The Investigator: Modellers and Analysts

9

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9.1 Roles and Responsibilities

In analogy to what is recommended by the ICH guideline on GCP for regular clinical trials, the roles, tasks, and responsibilities of the parties conducting a study involving in silico methodologies should be clearly stated and documented appropriately.[1,2]

In a clinical study, the Investigator is the person who runs the study. The Investigator may help prepare and carry out the study's protocol (plan), monitor the study's safety, collect and analyse the data, and report the study's results.

When in silico methodologies are involved, the term Investigator refers to the person, or in some cases the hosting institution, in charge of carrying out the modelling tasks and generating the in silico evidence. Experts who develop predictive models are

[1] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

[2] https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf.

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usually referred to as *modellers*, whereas experts who merely use models developed by others are sometimes called *analysts*. Here we will refer to both roles indistinctly with the term Investigator. Given that the role of the clinical Investigator and that of the in silico Investigator may involve different backgrounds in clinical studies where in silico methodologies are involved, the two roles may be separated and assigned to different persons or institutions.

The Investigator may be in charge of performing the simulations and analysis but also of activities described in the model development plan (c.f. Chap. 3) and the credibility-building activities (c.f. Chap. 4). The Investigator's role and responsibilities are defined in relation to the Sponsor and their mutual agreement:

- A documented agreement with the Sponsor should clarify the roles, responsibilities, and frequency of reports at the beginning of the project.
- The Investigator should be aware of and comply with applicable modelling and simulation standards and guidelines, such as the ones listed in Annex A.
- The Investigator/institution should have approval of the competent Institutional Ethics Committee and/or Review Board where required. The Investigator/institution and Sponsor share responsibility for the handling and protection of personal health data, together with the ethics committee.
- The Investigator must follow the model development plan as agreed with the Sponsor. In case of deviation from plan, this should be discussed early on and agreed with the Sponsor in written form. If applicable, new approval and opinion from the ethics committee should be obtained (e.g., when the deviation regards personal health data acquisition, storage, or processing steps).
- The Investigator is responsible for ensuring that the modelling and simulation activities are carried out with adequate pre-defined hardware and software infrastructures for which the protocol and credibility assessment measures have been designed and approved (c.f. Chaps. 3 and 4).
- Since part of the modelling activities may be delegated to third parties, it is the responsibility of the Investigator or of the Sponsor to record any tasks that have been delegated and the list of the qualified persons they were delegated to. In addition, the Investigator or Sponsor is responsible for adequately informing each third party assisting with the modelling and simulation process about the investigational product (see Investigator's brochure), the modelled system and agreed protocols.

9.2 Investigator's Brochure

Similar to regular clinical trials, the Investigator must be informed by the Sponsor about the medical product under investigation and subjected to the in silico trial. This can take place through handing of an investigator's brochure by the Sponsor to the Investigator, like recommended in the ICH Good Clinical Practice[3] and the European Commission Directives 2005/28/EC[4] and 2001/20/EC.[5]

The Investigator's brochure summarises the medical product characteristics and compiles existing clinical and non-clinical data (including pre-existing in silico data) about the medical products relevant to the study to facilitate understanding the rationale of the in silico trial (Döerr et al., 2017).

The information in the investigator's brochure shall be presented in a concise, simple, objective, balanced, and non-promotional form that enables potential investigators to understand it and make an unbiased risk–benefit assessment of the appropriateness of the proposed in silico trial.

9.3 Investigator's Qualifications

The Investigator needs to be qualified to fulfil his/her role. The required competencies range from practical skills regarding the use of the simulation software ("know your tools") to the capacity to judge whether the model at hand is suitable for the specific Context of Use (CoU), as detailed below. A lack of general understanding of the physiological processes and the lack of interdisciplinarity in the team are important pitfalls in applied modelling and simulation. In particular, the Investigator needs the following qualifications:

- Capacity to judge whether the in silico model technique and its boundaries (Intended Use) are compatible with the clinical purpose and objectives (CoU). This assessment requires that the Investigator has access to information on the biomedical context of the study and pre-clinical information about the medical product being modelled. In this context, the Investigator's brochure is of particular importance (see Sect. 9.2).
- Capacity to evaluate the adequacy of the modelling decisions to be taken during the design and the execution of the in silico trial and their implications for the intended CoU. This assessment includes biomedical and numerical aspects (for example, time and space resolution, convergence, and stability). When the expertise of the modeller

[3] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

[4] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32005L0028:EN:NOT.

