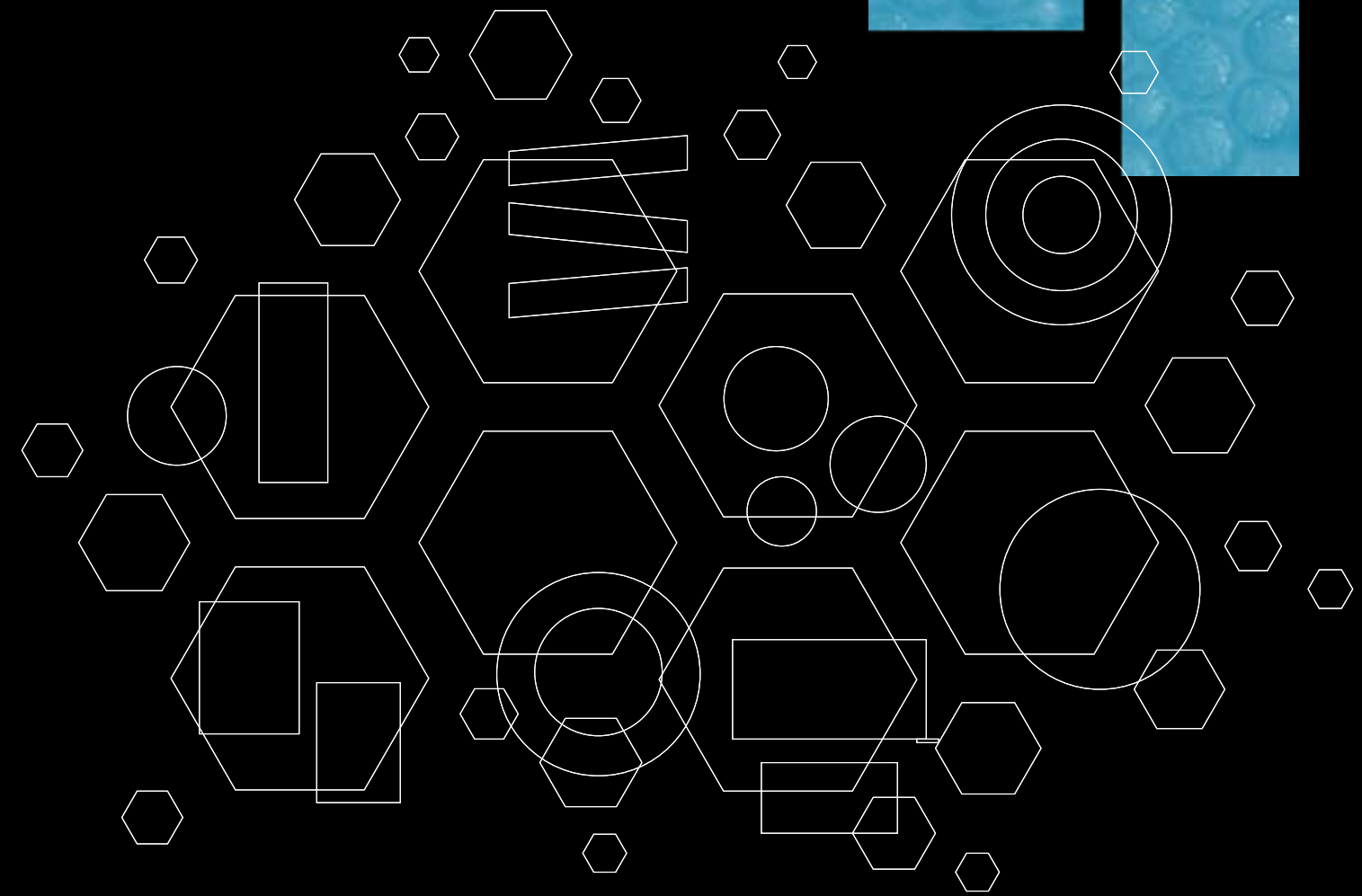
SCTO PLATFORMS

Monitoring in Non-Interventional Human Research Projects

Position Paper



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Position paper: Monitoring in Non-Interventional Human Research Projects

Introduction

This position paper discusses and provides recommendations regarding the implementation of monitoring strategies for non-interventional human research projects. This includes projects that prospectively collect health-related data and biological samples as well as "further use" projects that make use of data and samples that were collected for other purposes independently of the research project (e.g. routine clinical data and samples). In Switzerland, such projects fall under the Human Research Ordinance (HRO) of the Human Research Act (HRA).

