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Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions

CHAPTER 3

TRIAL MANAGEMENT

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Time required to complete this chapter

Core content:	3h 00m
Additional/advanced content:	1h 30m
Activities/practical exercises:	30m
Total time:	**5h 00m**

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1 Introduction to the chapter

Well-designed (with relevant control and intervention groups and adequate statistical power) and well-implemented clinical trials conducted in diverse settings are indispensable to provide high-quality evidence needed to inform public health policy, regulatory decisions, and medical practice. These clinical trials should be prioritised while preventing underpowered, poorly designed clinical trials and avoiding the exposure of clinical trials participants to unjustified and unnecessary risk.

Many clinical trials fail to deliver high-quality evidence because of the lack of a structured, practical, business-like approach to trial management.

This chapter aims to provide a comprehensive overview of the trial management process from the starting phase to finish.

Here, the principal aspects of developing, implementing, and overseeing a clinical trial will be addressed, regardless of scale and scope of the trial. This chapter will address legal requirements, best practices elements, practical examples, checklists and online project management resources available such as tools for developing project plans and timelines; evaluate risk and planning contingency; monitoring progress and quality assurance.

2 Trial Management

Managing a clinical trial is not much different from managing any other project or business, sharing many characteristics found in project management, such as having specific project objectives to achieve through effective teamwork, within an agreed budget and timeframe.[1] Like any other project, **trial management** comprises the five basic process stages, described in Figure 1.

Figure 1: Stages of clinical trial management

The three main goals in the management of clinical trials are: 1) to reach the trial objective(s), 2) to respect the budget and study timelines and 3) to minimize the risks that could negatively impact the first two goals.

The starting point for any trial is the research question (Chapter 1: Clinical Trial Designs)[2] that will therefore drive the overall purpose of the trial(s) and its objectives, thereby contributing to

[1] PMI – Project Management Institute (2021). The standard for project management and a guide to the project management body (PMBOK® Guide) - Seventh Edition. Newtown Square, Pennsylvania: Project Management Institute, Inc
[2] CONSCIOUS II Chapter 1: Clinical Trial Design; https://www.conscious2.eu/

the rationale of the clinical trial. It should therefore be clear from the planning stage which scientific question the trial is going to address and how it will address it.

The success of a trial depends on maintaining good communications with all relevant parties, determining the work required and developing a schedule with milestones, as well the number of resources (full-time equivalent – FTE) required during the different stages of the trial. Additionally, calculating the associated budget, defining the trial schedule, identifying, and mitigating risks, monitoring the progress of the trial in terms of quality, timelines, budget and resources are also essential for the success of a clinical trial.

In order to deliver a clinical trial to meet the trial objectives successfully, the following points described in Table 1, should be observed.[3]

Table 1: Important management aspects to be addressed during the planning phase of a clinical trial.

Scope/quality	Budget	Timeline
• define all activities required to produce each of the project's deliverables as well as the order or sequence in which the activities must happen and the relationship between them. • plan internal and external communications. • define project personnel and responsibilities. • carefully plan the initial and subsequent management.	• develop a comprehensive budget that accounts for all expected expenses, including personnel, equipment, site cost, participant compensation, data management and quality control activities. • carefully evaluate possible risks /potential deviations to trial budget during the planning phase and allocate a portion of the budget for unexpected expenses or changes to provide some financial flexibility. • determine the allocation of resources, including staffing, equipment, and facilities necessary to accomplish each activity.	• estimate the expected duration of all trial activities identifying key milestones and deadlines for different phases of the trial. • plan realistic timelines in the initial phase and regularly review them. • extend trial timelines may be necessary, so plan ahead considering that extra funding must be fully justified and requested early. • for some trials (like commercial trials or those involving high-stake interventions or time-sensitive products) timelines can take precedence over cost considerations. This is why it is common funders request a feasibility study or pilot phase, to ensure that the necessary population is available, to identify potential obstacles, refine protocol if necessary and also can help to refine the budget and resource allocation before committing to fund the entire study.

[3] The Sixth Edition (2018) of the Guide to Efficient Trial Management. UK Trial Managers' Network. https://www.tmn.ac.uk/resources/34-the-guide-to-efficient-trial-management

2.1 Sponsor role and responsibilities or sponsor's representative

A sponsor is an individual, company, institution, organisation, or a group of organisations that takes on responsibility for initiation, management and financing the clinical trial.

According to the type of sponsor trial can be divided in **commercial clinical trials** and **non-commercial trials** also refereed as investigator-initiated trials (IITs) or academic clinical trials.

Commercial clinical trials concern trials that are funded and sponsored by a commercial organisation, usually pharmaceutical, biotechnology, or medical device industries, with the primary goal of developing and gaining regulatory approval for a new drug or medical product.

These trials are driven by profit motives. The sponsoring company invests in research and development, to generate safety data for licensing a medicinal product and bring the product to market, which can be sold at a profit. As these trials are typically funded by the sponsoring company there maybe concerns about conflict of interest.

On the other hand, non-commercial trials are trials sponsored or conducted by academic institutions, non-profit organization, foundations, or government agencies with the primary goal generate scientific knowledge and improve patient care. Academic trials are driven by the pursuit of scientific discovery to answer questions that clinicians face in their day-to-day practice, generate data on effectiveness and safety of a drug in the real-world setting, compare different treatment options for a disease and provide evidence to enable policy makers to make informed and sustainable policy decisions on public health.

Usually, these trials are funded by grants, public funding, philanthropy, or charitable organization, with a strong emphasis on transparency, sharing results and contributing to the broader scientific and medical community.

2.1.1 Sponsor responsibilities

According to **ICH GCP E6 (R2) Guidelines Chapter 5**[4], the **sponsor should implement and maintain a system to manage quality** throughout all stages of the trial process to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s), essential to ensure human subject protection and the reliability of trial results.

The trial activities include the design of efficient clinical trial protocols, tools, procedures for data collection and processing, as well as to conduct the statistical analyses and collection of information that is essential to decision making.

The sponsor should adopt a **risk-adapted approach** to identify the critical processes and essential data for the trial and to define how any risks and/or vulnerabilities identified in these areas will be mitigated.

2.1.2 Sponsor's representative in trial management

The sponsor can delegate specific responsibilities to any other individual or third-party organization that is willing and able to accept them. Any delegation of responsibilities to

[4] ICH-GCP E6 (R2) https://ichgcp.net/5-sponsor

another party should be formally agreed and documented by the sponsor. The sponsor must then implement procedures to ensure appropriate oversight of all delegated functions. Nevertheless, the sponsor remains accountable for all aspects of sponsorship whether delegated or not and according with the regulations the sponsor retains all responsibility for the conduct and report of clinical trials.

