The Sponsor

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8.1 Introduction

For the purpose of this document, we define Sponsor as "an individual, company, institution, or organisation that decides to use computer simulations in a preclinical or clinical trial, aimed to a regulatory or decision-making purpose, conducted at any point in a product's lifecycle, both prior to and following marketing authorisation."

According to ICH E6 (R2),[1] the Sponsor is "An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial". A superimposable definition is given in the standard ISO 14155:2020.[2] Both definitions are confined to the concept of Sponsor in the context of human clinical trials.

As explained in the previous chapters, in silico methodologies can refine, reduce, or entirely replace human experimentation. This chapter focuses mainly on studies where in silico methodologies are used to refine or reduce human experimentation; in other words, studies that still involve humans. However, the Sponsor's basic responsibilities

[1] https://www.ema.europa.eu/documents/scientific-guideline/ich-E-6-r2-guideline-good-clinical-practice-step-5_en.pdf.

[2] https://www.iso.org/standard/71690.html.

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are applicable in all contexts, particularly regarding the requirements of implementing a thorough critical-to-quality risk assessment process and to assure the reliability of results. Whatever the aim of the trial and its place in the development path of medical treatment, the Sponsor has an obligation to follow the fundamental principles of Good Clinical Practice (GCP) and/or Good Laboratory Practice (GLP) and/or other GxP, beyond and above the need to follow the present Good Simulation Practice.

In the context of this chapter, when referring to computer simulations or in silico trials, we imply the use of models developed and validated according to the requirements covered in Chaps. 3 and 4. We also imply that fulfilling all regulatory requirements and guidelines applicable to preclinical and clinical trials related to medicinal products or medical devices is ensured. We will therefore focus on additional requirements to be followed when including computer simulations/in silico trials in the development process of new medical treatments.

The Sponsor willing to include in silico trials in the frame of the pre-clinical and/or clinical development of a new medical treatment should:

- extensively assess and clearly define the context of use of the in silico trial in the development path of its product;
- allocate a project manager and adequate resources;
- identify the computer simulations provider (internal/external);
- draft the trial's protocol;
- analyse regulatory constraints and where necessary seek advice from regulatory authorities;
- ensure continuous oversight of the project;
- critically evaluate the study's outcome and discuss the results with the regulatory authority.

8.2 Relevant Expertise

The Sponsor may have internal technical resources/computational specialists or depend on computer simulations vendors/consultants. In any case, the Sponsor should have internal personnel knowledgeable about computer modelling and simulations, at least to the extent needed for adequately assessing technical, regulatory, and logistic constraints. It is recommended that Sponsors with no prior experience in using in silico trials put in place a specific implementation plan, including basic training of personnel (e.g., attendance to specific courses, learning of available guidelines and documents, "hands-on" training) or refer to a specialised consultant.

In particular, the Sponsor of an in silico clinical trial, whether intended to refine, reduce, or replace human experimentation, should have adequately trained personnel capable of performing the necessary credibility assessment for the in silico methodologies,

follow available international guidelines and ensure that a quality management system throughout all trial stages is in place.

Adherence by the Sponsor to specific training certification programs would be advisable although of limited feasibility in practice due to the broad range of skills and experience required by in silico methodologies. To ensure nurturing of these in silico skills and experience, higher education institutions should revise their programs to include elements of in silico medicine related to human health in all scientific degrees. They should also consider more specialised profiles that currently do not exist. The academic experts in in silico medicine should collaborate toward defining such curricula.

8.3 Quality Management, Quality Assurance and Quality Control

The Sponsor of an in silico trial should implement a critical-to-quality risk assessment process to ensure:

- the protection of the rights, safety, and well-being of study participants (when these are involved),
- the generation of reliable and meaningful results, and
- the appropriate management of risk factors using a risk-proportionate approach.

8.3.1 Risk Identification, Evaluation, Control, Communication, Review, and Reporting

A basic set of factors relevant to ensuring trial quality should be identified for each study, focusing on critical factors. Examples of possible critical factors are:

- Protocol development: the trial protocol should be scientifically sound and adequately sized, with well-defined and relevant endpoints and statistical methods. Study procedures and conditions for premature study interruption should be detailed. For hybrid studies, measures to protect study participants' rights, safety, and well-being should be defined, in addition to unambiguous identification of stopping rules for adaptive studies. Studies should also follow the respective good practice documents for the modalities other than in silico (e.g. GCP).
- Selection of the clinical Investigators, as discussed in Sect. 8.6.
- Selection of the modeller, as discussed in Chap. 9.
- Trial monitoring/supervision, as discussed in Chap. 9.
- Training of personnel: internal, CRO, and local study staff.
- Data collection and analysis.
- Data interpretation and reporting.

