an RBM approach, findings made by CDM shall be used to trigger other monitoring activities, CDM reports should also be made available to project managers, on-site monitors, and other stakeholders as needed.

[1] When people invent numbers, a commonly found phenomenon is that they tend to use certain end-digits substantially more often than the general pattern of the distribution suggests.

Conclusion

The trend to RBM results in the implementation of alternative monitoring methods with CDM becoming more and more important not only in industry-sponsored trials but also in investigator-initiated trials. CDM is a valuable addition to on-site monitoring and may help reduce the number of (cost-intensive) on-site monitoring visits. However, certain aspects of monitoring, such as source data verification or the important direct contact with the site personnel cannot be covered by CDM. A well-thought-out and well-balanced combination of on-site monitoring, centralised monitoring (including CDM), project and site management, and other sponsor activities are thus essential to achieve a high quality of study data.

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