Sponsor responsibilities can be delegated to third parties' organizations through outsourcing, like **Clinical Research Organizations (CROs)** or **Clinical Trial Units (CTUs).** CROs and CTUs are organizations contracted with the capacity of provide support services on the management of clinical trials, namely randomised clinical trials (phase I-IV) and prognostic, diagnostic studies, and dealing with the design of the study, its organisation, logistics, centre selection, data management, monitoring, data analysis, pharmacovigilance, and reporting.

CTUs (also called academic CROs) are non-profit organizations that respond to the growing need for support of academic investigators and academic sponsors in different areas of study planning and conduct, creating awareness of the challenges that exist at a national level, and thereby foster a more favourable environment for academic clinical research. CTUs are usually units linked to University Medical Schools, Health Care Units or University Hospitals with the main function to support efficiently research active clinicians in the planning and execution of patient-oriented clinical research projects, and to advance the quality of clinical research.

On the other hand, CROs are for-profit companies and, despite the fact that they perform the same support services as CTUs, the target clients are the pharmaceutical industry and hence prices charged are usually higher. Nowadays, more and more of the major corporations are using CROs to lead their clinical trials and develop new medications because this way they acquire specific expertise without hiring permanent staff.

CTUs and CROs may substantially contribute to the quality and safety of clinical research and, although a trial sponsor may transfer all trial functions to a third-party CRO or CTU, the sponsor remains responsible for the integrity of the trial data and to ensure it is all factual and backed by sound science.

To review the key players in clinical trials please consult Chapter 12 of CONSCIOUS project[5] and watch this video "Key Players in Clinical Trial".[6]

QUIZ

1. According to section 5. Sponsor ICH GCP E6 (R2) guideline,[4] sponsor may transfer any or all of the trial related duties to third parties' organizations like CTUs/CROs but what always resides with the sponsor?
   a) the responsibility for ensuring guidelines are complied
   b) the responsibility for the quality and integrity of the trial data
   c) the responsibility for the protection of privacy of subject data
   d) the responsibility for ensuring the SOPs are followed

[5] CONSCIOUS: Chapter 12, Trial Managment; http://conscious.novaims.unl.pt/my/
[6] Key Players in Clinical Trial https://www.youtube.com/watch?v=nSvg6O9e9u0

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2. According to section 5. Sponsor ICH GCP E6 (R2) guideline,[4] before initiating a trial the sponsor should do what?
   a) ensure that all essential documents are defined and filed
   b) ensure that all teams involved in the trial has received adequate training
   c) define, establish and allocate all trial related duties and functions
   d) document the roles and responsibilities of the sponsor, third parties' organizations

The ECRIN is a not-for-profit intergovernmental organisation that supports the conduct of multinational clinical trials in Europe. ECRIN was created in 2013 with the legal status of a European Research Infrastructure Consortium (ERIC) and is an ESFRI landmark since 2016.

ECRIN provides sponsors and investigators with advice, management services and tools to overcome hurdles to multinational trials and enhance collaboration. Services range from trial preparation (e.g., advice on funding applications and trial design, from site selection to logistics and insurance issues), protocol review (scientific and logistical advice), and trial management (regulatory and ethical authorisation, adverse event reporting, monitoring, data management, statistical analysis and project management).

ECRIN works with diverse stakeholders in its member and observer countries as well as in other countries involved in ECRIN-supported trials and projects through their national networks of clinical trial units (CTUs).

To better understand how ECRIN works you can consult the website[7] and watch this video "ECRIN: Opening doors to European Clinical Research"[8]

2.2 Trial management plan (goals, deliverables/procedures, and risk assessment and mitigation)

A project management plan in the context of clinical trial defines and represents the agreed-upon document of scope, responsibilities, and guidance for key steps of the clinical trial process. It should outline the how, when and what-ifs of a project's execution. This not only ensures that those performing the tasks have a clear plan of what, when and how the trial activities are undertaken, but also enables auditors/inspectors to reconstruct how a trial was managed.

Trial management procedures/responsibilities that are common across all trials are usually defined in the **standard operating procedures (SOPs)** which are detailed, written instructions to achieve uniformity of the performance of a specific function. SOPs are an integral part of a successful quality management system – including quality assurance and quality control.

SOPs should be written by individuals knowledgeable with the activity and the organization's internal structure and with sufficient detail (however may differ based on whether the process

[7] https://ecrin.org/
[8] https://youtu.be/nhX0TumWt6E

is critical or not) so that someone with limited experience with, or knowledge of the procedure, but with a basic understanding, can successfully reproduce the procedure when unsupervised.

There is no one "correct" format; and internal formatting will vary with each organization and with the type of SOP being written.

A generalized format should include:

- Title that clearly identifies the activity or procedure;
- SOP identification (ID) number and date of issue;
- Table of Contents;
- SOPs Text:
    - describe the purpose, including any regulatory information or standards,
    - the scope to indicate what is covered,
    - responsibility,
    - the procedure written in a format that clearly describes the steps in order (with often use of diagrams and flow charts help to break up long sections of text);
- Annexes: if other SOPs are referenced or any checklists or forms included as part of the procedure should be attached to the SOP;
- Bibliography supporting the information/procedure described.

Free available SOPs and templates:

- Cambridge Clinical Trials Units[9]
- Global Health Training Centre[10]
- Imperial College London[11]
- Community Health Network[12]

The trial management plan should also outline procedures regarding the data management (Data Management Plan) describing the data management life cycle, what data are expected to be collected, how data will be collected, analysed, and stored after the end of the trial, and what processes will be used to share and preserve trial data. Chapter 6[13] describes all information included in a Data Management plan and the best practices to develop one.

Every clinical trial will have difficult milestones. However, a well-designed management plan increases the likelihood of success of a clinical trial, helping to sidestep some of the regular issues, supporting a coherent organization and facilitating the transparency between all the parties involved.

It is common to use outline-based and/or graphical tools for calendars and schedules to elaborate a trial management plan, and they must include how the day-to-day running of the

[9] https://cctu.org.uk/governance
[10] https://globalhealthtrials.tghn.org/resources/templates/
[11] https://www.imperial.ac.uk/research-and-innovation/research-office/research-governance-and-integrity/sop-associated-documents--templates-/
[12] https://www.ecommunity.com/sites/default/files/uploads/2018-06/CHNw_ORA_SOPs_for_the_Conduct_of_Clinical_Research.pdf
[13] CONSCIOUS II: Chapter 6, Data Management and statistical analysis; https://www.conscious2.eu/

trial will be managed, with focus on protocol adherence, subject care, and service quality, along with how to achieve each standard.

