Seminar Series:

Facts and pitfalls of observational studies - How to plan and conduct HRO projects

Q&A from the session

"Quality: Law, practice and common hurdles"

Is it true that the Ethics Committees (ECs) in Switzerland expect that all HRO projects also have to follow the GCP guidelines (incl. monitoring requirements)?

The ECs in Switzerland can only expect what is defined in the law. Whereas for the conduct of clinical trials the specific GCP guidelines (e.g. ICH E6(R2), ISO 14155) are explicitly mentioned in the Swiss law, there are no specifications for research projects according to HRO. However, traceability is an explicitly stated requirement in the HRO (see presentation). One way of ensuring traceability is the implementation of quality control measures. The ECs provide some examples (see below example excerpt from the swissethics protocol template for research projects according to HRO chapter 2), which also include «planned quality visits or independent data reviews», that corresponds to (internal or external) monitoring activities.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Describe measures taken for quality assurance and quality control: e.g. double data entry, project personnel trained on all important project related aspects, planned quality visits or independent data review, etc. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

How to ensure scientific quality and transparency of research involving humans?

In the session 4 of the HRO lunch series about quality / quality management in HRO research projects we provided several recommendations of activities to ensure scientific quality (making use of tools/ instruments to define a proper research question, swissethics templates, adequately trained project staff, installing a quality management system, operational and organizational aspects, quality control measures) or transparency (e.g. publication according to the Open Research Data principle). Please see the presentation of the HRO lunch series session 4.

With clinical trials the level of required continuous documentation is very high (e.g. temperature logs should be printed and signed and so on. Scales should be regularly calibrated and this should be documented). What are the "legal" requirements for observational studies?

In the law (see HRO Art. 5 and presentation of the HRO lunch series session 4) there is a clear requirement for traceability of all operational steps and that all processing operations with data or samples have to be documented to ensure this traceability. Therefore, yes you should also prepare and maintain temperature logs, etc.

Types of consent needed was a bit quick - where can I find details?

For research projects according to HRO chapter 2 always a project-specific study information/ informed consent form has to be used (see HRO Art. 8-9)

For research projects according to HRO chapter 3 (see HRA Art. 32-33) either a project-specific study information/ informed consent form has to be used (see HRO Art. 28) or a study information/ informed consent form for research purposes, which may also be a General Consent (GC), has to be used (see HRO Art. 29 and 31) or an information with the right to dissent for research purposes, which can be covered by a General Consent, has to be used (see HRO Art. 30, 32). The type of information and consent depend on the type of data (genetic versus non-genetic / samples) and the possibility of person identification (un-coded, coded, information on the anonymization) and subsequently on the further use for a specific research project versus for research purposes. The surrogate consent by the Ethics Committee can be requested for further use of existing data / biological material and may be granted by the Ethics Committee under certain circumstances (see HRA Art. 34).

We have a project that is a combination of HRO2 and HRO3 project (retrospective and prospective data). What kind of informed consent is necessary for such a project?

Overall, the project has to be categorized as a HRO2 project. If the HRO3 parts and the HRO2 parts apply to all study participants to be included, a project-specific patient information/ informed consent form should be prepared, addressing the HRO2 aspects AND the HRO3/ further use aspects. So prepare a combination of the study information templates for HRO2 AND HRO3 projects. If there are potential study participants whose data / sample should only be further used but the participants do not take part in the HRO2 part of the project, then several different study informations/ informed consent forms (or the General Consent) may be prepared / used in the project to inform the different groups of participants according the need).

What effect does it have when the manually extracted data is un-coded?

If the researcher extracts the data him-/ herself, then the data are considered as un-coded data, even if the researcher would code them after extraction and store the code list/ key with an independent person/ entity. If an project-independent person (not involved in the research project!) extracts data according given inclusion criteria, then does code it, and then remains the code list/ key and then transfers the data to the researcher in coded form, only then the data are considered as coded data.

If the data is coded or un-coded, has an impact on the study information/ consent to be used. If data or biological material is coded (from the perspective of the researcher) then data / sample subjects, that have consented to the General Consent (GC), can be included in the project - independent if it is genetic data (or samples) or non-genetic data. If the genetic data / biological material is un-coded, then the GC can NOT be used, the data / sample subjects have to be informed project-specifically and need to sign a project-specific consent.

Is REDCap really necessary for HRO projects?
What if I only have a small master Thesis, do I really need that? What about Excel?

Using Excel as a database for HRO projects?! Many Researchers perfer this - how do you deal with this in ZH?