In interventional drug, medical devices, and "other" clinical trials, the HRA, referring to the Good Clinical Practice (GCP) guidelines, requires the sponsor to implement adequate, risk-adapted monitoring procedures as part of the overall study-related quality assurance strategy. No such rules exist for non-interventional research projects. Consequently, researchers do not usually deploy any monitoring procedures to these projects. A reason for this may also be that researchers consider the risk of such projects to be low as compared to interventional clinical trials.

Nevertheless, it may be advisable to perform monitoring also for such non-interventional projects as monitoring can significantly increase data quality and project integrity independently of the interventional or non-interventional nature of the project. Needless to say, (monetary) resources in non-interventional research projects are usually even more scarce than in interventional clinical trials, especially in the academic setting, which limits the leeway for implementing extensive (on-site) monitoring activities. Care should thus be taken to assigning resources to areas where their expected impact is the highest. In this context, off-site / remote and in particular, Central Data Monitoring approaches may be the strategy of choice in many cases.

This position paper aims at providing guidance for sponsors planning to conduct non-interventional human research projects in terms of best practice monitoring strategies for their project.

Planning of monitoring procedures

Assessing the monitoring requirements for a non-interventional research project generally requires the same considerations as when planning the monitoring of an interventional clinical trial. No simple recipe can be provided that applies for all projects.

In alignment with the requirement of ICH-GCP E6 (R2) that "*The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected*", we recommend performing a **formal risk analysis**[1] to uncover and define the specific risks of the project. The identified risks will be rated according to their criticality and potential impact on the success of the project, and, for each risk that is considered controllable, mitigation strategies will be defined. This may include the monitoring procedures that are the topic of this paper. Risks will then need to be prioritized and available project resources be allocated to the most critical risks first.

1 Recommended tools for assessing the risks of (clinical) research projects:
Swiss Clinical Trials Organisation: https://www.sctoplatforms.ch/en/tools/risk-assessment-form-for-clinical-research-projects-30.html
Swiss Biobanking Platform: https://swissbiobanking.ch/documents/

Risk considerations

Data and biological samples used in **"further use" research projects** may stem from both retro- and prospective data and sample collections and may include routine data / samples as well as data and samples from other (interventional or non-interventional) research projects[2]. To make those data and samples accessible and usable, data are usually gathered and pooled in databases and samples transferred into biobanks, respectively. Important risks to be considered are e.g. those related to the set up and maintenance of the database and biobank infrastructure itself, including built-in data protection measures, to the process of recording the data in the database and all risks associated with handling and analyzing the samples. If data are copied into the database via direct import, technical issues related to the import should be considered. A multi-center project may have a higher risk than a single-center project in this regard as complexity is added by the larger number of systems from where data need to be imported. If data are (also) manually entered into the database, additional risks with regard to data completeness and data quality arise. This may be of particular concern when data are collected prospectively and on a continuous basis (e.g. a registry with prospective data collection). Structural risks, such as resources at sites to ensure continuous feeding of the eCRF with new data should be considered, as well as experience of sites with entering data into (complex) eCRFs. Multi-centricity adds to the complexity of such projects.

In **projects with prospective, (non-routine) data and sample collection**[3], additional risks should be considered as the project protocol requires the researchers to adhere to provisions with regard to the type, timing, etc. of data and sample collection. Apart from the risks related to data completeness and quality and sample handling described above, there may thus be additional risks related to the collection of the data and samples from the participants. Complex consenting procedures and / or enrolment of a vulnerable participant population may also be important risks in such studies. Furthermore, structural risks such as multi-centricity, staff experience, and availability of a functional infrastructure at sites should be included in the considerations.

Monitoring procedures

When deciding on the tools to mitigate the risks of his or her project, the sponsor should consider the different types of monitoring procedures that may be applied either alone or in combination or complementary to other mitigation strategies. In the following, we provide a brief description of the different procedures and their particular characteristics and capabilities.