A trial management plan should include the following sections:

1. **Project goals/deliverables/milestones**: in accordance with what is defined in trial protocol.
2. **Team Organization**: outlines the structure of the team and defines the individual roles of the team members. It should also describe who will be responsible for essential activities, such as staff recruitment, staff management.
3. **Management of the study**: details a responsibility blueprint with a clear distribution of tasks, goals and deadlines for each project objective and for each team member.
4. **Management of internal and external communications** creates a communication plan that outlines the method and schedule for relaying information, updates and requests between and within teams (such as regular meeting, e-mails, training, newsletters, trial webpage, dissemination of results).
5. **Risk Assessment**: identifies potential risks associated with the trial, assesses the likelihood of these risks to occur and presents a detailed plan to mitigate them.

2.2.1 Team Organization

The management of diverse multidisciplinary teams to run the day-to-day activities of a clinical trial and its complexities requires the definition of an organisational structure. Commonly, trials are overseen by three committees: the Trial Management Board, the Trial Steering Committee and the Data and Safety Monitoring Board (DSMB), divided into management, strategic, and operational levels. The arrangements for trial oversight may vary from trial to trial but they should be detailed in the protocol. Figure 2 summarizes an example of a trial administrative organization.

The **Trial Management Board** role is to provide a leadership during the clinical trial overseeing the day-to-day operational management of the clinical trial focusing on the practical aspects of trial execution, resource allocation, problem-solving and handling with numerous administrative components, including:

- Liaison between the sponsor and the clinical research team,
- Hiring and training all staff,
- Ensuring all parties are aware of their roles and responsibilities,
- Coordination among research teams across sites,
- Tracking study finances,
- Regulatory compliance in trial protocol, subject safety and data quality,
- Tracking subject recruitment and retention,
- Adverse Event (AE) documentation and reporting,
- Oversight of trial drug storage and use,
- Data Management – data collection, electronic data capture (EDC),
- Timely renewal of necessary financial and regulatory approvals.

The group normally includes the Chief Investigator, the Trial Manager, the Statistician, the Database Manager, and other relevant members of a lead CTU/CRO team. It may also include

other members of the trial team with specific expertise, such as the Database Programmer, Pharmacist, Health Economist and one or two site Principal Investigators.

This group should meet regularly to ensure the efficient day-to-day running of the trial, to keep members up-to-date with the trial and to monitor progress and to prepare reports for the steering committee.

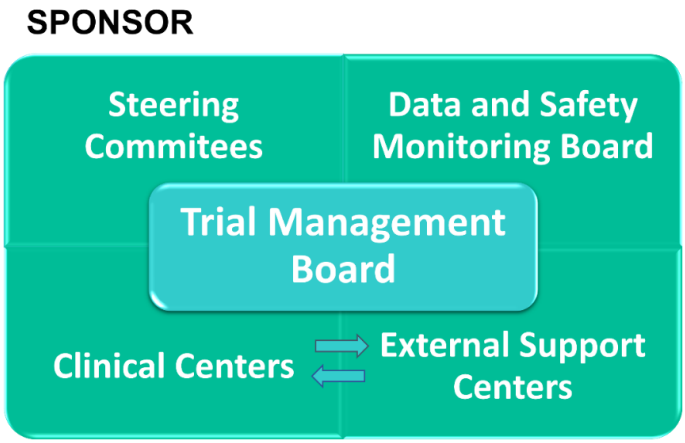


Figure 2: Common clinical trial's administrative organization

The role of the **Trial Steering Committee** is to provide independent oversight of the trial on behalf of the sponsor and funder and to ensure that the trial is conducted in accordance with the principles of GCP and relevant regulations, focusing its activities on strategic and scientific aspects of the trial, particularly supervising the progress of the trial towards its overall objectives, adherence to the protocol and participant safety. In addition, the Steering Committee should review any relevant emerging information regarding the intervention or clinical procedure that may have an impact on the trial.

To avoid real or perceived conflict of interest or bias it is recommended that the Steering Committee includes a majority of voting members who are independent of the trial, namely an independent chairman and public/patient representatives. In addition, it also includes the Chief Investigator and one or two other investigators (non-independent members), representatives from the sponsor and funder. When required, the relevant members of the Trial Management Board may attend the Steering Committee meetings to present information. The Steering Committee meetings should be periodically (e.g. 6–monthly), but less frequently than the Trial Management Board meetings.

The **Data and Safety Monitoring Board (DSMB)** main role is to monitor the data accumulated from an ongoing clinical trial, assess the safety and efficacy of the intervention, and review external evidence with an impact on risk/benefit balance. Based on these tasks/roles/functions, a DSMB has the capacity to make recommendations to the Trial Steering Committee and Trial Management Board regarding any safety issues, critical efficacy endpoints and any ethical reasons that might impact the future conduct of the trial, such to continue, modify, or stop a trial.

The DSMB is a group of independent members external to a study,
namely an independent chair and experts in the field such as clinicians with expertise in the relevant area and expert statisticians. The independence of the members is extremely important in the case of access to unblinded information during a clinical trial, as it increases the potential to introduce bias to future trial results.

The Committee for Medicinal Product for Human Use (CHMP) of the European Medicines Agency (EMA),the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have published guidelines providing clarification on the role and necessity of DSMB in different phases of drug development and throughout the product lifecycle as well as with regard to the responsibilities for implementing DSMB decisions, ensuring the scientific integrity of a clinical trial involving a DSMB.[14,15,16]

The frequency of DSMB meetings depends on several factors including the rate of enrollment, scheduled interim analyses, safety issues or unanticipated adverse events and availability of data.

2.2.2 Management of the trial

Like in any project, a key component of the trials's success is the management of its timelines. The Trial Management Board or the project manager should:

- Define all activities required to produce each of the project's deliverables,
- Define the order or sequence in which the activities must happen and the relationship between them,
- Establish the resources (both human and material) necessary to accomplish each activity,
- Estimate the duration of all activities consequently during the trial duration.

All these information should be outlined in the trial management plan and can be organized using several management tools like project timelines, flowcharts, Gantt Charts, and network diagrams. There are several free or open-source tools available for various aspects of clinical trial management. These tools can be helpful for academic institutions, small research organizations, or anyone with a limited budget. Throughout the chapter we will give some examples of free clinical trial management tools and templates.

Project Timeline

Project timeline is a display of events arranged in chronological order over a certain time frame. The layout of a project timeline can vary depending on the specific structure of the trial in question. However, there are a few elements that a project timeline typically includes regardless of the project type:

- A timeband (usually horizontal) which represents the timescale of the project,
- List of underlying tasks and milestones,
- Task descriptions,

[14] FDA Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees
[15] EMA GUIDELINE ON DATA MONITORING COMMITTEES https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf
[16] https://www.nidcr.nih.gov/research/human-subjects-research/toolkit-and-education-materials/interventional-studies/data-and-safety-monitoring-board-guidelines

- Start dates,
- End dates,
- Task durations,
- Percent completed.