Once identified, the risks should be evaluated regarding the likelihood of occurrence, the extent to which those errors would be detectable and their impact (risk evaluation). Factors identified as critical to quality should be carefully evaluated in advance, and appropriate risk-mitigation activities should be put in place (risk control); in hybrid studies, these should be proportional to the impact of such factors on human subject protection and on the reliability of trial results. Quality management activities and periodic revision and re-assessment of critical factors should be documented. Any change to trial conduct deriving from corrective measures to mitigate critical risks should be documented and reported.

For pilot trials, an external, independent Data Safety Management Board is recommended to set up that periodically reviews data as they accumulate. Studies with adaptive features and/or interim decision points need specific attention during proactive planning, ongoing review of critical quality factors, and risk management.

8.3.2 Standard Operating Procedures

The Sponsor should have in place a quality manual and written standard operating procedures (SOPs) to ensure that:

- roles and responsibilities of the personnel (internal/external) are clearly defined and communicated;
- the trial is carried out in compliance with the protocol and applicable regulations. Any deviation from the original plan is recorded, appropriately documented and justified, and its impact on the reliability of the results is properly assessed;
- data generation, data collection, data handling, analysis and reporting are accurately managed to ensure data integrity and reproducibility;
- the process of quality management is defined;
- the process of vendor selection is defined.

8.4 Contract Research Organisation (CRO)

The ICH E6(R2) defines a CRO as "a person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions". As previously discussed for the definition of Sponsor, in this chapter, the focus will be on the role of a CRO in the context of human clinical trials. Nonetheless, most of the topics discussed here are general and applicable also to CRO managing pre-clinical trials.

8.4.1 Relevant Expertise

The use of CM&S in clinical studies will require a change in the current *status quo* of how CROs operate in drug development projects.

CROs offering services for managing projects that include the adoption of CM&S in any context (like patient-specific models, virtual populations, hybrid trials, in-silico augmented clinical trials, etc.) should have adequate internal staff (highly preferable) or consultants with a good understanding of CM&S, in addition to the expertise in the management of clinical trials. The role of the CRO may or may not include that of developing and running the models. Whenever the CRO also provides computer simulation services, relevant expertise and qualifications, as detailed in Chap. 9, must be ensured.

When the CRO does not have an internal technical department with computational specialists, it might support the Sponsor in identifying the third-party vendor if required by the Sponsor. In all cases, the CRO should have a deep knowledge of applicable regulations, guidelines and best practices related to in silico trials and should remain constantly updated as knowledge in the scientific and regulatory fields progresses.

Given the complexity of in silico clinical trials, it would be advisable that a specialised professional figure be dedicated to this type of study.

8.4.2 Allocation of Roles and Responsibilities

The Sponsor may transfer some or all its responsibilities to a CRO but the ultimate responsibility for the quality, and the integrity of the trial remains with the Sponsor. When delegating activities, including in silico activities, the Sponsor's role is to provide the so-called Investigator's Brochure (see Chap. 9) to the mandated Investigator.

The allocation of responsibilities must be in writing, usually in the form of a contract. The Sponsor is also responsible for overseeing the activities performed by the CRO.

Delegated activities may be related to:

- trial design,
- assessment of project feasibility and centres identification,
- model building and development,
- regulatory activities,
- set-up of data collection tools,
- sites initiation and training,
- supervision of the trial conduct (simulations or in human studies),
- site monitoring,
- safety monitoring,
- data handling and data privacy,
- data analysis and reporting,
- maintenance of trial documents.

In addition, when the CRO provides computer simulation services, all responsibilities detailed in Chap. 9 must be fulfilled.

8.5 Adoption of Computer Simulations in the Definition of the Global Development Plan

8.5.1 Pre-clinical Development Plan

Computer simulation services required to support preclinical studies should be adequately described in a plan, including a description of the in silico trial objectives, available knowledge and data, modelling and simulation methodology to be applied, and outcomes evaluation criteria. If the services would be part of application submission to regulatory bodies, Computer simulation activities, including reporting, should be performed according to the recommendations described in Chaps. 3 and 4.