[5] https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-directive-200120ec_en.

on the pathophysiology of the biomedical process being simulated is not documented, an expert on the specific pathophysiology in question should also be consulted.
- Proficiency in using the M&S software for the in silico trial. We refer to Chap. 3 for cases where the software needs to be adapted.
- Capacity to post-process, analyse, and condense the results of the in silico trial, including statistical analysis.
- Capacity to identify relevant ethical aspects related to the in silico trial. These can be evaluated by the Investigator or discussed with the institutional ethics committee if required.

Formal training, degrees, and certificates will often be evidence for many of these competencies. However, there is no specific set of degrees of certificates that would be comprehensive enough to cover all aspects and, at the same time, general enough to be applied to all fields of in silico medicine and the wide range of possible CoUs. Considering the wide range of required qualifications, one person is unlikely to fulfil all of them on an expert level. The Investigator needs to ensure that all required competencies are available in the team of experts involved in the study.

The qualifications of the people involved in a simulation study may need to be reported. For instance, in the NASA-hdbk-7009a[6] about CM&S in mission-critical applications, it is requested to "provide an understanding of the education and experience of the people developing and using the M&S" in a dedicated table.

In conclusion, the Investigator needs to convince the relevant stakeholders (Sponsor, regulatory agencies, ethics committee) that the relevant qualifications are available.

9.4 Adequate Resources

To exectute the in silico trial, or other modelling tasks agreed on with the Sponsor, according to the state of the art, the Investigator needs access to human resources, support, computing resources, and feedback.

In most cases, human resources will be the most expensive part of the in silico activities budget. The Investigator and his/her team need to be funded adequately to be able to commit the required time to the execution of the in silico experiments and their analysis. The team needs to be formed with persons covering all the required qualifications as detailed in the previous section.

For situations in which the expertise within the team is not sufficient or solutions can be obtained more efficiently with help from the outside, the Investigator should have access to external support. Demand for such support can arise in various fields as evident from the wide range of required qualifications (see sect. 9.3): for example, technical support from the developers/vendors of the simulation software, support for collecting

[6] https://standards.nasa.gov/standard/NASA/NASA-HDBK-7009.

data, statistical support, support regarding ethical questions or legal and regulatory issues. Resources need to be allocated to pay for such support in case this is not covered by existing agreements. The participation of external experts must be properly documented and tracked throughout the study.

To run the in silico experiments, the Investigator depends on adequate computing resources. These can range from a personal computer to high-performance computing resources in a dedicated computing centre or in the cloud, depending on the characteristics of the model and the number of simulations to be run. The specific requirements need to be discussed and agreed upon with the Sponsor in good time. Remote access needs to be secured according to the state of the art. The choice of the computational platform must also be made keeping in mind the legal and ethical requirements that the treatment of sensitive data imposes.

To ensure that the results of the in silico activities will be as valuable as possible, the Investigator should have access to feedback from experts of the biomedical context and/or "users" of the results (e.g., physicians, product managers, regulatory agencies, etc.) during the modelling process unless explicitly designed differently in the study protocol.

9.5 Records and Reports

The sequence of steps and decisions made during the modelling process are context-specific and may be subjective, impacting the conclusion and hindering the results' reproducibility (Erdemir et al., 2019). Therefore, concerning a quality approach and/or regulatory evaluation, the M&S tasks and decisions must be documented and reported. Since the Investigator carries out these tasks, here we focus on his/her main responsibilities concerning recording and reporting.

The Investigator must identify, justify, and document every expert-based choice potentially prone to modeller bias (e.g., parameter selection, model structure). All source documents, codes, results, and data should be adequately recorded, maintained, and retained by the Investigator/institution, with the support of the Sponsor, for the duration initially agreed with the Sponsor. It is the responsibility of the Sponsor to agree in advance on an adequate period of time. The tasks that have been delegated should also be subject to recording. In addition, the Investigator must make all records available upon request of the Sponsor or relevant regulatory authorities. As such, the Investigator/institution should ensure the adequate accessibility and legibility of documents and data and support audits.

Regarding reporting activities, the Investigator should provide frequent written progress reports to the Sponsor as defined in the initial agreement. Those reports should document the technical progress and results, as well as potential model deficiencies, limitations, and ideas for improvements discovered during the process. Any deviation from the agreed protocol should also be justified and reported by the Investigator when they occur.