To create your clinical trial timeline you can use free online templates, available for example here[17] and here[18].

Another commonly used project management tool is the Gantt chart that illustrates the work completed over a period of time in relation to the time planned for the work. Typically, on the left of the chart is a list of the activities, while on the right side of the chart it has a timeline with schedule bars that visualize work. To create a Gantt Chart use tool.[19]

Budget

As mentioned in sub-chapter 2.1 depending on the type of sponsor there may or may not be a financial implication to running the study. Funding for clinical trials comes from a wide variety of sources, including government, private investors, charities, universities, and other research institutions. Commercial clinical trials are funded and sponsored by a commercial organisation, usually pharmaceutical, biotechnology, medical device industries. Since most academic clinical trials are funded through grant awards with a fixed budget, carefully evaluate costings for an initial clinical trial budget and an effective budget management is a critical factor of running a clinical trial successfully.

The clinical trial overall budget should cover all trial-related costs, including fees and indirect costs (overheads). To prepare an overall budget there is a range of information about the clinical study/trial that needs to be known, such as:

- What is the clinical question to answer?
- How many patients are needed to answer question?
- How many sites in how many countries are needed to recruit patients over what period of time?
- What will be measured to determine safety and clinical outcomes?
- What are the per patient costs in terms of technology (imaging, labs, etc.), treatments (drugs, devices), and personnel time to screen, enrol, measure outcomes, follow subjects, and data entry?
- Who is running/coordinating the trial and what are their effort/costs/expenses?
- Who is providing statistical analysis, managing, and monitoring data and what are their effort/costs/expenses?
- What are the travel and communication costs to train trial staff and sites?
- What additional costs of technologic measurements (image analysis, laboratory analysis, etc.) that are required?
- Are you using consultants/advisors and how much do they cost?

[17] https://www.officetimeline.com/gantt-chart/templates/clinical-trial-roadmap
[18] https://www.smartsheet.com/content/clinical-trial-templates-samples
[19] https://www.onlinegantt.com/#/gantt

The key cost drivers for any clinical study/trial are the following:

- **Patient Costs:** include the costs for screening failures, baseline patient measurements, procedural costs and expenses reimbursment,
- **Site Costs:** covers any expenses associated with the site, such as start-up fees, administrative costs, fees, storage fees for trial records, and site management costs,
- **Non-Patient Costs:** includes consultation fees, monitoring board fees, and IMP/intervention/device costs including: drug/placebo manufacture, labelling, blinding, device or intervention purchase, testing, shipping and destruction and unblinding arrangements,
- **Labor Costs:** includes cost for all the staff required for the project and their full-time equivalency (FTE),
- **Trial Management Cost:** includes costs related with the regulatory (submitting the trial to the regulatory authorities and ethics committees, regulatory fees) and monitoring activities (pre-study visits, initiation fees, monitoring, and close-out fees) and costs for project management, quality management, data management, fees for biostatistician,
- **Miscellaneous:** include travel and meeting costs and any technology needs; document translation costs,
- **Unexpected Costs:** covers costs resulting from protocol amendments, costs that may incur from adverse events, value added tax (VAT), delays, and inflation.

Costs are usually biggest during the implementation phase but may also be significant during trial set-up. Expenses should be monitored in comparison with the planned budget schedule, considering the actual work completed.

UKTMN Guide to Efficient Trial Management provide a trial/research budget checklist[20] and you can find a free available template here.[21]

2.2.3 Communication Plan

The purpose of the communication plan is to ensure relevant, accurate, and consistent information about the clinical study/trial. It is provided to all involved parties (internal and external stakeholders), ensuring their timely and efficient involvement, support and cooperation when required.

The communication plan provides a framework to manage and coordinate the wide variety of communications that take place during the trial. The communication plan defines:

- What information should be communicated,
- When and how the communications should be delivered,
- Who will receive the communications,
- Who communicates,
- Where e.g. emails, social media, newsletters, dissemination of results,
- Frequency of the communications,
- It will also include status reporting and issue escalation process.

Clinical trial participants have a right to be informed throughout the entire process of human subject research. Effective communication on the purpose of the research, risks and benefits of participating, how participants will be protected and sharing of research results with

[20] https://www.tmn.ac.uk/resources/34-the-guide-to-efficient-trial-management
[21] https://www.smartsheet.com/sites/default/files/2020-03/IC-Clinical-Research-Budget-10628.xlsx

participants and other stakeholders is vital to the success of a clinical trial, as it can improve recruitment and retention, build trust through transparency, foster collaboration, and reduce health disparities.

2.2.4 Risk Assessment

In compliance with the **ICH-GCP E6 (R2) Guidelines,**[4] the sponsor is responsible for implementing a robust **system to manage quality** throughout all stages of the trial process and should **adopt a risk-based approach** to identify those processes and data that are critical to ensure human subject protection and the reliability of trial results and how can any risk and/or vulnerability identified in these areas be mitigated.

Chapter 4: Quality and regulatory affairs and sources of regulatory information[22] has a sub-chapter 4.2 dedicated to Quality, namely to the Clinical Quality Management System (CQMS) and Risk Assessment, here we will provide some complementary information.

The risk associated with a clinical trial can be considered at various levels, depending on the institution/team and stakeholder specific responsibilities/duties with respect to the trial. For example, the funder is concerned with the scientific and financial risks, while the sponsor considers the legal and reputational risks and the clinical centers are concerned with the compatibility of the trial with its duty of care to patients.

For every trial, however, there is also a core set of risks inherent to the trial design/protocol and methodology that relate to the safety of the participants and the integrity/reliability of the results.

A risk-based approach implies that risk assessment should be undertaken since the very start, during the trial planning stage, and that the chosen strategy should be periodically reviewed and adapted during the conduct and closing phases of a trial.[4]

The OECD Recommendation on the governance of Clinical Trials[23] introduced in 2012 a risk-based oversight and management methodology for clinical trials to facilitate international cooperation in clinical trials on medicinal products, particularly for trials initiated by academic institutions.

European Commission through an expert group on clinical trials for the implementation of Regulation (EU) No 536/2014, published in 2017 recommendations on Risk Proportionate approaches in clinical trials[24] to facilitate the development of a systematic, prioritised, risk-based approach to quality management of clinical trials.

Risk assessment process starts with the **identification of risk critical to trial processes and data**, by examining the trial design, intervention, investigational medicinal product, methodology, population, and procedures specified in the protocol to identify specific categories of vulnerability. Table 2 illustrates some categories with the main types of risks which may affect the achievements of the objectives in those categories.