Central Data Monitoring

Central Data Monitoring (CDM) is the (central) review of the data in the project database in terms of completeness, plausibility, and consistency. It also allows the sponsor to keep continuous oversight of site performance which may not only be directly related to data entry per se. CDM is of particular value in multi-center projects as a direct and continuous supervision of project conduct by on-site monitoring (see below) is beyond the scope of probably most budgets of non-interventional human research projects. Importantly, CDM does not generally comprise any form of source data verification (SDV), i.e. the direct verification whether data recorded in the eCRF are correct and consistent with the source data at the site. The concern is here that such remote SDV could relatively easily lead to a breach of data protection rules -

2 In Switzerland, "further use" clinical research projects are regulated under HRO chapter 3 / Further Use of Biological Material and Health-related Personal Data for Research.
HRO Art. 24 defines "Further use" as "[…] any handling, for research purposes, of biological material already sampled or data already collected […]". Nevertheless, there is an agreement to also consider the use of data and samples that are prospectively collected as "further use" provided they are collected independently of the research project. HRO chapter 3 thus covers all non-interventional research projects that use data and biological samples that were and will be collected independently of the research project.

3 In Switzerland, non-interventional research projects with (non-routine) prospective data and biological sample collection are regulated under HRO chapter 2 / Research Involving Measures for Sampling of Biological Material or Collection of Health-Related Personal Data from Persons.

it is therefore only implemented in exceptional cases with appropriate precautions and according to local regulations and guidelines.

The individual routine data checks to be performed by the central data monitor should be carefully selected. Focus should be on the most important data (e.g. data concerning the main project endpoints and critical time points for the collection of data and biological samples), as doing all possible consistency checks with the complete data set can be a huge endeavour which may well drive the associated costs beyond the scope of the project budget. Involving the project statistician in selecting the most useful checks may be advisable as he or she can judge best which data are the ones most important for analysis.

To learn more about central data monitoring and its potential to improve data quality, you may refer to the SCTO Fact sheet "Central Data Monitoring in Clinical Trials".

Off-site / remote Monitoring

Remote monitoring is performed to investigate project conduct at the site in more depth and focuses also on other aspects than the data recorded in the eCRF. This includes remotely checking copies / scans of the site delegation log, documentation of staff training, documentation of sample processing, and temperature logs for sample storage, etc. that the site provides to the monitor e.g. via email. Also, it includes phone or video calls with sites to verify proper conduct of project procedures such as participant consenting (including whether the current approved version of the participant information and informed consent form was used), sample processing, and storage, etc. Typically, during remote monitoring phone calls, the monitor also addresses any site performance issues observed during CDM. Furthermore, at remote monitoring calls, the monitor may ensure follow-up on action items raised during on-site monitoring visits (see below). Again, as for CDM, SDV is not usually a part of remote monitoring activities.

Remote monitoring is either done at predefined times during project conduct or ad hoc, based e.g. on findings during CDM. Sites may also be selected randomly for a remote monitoring phone call.

On-site Monitoring

On-site monitoring visits allow the monitor to investigate aspects of the project which cannot be investigated off-site, e.g. because this requires access to participant-identifying information, or because an off-site assessment would require a substantial and non-justifiable effort for the site personnel. Important tasks at an on-site monitoring visit are e.g. to check the informed consent documents, to verify the proper recording of the data in the project database (SDV), to ensure completeness of the essential project documentation, and to check maintenance of a suitable infrastructure (e.g. balances, centrifuges, refrigerators, etc.) at the site. Also, if needed, project procedures such as sampling and sample processing may be observed by the monitor during an on-site visit.

Similar to remote monitoring, on-site visits may be done at prefixed times or ad hoc, e.g. based on findings during CDM and remote monitoring, but randomly selecting sites for a visit is also an option.

Defining the monitoring strategy for a project

Depending on the risks of the project and considering whether or not monitoring can control and mitigate those risks, the sponsor decides on the appropriate monitoring strategy for his or her project, thereby also taking into account any budget-related considerations. The extent and intensity of monitoring applied may range from no monitoring at all to monitoring comparable to the one applied in (complex) interventional clinical trials.