Finally, the Investigator must provide the Sponsor and regulatory authorities with a final report summarising the outcome of the in silico study after termination. This report should include the actual workflow employed by the Investigator, the generated in silico evidence, and their analysis concerning the CoU. The Investigator is responsible for the scientific integrity of the reported research and data. The FDA has issued a guidance document providing modellers with a general outline for reporting computational modelling and simulations in medical device submissions.[7] Although detailed content may not entirely apply to all types of in silico models (e.g., for drug approval submission), the general outline is rather generic. It may be considered for guiding the final report of in silico trials. In addition, the EMA provides guidelines to physiologically based pharmacokinetic modellers that describe the expected content of M&S reports for regulatory submissions.[8] Similar guidelines were also released for reporting population pharmacokinetic analyses.[9] Overall, the content is specific to drug applications, but many recommendations also apply to other modelling applications.

9.6 Safety and Security

In silico methodologies can be used to refine, reduce, or replace human experimentation.

When in silico methodologies are used to reduce or replace human experimentation, given the digital nature of in silico trials, there is no direct involvement of human participants from which health-related safety issues could arise during the Investigator's modelling activities. The major risk for humans regards personal data, which must be handled according to data privacy standards and rules.

Regarding simulation input measurements and validation activities, any clinical trial necessary to generate input data for the model is not the modeller's responsibility and should comply with other relevant guidelines, such as good clinical practices (GCPs). However, the Investigator must consider the safety and security aspects of in silico activities. Data safety, i.e., protecting data against loss by ensuring safe storage and back-up of the data, must be ensured by the Investigator/institution. This means input (patient) data and codes, analyses, results, records, and reports. Therefore, appropriate hardware or cloud facilities with backup systems and version control should be available and used by the Investigator (c.f. Sect. 9.4). The Investigator should follow the data storage and

[7] FDA, Reporting of Computational Modeling Studies in Medical Device Submissions - Guidance for Industry and Food and Drug Administration Staff. (2016). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions.

[8] https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation.

[9] https://www.ema.europa.eu/en/reporting-results-population-pharmacokinetic-analyses.

version tracking strategy as defined in the model development plan (c.f. Chap. 3) with the Sponsor.

Data security is also the responsibility of the Investigator/institution and/or the Sponsor, who should protect personal health data and patient privacy by ensuring adequate use and access restriction to the data. As such, the Investigator based in the European Union must comply with the current General Data Protection Regulation (GDPR)[10] and related directives; most other countries now have similar legislations, although the details may vary considerably. It should be noted that if the country where the data were collected is subject to legislation different from that in force in the country where the data are being treated, the treatment of the data must follow the rules of the country where the data were collected.

Specific attention must be paid to the level of data anonymisation and the possibility of relating some of the data-derived model characteristics (e.g., organ geometry) to the patient's identity. The ethics committee will commonly evaluate the data security and privacy strategy and specific measures, which may require a full Data Protection Impact Assessment (DPIA). The Investigator should use patient data according to what was defined in the protocol and approved by the ethics committee.

In the case of refinement of human experimentation, the in silico methodologies are used alongside the experimental ones, thus posing the same risks to the patients. A typical example is a PKPD model used to calculate the next drug dose in an escalating dose–response study. In these cases, the study design should be reviewed by an ethical committee before it starts and also adhere to other relevant good practice documents like the Good Clinical Practice (GCP), as well as FDA and EMA guidelines on population PK and exposure–response modelling. The documentation should include evidence that the in silico methodology is fully qualified from a regulatory standpoint.

Finally, any safety issues related to the use of the model within its intended CoU or that emerge as a result of the simulation and/or identified by the Investigator (c.f. Chap. 3) should be detailed in the report to the Sponsor and to the regulatory authorities.

9.7 Essential Good Simulation Practice Recommendations

- Role and responsibilities of the Investigator are defined in relation to the sponsor and their mutual agreement, which should be documented.
- A record should be kept of eventual third parties contracted to assist in the CM&S activities and they should be adequately informed about the investigational product by the Investigator.
- The Investigator needs to ensure and convince stakeholders that all relevant qualifications are available in the team of experts involved in the study.

[10] https://eur-lex.europa.eu/eli/reg/2016/679/oj.

- The Investigator needs access to human resources, support, computing resources, and feedback necessary to accomplish the task as agreed with the Sponsor.
- All source documents, codes, results, and data should be adequately version controlled, recorded, maintained, and retained by the Investigator/institution, with the Sponsor's support, for the duration initially agreed with the Sponsor.
- The Investigator is responsible for providing regular and final written reports on the conduct of the study and its conclusions by following appropriate reporting guidance.
- The Investigator and the Sponsor should implement proper data safety and security measures, complying with relevant regulations (GDPR, etc.).

References

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