[22] CONSCIOUS II: Chapter 4; Quality and regulatory affairs and sources of regulatory information; https://www.conscious2.eu/
[23] OECD Recommendation on the governance of Clinical Trials https://legalinstruments.oecd.org/public/doc/281/281.en.pdf
[24] https://health.ec.europa.eu/system/files/2017-08/2017_04_25_risk_proportionate_approaches_in_ct_0.pdf

Table 2: Examples of risks identified in specific vulnerability categories[25]

Categories	Examples of Types of Riskc/Events
Timelines	Patient recruitment rate Regulatory approval timelines CRFs incompletions rate
Safety	Number of Aes/SAEs per patient Number dropped out due to AE Number of Aes /SAEs with define causal relationship
Quality	Number of protocol deviations/ violations per site Number of DCFs generated per site Number of incidences with incomplete/ missing subject diary
Compliance	Number of deviation in SAE reporting Number of incidences with impropwe ICF process/documentation Inadequate monitoring of clinical investigations
Budget	Increase inmonitoring visits per site Increase in clinical trial duration Increase of sites'budgets

Then, the **risk analysis based on the perception of the risk's probability** (likelihood) of occurring and severity/gravity of its consequences should be evaluated. Next, the **risk evaluation**, identified **against existing risk controls** needs to be addressed to determinate the risk score/grade. For each trial it is important to decide which risks are critical and carry the highest consideration during risk assessment, to ensure that monitoring efforts are focused on preventing or mitigating important and likely sources of error in their conduct, collection and reporting. Up to certain limits some risks are acceptable, the definition of tolerance threshold will vary from trial to trial and will help in deciding trigger points to initiate controlling/mitigation measures. An example of a risk matrix 3X3 with these tolerance thresholds is given in the sub chapter 4.2.1 Risk assessment process with examples.[22]

Once developed, the risk assessment is incorporated into the protocol, the management and monitoring plans, and into agreements between the parties by defining roles and responsibilities. This then would form the basis of a common understanding by all organisations/teams involved in the trial, so that the control measures, resources, procedures, and processes implemented during the trial ensure the participants' rights, safety and well-being and the reliability of trial results.[26]

QUIZ

1. In a clinical study/trial, who is responsible for the risk assessment?
   a) The clinical site teams
   b) The monitor
   c) The sponsor
   d) The regulatory authority

2. When evaluating risks in clinical trials what aspects should be considered?
   a) Impact, Cost and Likelihood
   b) Likelihood, impact, detectability

[25] https://www.ddismart.com/whitepaper/risk-assessment-in-clinical-trials/
[26] ICH-GCP E6 (R2) https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

c) Cost, Predictability and Quality
d) Time, Impact and Predictability

3. In a clinical trial increasing the number of active sites to ensure that recruitment time is met is referred to what?
   a) Impact reduction
   b) Risk Assessment
   c) Slack
   d) Risk Mitigation

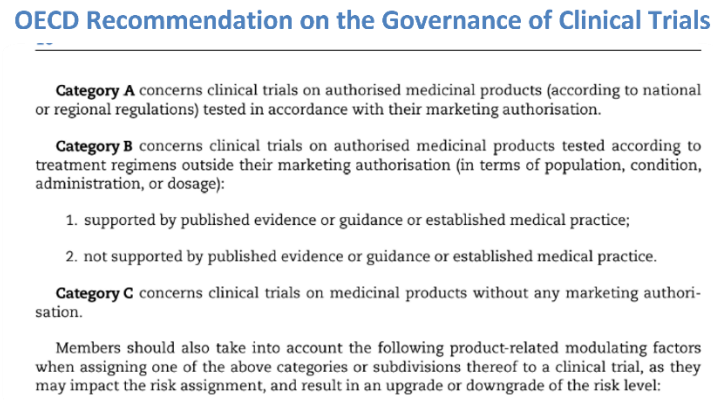
The concept of risk-based approach implies that the trial-specific strategy varies from trial to trial. Here you can find some tools available to create the risk assessment of your trials:

- ECRIN Risk-Based Monitoring Toolbox[27] provides information on tools available for risk assessment, monitoring and study conduct, the institutions where they are used, and other relevant details such as links and user feedback.
- Risk Assessment Form of Swiss Clinical Trials Organisation[28] provides step-by-step guide for sponsor-investigators that helps them ensure that the potential risks of a clinical research project in line with current requirements (ICH GCP E6(R2))
- TransCelerate Risk Based Monitoring solutions[29] provides an interactive guide, original position paper, informational materials, examples and templates for risk planning and assessment.
- Global Health Trials' has free available a templates library, including Risk assessment template.[30]

The Clinical Trials Regulation (EU) No 536/2014,[31] that came into force on 31 January 2022 introduce the concept of low-intervention clinical trials.

The definition of a low-intervention clinical trial and clinical trial as set out in Clinical Trials Regulation (EU) No 536/2014 is compatible with the different risk categories for clinical trials introduced in December 2012 in the Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials.[6] The OECD Categories A and B(1) correspond to the definition of a low-intervention clinical trial as set out in the Clinical Trials Regulation (EU) No 536/2014, and the OECD Categories B(2) and C correspond to the definition of a clinical trial as set out in Clinical Trials Regulation (EU) No 536/2014) (Figure 3).

[27] https://ecrin.org/risk-based-monitoring-toolbox
[28] https://www.sctoplatforms.ch/en/tools/risk-assessment-form-for-clinical-research-projects-30.html
[29] https://www.transceleratebiopharmainc.com/assets/risk-based-monitoring-solutions/
[30] https://globalhealthtrainingcentre.tghn.org/site_media/media/medialibrary/2015/08/Risk_assessment_template.docx
[31] https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05



OECD Recommendation on the Governance of Clinical Trials

Category A concerns clinical trials on authorised medicinal products (according to national or regional regulations) tested in accordance with their marketing authorisation.

Category B concerns clinical trials on authorised medicinal products tested according to treatment regimens outside their marketing authorisation (in terms of population, condition, administration, or dosage):

1. supported by published evidence or guidance or established medical practice;

2. not supported by published evidence or guidance or established medical practice.

Category C concerns clinical trials on medicinal products without any marketing authorisation.

Members should also take into account the following product-related modulating factors when assigning one of the above categories or subdivisions thereof to a clinical trial, as they may impact the risk assignment, and result in an upgrade or downgrade of the risk level:

Figure 3: Risk categories for clinical trials introduced in December 2012 in the Recommendation of the Organisation for Economic Cooperation and Development (OECD) Council on the Governance of Clinical Trials[32]

2.3 Main essential documents for conducting a clinical trial

The Chapter 8 of the ICH-GCP E6 (R2) Guidelines[26] **defines a minimum list of essential documents** that demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. These essential documents can be grouped in three sections according to the stage of the trial during which they will normally be necessary: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. Most of the documents are generated and used in the planning phase, but there are some that will be used in later phases. These documents should also be prepared as templates during the planning phase and will be used throughout the study.