CM&S activities should be integral to the sponsor's strategic preclinical development program for the medical product under consideration.

8.5.2 Clinical Development Plan

Computer simulation services required to support clinical development studies should be performed in line with the recommendations provided in ICH E9 Statistical Principle for Clinical Trials,[3,4] Specific regulatory guidance documents should be consulted and followed when including model-informed drug development approaches.[5]

Modelling activities aiming to analyse the data obtained from a clinical trial should be described in a specific plan, including a description of the objectives, modelling and simulation methodology to be applied, and outcomes evaluation criteria. The in silico trial plan should be finalised before the start of the trial. In silico trials should be integral to the sponsor's strategic clinical development program for the medical product under consideration.

[3] https://www.ema.europa.eu/documents/scientific-guideline/ich-E-9-statistical-principles-clinical-trials-step-5_en.pdf.

[4] https://www.ema.europa.eu/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.

[5] Madabushi, R., Seo, P., Zhao, L. et al. Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making. Pharm Res 39, 1669–1680 (2022). https://doi.org/10.1007/s11095-022-03288-w.

8.6 Investigator Selection

In the context of this chapter, the Investigator is "a person responsible for the conduct of the clinical trial/clinical investigation at a trial site", as defined in the ICH E6(R2) and ISO 14155:2020. Here again, we differentiate the clinical Investigator (i.e., a non-computational specialist) from the modeller, which is discussed in Chap. 9. Although the role and responsibility of the clinical Investigator and the modeller are conceivably different, in the context of hybrid or adaptive clinical trials, the interplay between the two "Investigators" is crucial. There is so far limited experience with the inclusion of computer simulations in the context of clinical trials in human subjects. As experience is accumulated, such interplay will be formalised.

8.6.1 General Requirements

The selection process of a clinical Investigator should consider the context of the use of the in silico trial (whether to reduce, refine, or partially replace clinical experiments), the specificities and the complexity of the trial design, and follow a preliminary careful risk evaluation process. In particular, the selection of a clinical Investigator must take into consideration the role and the actual involvement of the Investigator:

- The clinical Investigator is involved in human clinical trials run to validate predictive models,
- The clinical Investigator is involved in a clinical trial simulation (*e.g.*, use of synthetic control arm, virtual populations, digital twins), to inform or to complement the clinical trial,
- The clinical Investigator participates in a hybrid in silico/in human trials.

Although a general understanding of modelling and simulation technologies is required in all cases, the level of knowledge in computer simulations the Investigator has should be proportional to the risk: the higher is the risk (which can be quantified with a risks analysis such as the one part of the ASME VV-40:2018 standard), the more qualified should be the Investigator.

Similar considerations apply to Investigator selection in the context of preclinical development.

8.6.2 Investigational Centre Selection

Based on its role and involvement, the Investigator selection process—in addition to the verification of the requirements established in the ICH E6(R2) and in the ISO 14155:2020

for centre selection—may require the need to perform additional verifications to ensure that the centre has adequate facilities for the in silico aspects. It is also important to secure that the Institution and the competent Independent Ethics Committee/Institutional Review Board are well-informed and involved in the process, particularly in the case of complex trial designs.

8.7 Study Design, Setup, and Management

The scope of this section is not to analyse and discuss the different possible designs of an in silico trial in the development of a medical product but to provide general guidance and overarching principles.

An in silico trial design should align with the Clinical Development Plan established for that medical product and be preliminarily submitted for advice to regulatory authorities. The regulatory pathway chosen depends on the clinical development plan and the proposed use of the data generated from the in silico trial.

The Sponsor should provide an updated Investigator's Brochure detailing all available information related to the medical product, including, in the case, results of performed CM&S.

A study-specific protocol with clearly defined endpoints, a rigorously described methodology, and a proper statistical section must be in place. The rationale and the model's aim (context of use) should be well described, and the level of the model risk, based on a risk-informed credibility assessment of the computational model. It is recommended that the clinical Investigators are involved in designing the protocol and definitions of the endpoints to ensure that clinical endpoints and engineering outputs are well aligned. The clinical Investigator should also be consulted in preparing the patient's information leaflet and informed consent form, if applicable.