The Ethics Committees in Switzerland state quite clearly how to perform the data management and recommend also for HRO projects to make use of a GCP-compliant data management system, such as REDCap, since it provides role-based access control and traceability (by automated audit trail), both what is required by law (see HRO Art. 5, see presentation of HRP lunch session 4). MS Excel is NOT built with the level of permission and access management, role assignment, or audit trail. However, if Excel is still used, then there are instructions by the Ethics Committee how to proceed to provide a minimum level of access management and traceability (see below excerpt of the protocol template for research projects according to HRO chapter 2: protected cloud system that combines controlled access and user rights with tracking of changes at file / document level, and using the feature/ mode «track change» (details under: Track changes in a Shared Workbook - Microsoft Support and How to Use Track Changes in Excel - YouTube[1353957186]))

7.2 Data recording and source data

Describe how project data is recorded, e.g. with paper Case Report Forms (CRF) or an electronic Case Report Form (eCRF) such as secuTrial® or Redcap®. Efforts should be made not to use any software, like Microsoft Office software's (e.g. Excel), that do not have an audit trail and do not guarantee data privacy and data reliability, as changes can be made in an uncontrolled manner. If a software without audit trail is used nonetheless, describe how data quality and data traceability throughout the research project is guaranteed.
If Microsoft Excel is used, a system must be put in place to improve data privacy and data reliability. That is with a protected cloud system that combines controlled access and user rights with tracking of changes at file / document level, and using the feature "Track changes" (see instruction for use of this functionality here. Training videos on how to use this feature are available on the YouTube channel, e.g.: https://www.youtube.com/watch?v=Itz8v_z7ha4).
If paper CRFs are used, describe how data is transferred to an electronic database for later analysis. An electronic database is recommended.
List the source data used in the project. Source data is all information in original records, certified copies of original records of clinical findings, questionnaires, observations, or other recorded activities in a clinical investigation. Clearly differentiate between source data collected on project specific documents (e.g. project CRF, project specific forms or questionnaires, not part of participant file), and routinely collected data during the daily practice. The routinely collected data is part of participant file but can also be transferred to the participant CRF.

Which public repositories do you recommend for the publication of studies and results for public a ccess?

There are institution-specific or discipline-specific long term repositories.

Please see: Swiss National Science Foundation (SNSF): *Open research data: which data repositories can be used?*: Open Research Data (ORD): Welche Datenarchive sind geeignet (snf.ch) and e.g. Store and Publish Data | University Library Zurich | UZH

I think that budget issues are the always present issues of every project, and normally HRO project s have lower available funds than clinical trials, how do you manage this aspects for quality in HRO projects? Do you really manage to monitor HRO projects lightly for example?

If you consider quality control aspects early on in the application for funding, than usually founders are willing to support this aspect as well. We do monitor HRO projects at the CTC Zurich. We perform either classical monitoring (risk based) or “monitoring coaching” (in case quality control is performed by the clinic, or an independent person and we review if they cover all aspects and coach them how to plan and perform QC). Either you can calculate an external classical monitoring, or also internal quality control if you have qualified personnel to do that. In this case you should also consider the costs / time of your own personnel. Sometimes you can save time and money if QC is carried out by CTUs, as they have more experience.

One needs to emphasize, that QC is always planned risk-based, therefore you should start with consideration of which processes can negatively influence the quality of the data and the safety of participants. By planning the monitoring of HRO projects – which are almost always low-risk projects, we usually plan less percentage of participants to be reviewed, but the processes of the risk-analysis should always be covered.

And indeed, there are now and then also very well-funded HRO projects, primarily highly complex and / or multicenter projects.

Do you have any recommendation how to set a strategy for QC for Sample Management and Data Management in a multi-centric study?

In a multicentre study all study sites should preferentially use the same strategy for data management and sample management. During the preparation phase of the project, the Sponsor/ Sponsor-Project Leader always has to check the infrastructure at the study sites intended to be involved in the multicentre project and to ensure that the technical pre-requisites are fulfilled. E.g. he /she is responsible to define if data are paper-based or electronically recorded (pCRFs versus eCRFs), and if in an electronic manner, has to define the electronic systems to be used for. The data or sample life cycle (from collection / extraction of data or sampling of material up to the deletion / destruction of data / samples) should be described in the protocol or may be even in a separate Data / Sample Management Plan as annex to the protocol. Based on these aspects, a project-specific QMS (incl. SOPs and working instructions for steps primarily vulnerable to errors) should be set-up, implemented and trained at all involved study sites. Likewise, equal sample management systems should be utilized. A potential option could be to store, administrate and manage samples only on one site (e.g. the site of the coordinating Project Leader).

There are many master studies or user research studies for scoping user experience for wearables or digital health tools. These are typically interviews or surveys and may recruit patients or familie s, and specifically ask about therapy or tretament experiences. What is the view regarding such st udies in terms of being subject to HRO?

It always has to be considered if the scientific question comprises really research with human beings (e.g. if really health-related data are collected and / or further used) or if the investigation is rather about to evaluate settings / parameters / conditions to ensure quality of a certain process and / or at the specific institution (e.g. data regarding applicability or user-friendliness of a tool/ app/ device). The position paper/ guideline of the swissethics: **Quality assurance, or research subject to**

approval? 191223_abgrenzung-qualitatssicherung-von-forschung_finalisierte-version_de_en.pdf (swissethics.ch) helps to discriminate between human research requiring approval by a cantonal ethics committee for research with humans and research for reasons of quality assurance.

Are similar guidelines for HRO2/HRO3 projects like written guidelines at the USZ planned for other hospitals too, e.g. University Hospital Basel?

At the moment, the University Hospital Basel does not have such extensive and detailed guidelines. The creation of such documents is currently being discussed and is in preparation. However, there are already guidelines for the procurement of personal data from the routine for further use (please contact verena.golz@usb.ch for details).