To learn what essential documents should be **generated before each phase of the trial**, as well as the **purpose of each document,** and whether they should be filed in either the investigator/institution or sponsor files, or both, **please consult the 8.2 Before the Clinical Phase of the Trial Commences, 8.3 During the Clinical Conduct of the Trial** and **8.4 After Completion or Termination of the Trial.**[26]

Essential documents include the trial protocol, information given trial participants – informed consent form (ICF), case report form (CRF), and other operational documents. To review the essential documents in clinical trials, you can watch this video "Basics - Part 22 - Essential Documents"[33] and review the **Chapters 5 and 9 of CONSCIOUS**.[34,35] To create your clinical trial documents you can use free online templates, available for example here[36] and here[37].

All these documents should be filed in the **Trial Master File (TMF)** established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. In December

[32] https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0397#annex
[33] https://www.youtube.com/watch?v=9_cBEDpzym4
[34] CONSCIOUS: Chapter 5 Informed Consent Form; http://conscious.novaims.unl.pt/my/
[35] CONSCIOUS: Chapter 9 Clinical Trial Protocol & Case Report Form; http://conscious.novaims.unl.pt/my/
[36] https://globalhealthtrials.tghn.org/resources/templates/
[37] https://www.smartsheet.com/content/clinical-trial-templates-samples

2018 EMA published a guideline[38] to assist the sponsors and investigators/institutions in complying with the requirements of the current legislations, as well as ICH E6 GCP Guideline regarding the content, management and archiving of the clinical TMF (paper and/or electronic).

TMFs enable the operational staff, as well as monitors, auditors and inspectors to evaluate compliance with the protocol, the trial's safe conduct and the quality of the data obtained. The TMF documentation should be sufficient to adequately reconstruct the activities undertaken in conducting the trial, along with decisions and justifications made concerning the trial.

The TMF is usually composed of a sponsor TMF, held by the sponsor organisation, and an investigator TMF held by the investigator/institution. The investigator TMF is often referred to as the investigator site file (ISF). The TMF kept by the sponsor and the ISF kept by the investigator/institution may have different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor. (e.g. subject identification code list filed in ISF only and master randomisation list filed in the sponsor TMF only).

The legislation does not differentiate between paper and electronic TMFs (eTMFs). eTMFs should enable appropriate security and reliability, ensuring that no loss, alteration or corruption of data and documents occur.

Access to the TMF should be based on a role and permission description that is defined by the sponsor and/or investigator/institution.

At closing of the trial, the TMF including the audit trail for eTMF should be archived appropriately to enable review after the clinical trial has ended. The dynamic character of the audit trail of an eTMF should be preserved. Archiving should be undertaken after the investigator/institution and sponsor have confirmed that their filed TMF documentation is complete.

QUIZ

1. Which of the following documents need to be on file before a clinical trial can star?
   a) Agreements Sponsor trial master file only
   b) Regulatory and Ethical approvals
   c) Insurance
   d) All of them

2. According to ICH GCP E6 (R2) guideline where should the initiation visit report be filed?
   a) Sponsor trial master file only
   b) Investigator site file only
   c) Both sponsor and investigator files
   d) Not specified

3. According to ICH GCP E6 (R2) guideline where should the Subject Identification code list be filed?
   a) Sponsor trial master file only

[38] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

b) Investigator site file only
c) Both sponsor and investigator files
d) Not specified

List of the content of a TMFs according to ICH E6 Guidance regardless of the type of clinical study.

1) Investigator's Brochure (IB)
2) FDA Form 1572 (only applicabel for trials running in USA)
3) Delegation of Responsibilities Log
4) Protocol and Amendments
   - Typically there is a signature page in the protocol/amendment that should be signed by the Principal Investigator (PI) and returned to the study sponsor
   - A copy of the protocol/amendment signature page should be retained
   - When amendments are issued, they should be filed accordingly. Outdated protocols should not be removed from the file
5) Information Given to a Study Participant
   - Informed Consent
   - Other Written Information
6) Recruitment Advertisement
7) Financial Disclosure Form (FDF)
8) Master Clinical Trial Agreement (MCTA)
9) IRB Approval
10) IRB Roster
11) IRB Correspondence
12) Curriculum Vitae (CV)
13) Medical Licensure
14) Training Records
15) Laboratory Certification or Accreditation
16) Laboratory Normal Values
17) Monitor Visit Reports
18) Sponsor Correspondence
19) Miscellaneous Documentation
20) Source Documents
21) Notification of Serious Adverse Events by Investigator to Sponsor
22) Notification of Serious Adverse Events by Sponsor to Regulatory Authorities
23) Subject Screening Log
24) Subject Identification Log
25) Subject Enrollment Log
26) Signature Sheet
27) Investigational Product Accountability Log
28) Documentation of Investigational Drug Destruction

2.4 Overseeing the progress of the trial

Oversight the progress of the trial is a critical element of the trial management and is part of the quality management system implemented by the sponsor to ensure the protection of research participants and integrity of the collected data. Arrangements for the oversight of trials will vary according to the nature of the trial and should be proportionate to the complexity and

associated risks. These arrangements should be detailed in the protocol and in the trial management plan

Different sponsors may have particular requirements, but commonly, trials are overseen by three committees: the Trial Management Group (TMG), the Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC).

As explained in Chapter 4: Quality and regulatory affairs and sources of regulatory information[22]in clinical trials aims at establishing and consistently achieving compliance with ethical, regulatory and GCP standards and maintaining integrity of the data collected. Quality control and quality assurance are the standard components of the quality management system.

Clinical trial monitoring that will be described in the next sub-chapter is quality control, as it provides regular, timely feedback on the conduction of the trial in the clinical sites. Whereby, an audit of a clinical trial is a clinical assurance activity. It is an independent, top-down, systematic evaluation of the all trial process to ensure compliance with the protocol, the sponsor's SOPs, GCP, and all applicable regulatory and ethical requirements.

2.5 Monitoring

Trial monitoring is one of the key activities undertaken as part of the quality control in trial management. ICH GCP defines monitoring as the act of overseeing the conduct and progress of the trial, ensuring that management strategies (described in a Trial Management Plan) are followed and compliant with GCP, protocol and regulatory requirements.[4] The monitoring process should be performed in accordance with what was established in the monitoring plan.

Here you can find a video "CRA Basics: The Purposes of Clinical Trial Monitoring"[39] summarizing the importance of monitoring.