Before the start of the study, ethical and regulatory approvals—as appropriate—are to be obtained. Written agreements among all involved parties (e.g., sponsor, Investigators, institutions, CRO) defining the responsibilities of each party shall be in place.

The general guidelines set in the ICH E6(R2) and in the ISO 14155:2020 should be followed for the study setup, including maintenance of study documents and documentation, the conduct of the study initiation visits and the training of site personnel. The extent of training on computational models for the study site personnel will be customised depending on the specific involvement of the Investigators; in hybrid or adaptive clinical trials, there should be an ongoing interaction between the modeller and the clinical investigator.

The Sponsor should define in a targeted monitoring plan the extent and nature of monitoring appropriate for the study based on risk assessment (see Sect. 8.9).

8.8 Data Handling and Record Keeping

The Sponsor should utilise appropriately qualified (internal or external) individuals to handle and verify the data, conduct the computer simulations analyses, and prepare the trial reports.

For electronic data handling and/or remote electronic trial data systems, the recommendations included in Sect. 8.5 of the ICH E6(R2) should be followed.

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved and/or where the sponsor intends to apply for approval(s).

8.9 Compliant GxP Computerised Systems

GxP is an umbrella term that describes regulatory guidelines across the pharmaceutical and medical device industries. The term encompasses a variety of regulatory guidelines such as Good Laboratory Practice (GLPs), Good Clinical Practices (GLPs), Good Manufacturing Practices (GMPs), Good Distribution Practices (GDPs), and Good Storage Practices (GSP).

GxP compliance is establishing and documenting that the specified GxP requirements of a computerised system can be consistently fulfilled. Validation should ensure accuracy, reliability, and consistent intended performance from design until decommissioning of the system or transition to a new system.

Digital systems used for trial purposes should consider the factors critical to their quality in their design and be fit for purpose. To this end, validation of systems, data protection, information technology (IT) security and user management are essential elements to be addressed.

Sponsors should maintain Standard Operating Procedures (SOPs) for using these systems. SOPs should cover system setup, installation, and use. They should further describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the Sponsor, Investigator, and other parties concerning the use of these computerised systems should be clear, and the users should be provided with training in the use of the systems.

Sponsors should further ensure the integrity of the data, including any data that describes the data's context, content, and structure. This is particularly important when changing computerised systems, such as software upgrades or data migration.

The Sponsor may transfer responsibilities of a computerised system to a Technology Service Provider. Still, the ultimate responsibility for the quality and integrity of the computerised system remains with the Sponsor. The allocation of responsibilities must be in writing, usually in the form of a contract. The Sponsor is also responsible for checking that the SOPs of the Technology Service Provider are meeting the Sponsor's quality and integrity standards and overseeing its activities.

8.10 Monitoring Procedures

The role of a monitor in the frame of an in silico trial is so far not established. We assume that while a monitor has no role in the verification of the technical aspects of the model, he/she may be involved in ensuring that:

- adequate documentation is produced and maintained during the running of the in silico trial,
- the data used for the models can be tracked to the source,
- the data used for the models are accurate and complete,
- proper informed consent has been obtained from data subjects, where applicable.

Depending on the type of in silico trial, these activities should complement standard monitoring activities performed for clinical trials according to current guidelines and regulations to which reference is made.

In all cases, the Sponsor (or delegate) must develop a risk-based monitoring plan based on the risk assessment and tailored to the type and complexity of the study (pre- vs post-market) and its regulatory purpose. In addition to on-site monitoring, centralised monitoring (i.e., a remote evaluation of accumulating data) should be implemented extensively to ensure data quality.

The outcome of all monitoring activities must be documented in the form of reports, which must be timely provided to the Sponsor for review and follow-up.

A special case is when the results of the double-blind clinical experimentation are also to be used to validate the predictive model. In such cases, the clinical data collected during the study have a double use: they inform the safety/efficacy of the new intervention being tested and validate a predictive model. These two activities have different requirements: the analysis to assess safety or efficacy usually takes place once the study is finished, whereas the validation of predictive models may require some of the data (those used as input for the model) to be disclosed to the modeller as soon as they are collected so that the prediction can be made before the validation data are collected (which minimise the risk of bias). This creates a potential issue for the Sponsor, who should be asked to open the labels to the modeller while the trial is still running. A possible solution is this:

- Patients' assignment to study treatments is labelled as groups A and B. The key is disclosed to the modeller only, who is independent of the study team and bound to secrecy;

or

- the input data are identified and stored separated from the rest of the clinical data;
- the modeller is given access to this subset of the clinical data, but no label information;

– the modeller runs the simulations for each patient enrolled twice, once assuming the patient has been treated and one assuming the patient was given the placebo/comparator;
– once the study is completed and the labels are opened, the right simulation is chosen for each patient and compared to the clinically observed values to complete the validation study.