The sponsor must also decide who should be put in charge to perform the monitoring of the project. According to state-of-the-art procedures, monitoring is done by experienced monitors that are as independent of the other project team as possible – ideally, monitoring is outsourced to a specialized institution such as a Contract Research Organisation (CRO) or a Clinical Trial Unit (external monitoring). It

is, however, not forbidden that members of the sponsor's staff perform monitoring themselves (internal monitoring). Even if the monitor cannot be considered completely independent of the project team, it may still be better to have some sort of monitoring done in this way.

In a simple further use project, where data are directly imported into the database and where no samples are analysed, the risk assessment may identify the proper set up of the database and accuracy and completeness of the data import as the only relevant risks. These risks should be controlled during database development and at the time of the data import, and thus, no additional monitoring would normally be envisaged.

If data collection in the database involves the manual recording of data, additional risks related to data completeness and quality may apply. In that case, the sponsor may want to implement CDM to perform completeness checks, as well as plausibility and consistency checks for a selection of data points[4]. CDM may be particularly useful in multi-center projects and where the amount of data to be recorded is large.

Generally speaking, we recommend implementing CDM as a basic strategy in all projects where performing monitoring is considered useful to enhance data quality. At sites where CDM reveals frequent and significant data completeness and quality issues, it may be legitimate to apply additional monitoring such as remote monitoring calls or even an on-site visit.

In projects involving the prospective collection of (non-routine) data and biological samples, a more intense monitoring may often be useful to control the risks. In particular, in cases where the project requires extensive and complex laboratory or consenting procedures, the implementation of remote and even on-site monitoring activities may be recommended – if not required – in addition to CDM, to ensure a high data quality. Again, a multi-center project usually urges for more intense monitoring than a single-center project.

Examples

The following two real-world examples should give an idea of which monitoring strategies could be implemented for different types of projects:

- A research project with financial support from industry involving prospective, non-routine cerebrospinal fluid sampling for biomarker assessments in a vulnerable participant population. 180 participants will be enrolled at 6 sites in Switzerland and the EU.
  Monitoring strategy: CDM, remote, and on-site monitoring are performed by an academic Clinical Trial Unit. One fix on-site monitoring visit is conducted when at least 5 participants are enrolled at a site. 8 to 12 weeks after the monitoring visit, a remote monitoring phone call is done to ensure follow-up on the action items raised during the visit. Additional monitoring visits may be planned as needed.
- A registry collecting routine data retro- and prospectively. Data of over 2000 participants at 30 sites will be collected.
  Monitoring strategy: CDM is done by an academic Clinical Trials Unit. The central data monitor generates reports in Excel, listing the most essential data that are missing from the database and sends these to the participating sites quarterly. Sites complete the missing data based on these reports as far as data are available as per their clinical routine.

Conclusions

[4] Cave: When in a project that intends to further use routine data, data are missing in the database, this may be either because the site did not (yet) record those data or because they are simply not available at the site (as the site follows their routine procedures and thus did not collect those data [on that day]). In the latter case, it is important to accept those data as missing and that the monitor does not exert pressure on the site to collect those data in the future. If sites are asked to collect more data than they would do as per their routine procedures, the project would turn from a further use project into a project of prospective (non-routine) data collection where more stringent regulatory rules apply.

Although laws and regulations do not normally direct sponsors to implement monitoring for non-interventional research projects, depending on the type and complexity of the project, it is often advisable to do so nevertheless to achieve the intended quality of the data and for the overall success of the project. In that sense, a risk-adapted monitoring strategy has the same justification as in interventional clinical trials. As monitoring tools, the sponsor can apply CDM, remote monitoring, and/or on-site monitoring either alone or combined in a concerted manner, tailored to the specific needs and characteristics of the project.

Of note, just as in the setting of interventional clinical trials, investing in the training of the individuals that actually conduct the project is of utmost importance and can be crucial in assuring the project's overall success. Furthermore, a well-designed (electronic) CRF with extensive built-in edit checks for data completeness, plausibility, and consistency, is of great value.

Investing in a good project database, a proper biobank infrastructure, training of site staff, and applying a well thought-through monitoring strategy will always pay off in both, interventional and non-interventional human research projects.

References

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