Monitoring of a clinical trial is a sponsor responsibility and is an essential quality control process, ensuring:

- That the rights, well-being and safety of participants are protected,
- That reported data from the clinical trial is accurate, complete and verifiable from source documents,
- Compliance with the protocol, Good Clinical Practices (ICH-GCP)[4] and all applicable regulatory requirements.

The sponsor:

- Should determine the appropriate extent and nature of monitoring,
- Appoint a person or a team with appropriate training and scientific and/or clinical to monitor a clinical trial,
- Should develop a systematic, prioritized, risk-based approach to monitoring clinical trials and develop the monitoring plan.

[39] https://www.youtube.com/watch?v=qQqpLcIFsEU

2.5.1 Selection and Qualification of Monitors

The **Monitoring team,** including the clinical trial monitor, should be appropriately trained to be fully familiar with the protocol, informed consent form and any other written information to be provided to participants, the investigational product(s), trial documentation, the sponsor's SOPs ICH-GCP guidelines, and applicable regulatory requirements. Additionally, the Monitor´s qualifications should be documented.

Here you can find a detailed description of the main responsibilities of a Monitor/CRA.[4]

Monitor's responsibilities
• Verify if the clinical research center has appropriate staff, facilities and equipment to safely and properly conduct the clinical trial.
• Train the principal investigator and site team on the protocol and protocol related procedures.
• Verify that the principal investigator and staff are qualified to conduct the trial. • Verify that clinical research center follows the approved protocol or respective amendments (if any).
• Verify that informed consent was obtained from each participant before any procedures of the trial were made.
• Verify that only eligible participants are being enrolled.
• Verify that the principal investigator and trial staff are only performing procedures accordingly to the protocol, for which they are trained and have been delegated to do so.
• Verify that investigational products are properly stored, handled, used and returned.
• Verify that source documents and other trial related documents are accurate, complete, updated and properly kept.
• Verify that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and clearly identify the clinical trial.
• Identify if there are any missing visits, tests, examinations, or procedures that were not done and if these are clearly reported on source documents and Case Report Form (CRF).
• Review the completeness and accuracy of CRF entries.
• Inform the research team of any inconsistencies, incorrection, or omissions of CRF entries and assure that these are properly corrected.
• Assure that all adverse events (AEs), concomitant medications and intercurrent disease in are properly identified, classified and reported within time frame required by the protocol, GCP guidelines, the sponsor, the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), and regulatory authorities.
• Verify if withdrawals and dropouts of enrolled participants are reported and clearly explained on the source documents and CRFs.
• Communicate deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the principal investigator and take appropriate measures to prevent recurrence of the detected deviations.
• Write a Monitoring report describing after each monitoring visit including a summary of what was reviewed and if and which findings/facts, deviations and deficiencies were identified. This report should also state what actions need to be implemented to ensure compliance to protocol and GCP. This report should be sent to the sponsor of the trial and research team. Reporting of centralized monitoring activities should be regular and may be independent from on-site visits.

It is important to take into consideration the profile of a clinical trial monitor, also called **Clinical Research Associate (CRA)**, since he/she is the main communication player between the sponsor and the clinical research center.

2.5.2 Extent and nature of monitoring

Monitoring of a clinical trial should occur before, during and after the trial. Monitoring of clinical trials may include on-site visits, remote monitoring, centralized monitoring, or a combination of all three approaches:

On-site monitoring: performed as an in person (monitor) evaluation at the clinical research center where the trial is being conducted.

Remote monitoring: off-site evaluation performed by the monitor through telephone contact, and web-based platforms away from the clinical research center where the trial is being conducted.

Centralized monitoring: performed remotely in a timely manner at a location different from the site where the clinical trial is being conducted. Here, the data sets analyzed are gathered in the trial database and not at the research site, therefore differing from remote monitoring. It can be done by the monitor, data managers, biostatisticians. Central monitoring provides complementary information to the on-site monitoring since it can include statistical analyses. This will help to identify:

- Missing data, inconsistent data, and data outliers,
- Evaluate systematic or significant errors in data collection and reporting across research sites,
- Protocol deviation,
- Analyze site characteristics and performance metrics,
- Examine consistency and variability of data across research centers,
- Select research centers and/or procedures for targeted on-site monitoring (eg, adverse event evaluation and reporting).

On site, remote and centralized monitoring are an essential component of the **Risk-Based Monitoring (RBM) strategy**. The RBM focuses on oversight of the clinical study by the sponsor while preventing and mitigating potential risks related to data quality in processes that are crucial for participant 'safety and trial integrity.

In summary, RBM centers in:

- Identifying potential threats,
- Design a plan to monitor those threats,
- Adjust the monitoring plan as necessary.

Additionally, this strategy also has as a secondary objective: the efficient use of limited resources (human, financial time).

The following web-based RBM Score Calculator[40] is a questionnaire that provides an asset to evaluate the best monitoring strategy for a clinical trial.

The monitoring plan should take in account the following considerations:

- Objective of the trial,
- Purpose of the trial,
- Trial´s design,

[40] https://www.sctoplatforms.ch/en/tools/risk-based-monitoring-score-calculator-31.html

- Complexity of the trial,
- Blinding (unblind, blind, double blind, triple blind),
- Sample size,
- Trial's endpoints.

2.5.3 Monitoring plan

A **monitoring plan**[26] is a document specifically developed for a clinical trial, that describes the strategy, methods, responsibilities of all parties involved, and requirements for monitoring the trial.

The sponsor should develop a monitoring plan that is tailored to the risks of the trial specific for human trial participant protection and data integrity. The monitoring plan should also describe he various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

In the monitoring plan several topics should be addressed:

- Timing and frequency on monitoring visits,
- Activities to be performed during the visits:
  - source documentation to be verified;
  - confrontation of source data with data collected and reported in CRF;
  - endpoints to be verified;
  - site compliance to GCP and regulatory requirements;
  - safety reporting;
  - verification of trial documentation (ISF and patient binders containing protocol related medical records);
- Case Report Form (CRF) and query management,
- Monitoring reports and follow-up letters,
- Archiving.

Examples of monitoring plan for clinical studies can be found at the following links:

- Monitoring plan template from SCTO Platforms[41]
- Monitoring plan from The King's Health Partners Clinical Trials Office[42]

2.5.4 Monitoring Visits

During the course of a clinical trial the sponsor carries out several monitoring visits with different objectives. The first monitoring visit is performed to assess if the clinical research center has all the conditions to conduct the clinical trial. This meeting is called **Site Qualification Visit (SQV).**

Then, just before the clinical trial begins at the site, the entire research team at the site is trained on the protocol, handling of investigational product, trial documentation and procedures. At this point it is expected that all team members are already certified in GCP and have access to study platforms, such as the Interactive Web Response System (IWRS), CRF,

[41] https://www.sctoplatforms.ch/monitoring-plan-23.html
[42] https://khpcto.co.uk/SOPs/03_MonitoringSOP.php

central lab (among others). This visit is called **Site Initiation Visit (SIV)** and by its end, research team will be delegated to perform certain functions accordingly to their qualifications and training.