8.11 Audit

One of the critical responsibilities of a Sponsor is to ensure oversight of any clinical trial-related duties and functions, including oversight of the external organisations to which some activities have been delegated (ICH Q10, 21 CFR 211, 21 CFR Part 820.50). The Sponsor should redact an audit plan tailored to the level of risk, focused on critical-to-quality aspects identified in the risk assessment process. Appointed auditors must be independent of the Sponsor and qualified by documented training and experience to conduct audits.

In particular, when computer simulations are outsourced to external vendors, auditors should have the technical expertise to verify critical aspects such as version control for models and software, adherence to standards, and maintenance of adequate documentation.

All findings will be reported to the Sponsor in an audit report to be shared with the audited party. A corrective and preventive action (CAPA) plan should be implemented and followed up for relevant findings.

8.12 Non-compliance

Non-compliance with the protocol, procedures, and regulations can be detected during monitoring or may be a finding from an audit. The Sponsor is responsible for assessing the relevance of the non-compliance and implementing proper corrective actions or terminating the participation of a site/Investigator in the case of serious and /or repeated non-compliance, notifying the regulatory authorities when required by the regulation.

8.13 Premature Termination or Suspension of a Trial

The handling of a premature end of a study involging in silico methodologies is quite similar to that used in conventional clinical studies.

The possible reasons for premature termination or suspension of a hybrid/adaptive/in silico-augmented clinical trial should be described in the risk management plan and in the study protocol. If appointed, the independent Data Safety Management Board should be involved in evaluating potentially critical factors. Suppose a decision is made to terminate or suspend a trial, the Investigators and institution. In that case, regulatory authorities and Ethics Committees should be promptly informed and provided the reason(s) for the termination/suspension. The reasons for the premature termination/suspension of an in silico trial not directly involving human subjects should also be documented.

There are fewer reasons for in silico trials to terminate early than clinical trials. Nevertheless, this could happen when:

- In an in silico-augmented trial, the experimental observations made on the physical subjects enrolled in the study are not consistent with the predictions made for the virtual subjects.
- It becomes clear that the envisioned potential cannot be demonstrated based on an interim analysis.
- The sponsor terminates support and funding based on respective clauses in the agreements.
- The simulation software is not supported anymore by the developers/vendors, and issues or incompatibilities come up that do not allow completing the trial with the existing version. Considering such a scenario, risk should be minimised during model selection/development (see Chap. 3) but cannot be ruled out completely (e.g., bankruptcy).

One of the study arms demonstrates a clear benefit in an interim analysis. Ethically, this does not require trial termination as it could be completed without negative effects after publicising the initial results. Nevertheless, the sponsor could decide to terminate for economic reasons if the intended benefit has been demonstrated already.

Any premature trial termination requires detailed documentation regarding the reasons and circumstances and data acquired and analysed in a dedicated report.

8.14 Trial/study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the trial reports are prepared and, if applicable, provided to the regulatory agency(ies). The sponsor should also ensure that the clinical trial reports are adequately in line with the standards of the ICH E3 Guideline for Structure and Content of Clinical Study Reports[6] and model credibility assessment recommendations provided in Chap. 4.

[6] https://www.ema.europa.eu/documents/scientific-guideline/ich-E-3-structure-content-clinical-study-reports-step-5_en.pdf.

8.15 Essential Good Simulation Practice Recommendations

- The Sponsor of an in silico clinical trial, as well as the CRO that manages it, should have in staff the necessary technical expertise.
- Computer modelling and simulation services required to support clinical development studies should be performed as per the recommendations provided in ICH E9 Statistical Principle for Clinical Trials and be in line with existing regulatory guidelines on the use of CM&S in drug/medical device development plan.
- All computerised systems used in in silico clinical studies should be GxP-compliant.