After site activation (Sponsor's Green light), recruiting of subjects can begin and the sponsor will regularly return to the center to perform **Monitoring Visits (MVs),** according to the **monitoring plan.** The objective of these visits is to make sure that the trial is progressing well, and to verify that the reported data is complete and accurate. The monitoring visits can be on-site and are called **Site Monitoring Visits (SMV)** or they can be remote (by telephone or web platforms) and are called **Remote Monitoring Visits (RMV).** Additionally, the sponsor might also perform **Centralized Monitoring (CM)** to the trial.

When a research site completes or withdraws from a clinical trial, the monitor will perform a **Close-out Site Visit (COV)**. At this visit a final review of the data and documentation is performed.

The following videos summarize the sponsor visits:

- "CRA Basics: Good To Know About Visits - Part 1"[43]
- "CRA Basics: Good To Know About Visits - Visit Frequency - Part 4"[44]
- "The Various Clinical Research Monitoring Visits Deconstructed"[45]

To summarize, monitoring visits can be grouped in 4 types: pre-study visits (SQV), initiation visits (SIV), periodic monitoring visits (RMV; SMV; CM), and close-out visits (COV), As described in **Figure 4**. Study sites may also be monitored or audited by the sponsor, the CRO/CTU, IRBs or inspected by EMA/FDA.

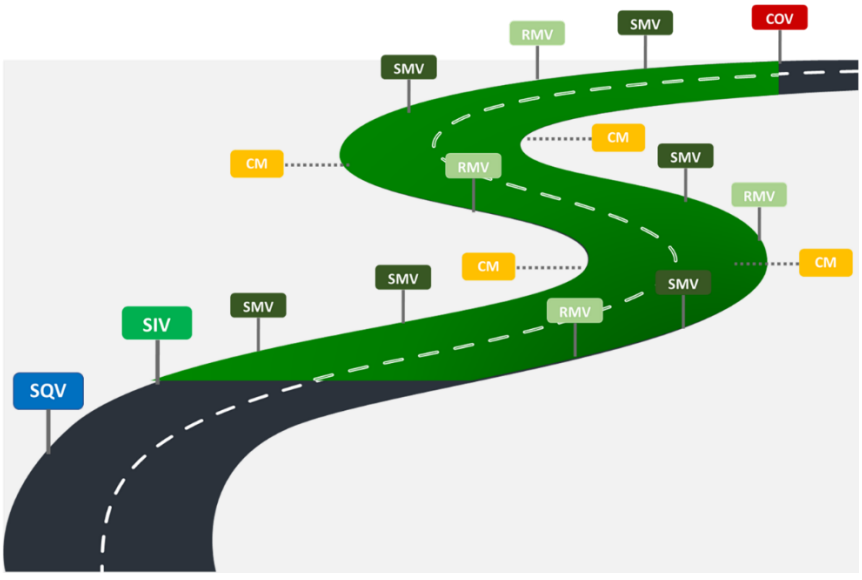


Figure 4: Clinical trial's monitoring visits

Legend: CM – centralized monitoring, COV – close-out visit, RMV – remote monitoring visit; SIV – site initiation visit; SMV – site monitoring visit, SQV – site qualification visit

[43] https://www.youtube.com/watch?v=UyEfv9JTpw4
[44] https://www.youtube.com/watch?v=9pBJ5jckfp0
[45] https://www.youtube.com/watch?v=BG9BgOvFDC0

Co-funded by the Erasmus+ Programme of the European Union

Site Qualification Visit (SQV)

Site Qualification Visits (SQV) are an essential part of the clinical trial site selection process. Once a potential site is selected for a certain clinical trial, the monitor will schedule a monitoring visit to confirm site eligibility.

This meeting is usually on-site, but if the sponsor already knowns the clinical research center and research team, it may be remote. SQV allows both research team and sponsor (or its representative) to clarify any doubts regarding the protocol and related procedures and to assess how those relate to the feasibility of recruiting potential participants. The Monitor/CRA will usually request a tour of the facility. SQV may also be referred as Site Selection Visit (SSV), Site Evaluation Visit (SEV) or Pre-Study Qualification Visit (PSQV)

The Monitor/CRA should send a request to meet with Principal Investigator, sub investigators, study coordinator, pharmacy and laboratory elements. Additionally, the trial documentation [protocol, schedule of assessments and investigator brochure (if applicable)] should be sent in advance so that it can be analyzed by the research team, before the SQV. The site should schedule a meeting room and reserve sufficient time for the SQV.

The objective of a SQV is to ensure that if the site is selected it will be fully capable to run a specific clinical trial. This meeting usually takes 3-4h and gathers the following players:

- Monitor/CRA (required, entire time);
- Principal Investigator (required, approximately 1 hour);
- Study Coordinator(s) (required, entire time);
- Pharmacist (required, 30 minutes) (if applicable);
- Laboratory (required, 30 minutes);
- Sub-Investigators (optional);
- Regulatory staff member (optional);
- Contracts/budgets Manager (optional).

The study coordinator will take the sponsor representative on a tour of the clinical research center to view exam rooms, equipment, and sample/IMP preparation areas. Usually, during SQV, the Monitor/CRA will fill in a questionnaire that addresses all topics discussed. If there are any questions raised during SQV that cannot be answered during this meeting, both Monitor/CRA and site will further communicate to solve the remaining questions.

After SQV, the site will send all documentation requested by Monitor/CRA (e.g., PI *CV*, GCP certification, laboratory documentation) and Monitor/CRA will write a monitoring report that will be sent to sponsor.

Once a decision is made by the sponsor regarding the participation of a certain research site on the clinical trial, the sponsor should notify the site of the result of the selection visit and the reasons for the decision. Once the trial protocol is finalized and in case the site was selected, the site should assist the sponsor in the submission of the trial to the regulatory agencies by providing the necessary site documents (CVs, GCPs certificates, etc).

Here you can find detailed information regarding the topics usually depicted on a SQV, taking in account sponsor and site point of views.

Sponsor´s evaluation of the Site	Site evaluation of the trial
Protocol Review and Discussion Study objectives. Inclusion/exclusion criteria. Schedule of assessments. Expected recruitment rate. Recruitment in other sites/countries. There are any competing trials at the site?	**Protocol Review and Discussion** Inclusion/exclusion criteria – is there any that can impact the recruitment of subjects? There are any special procedures or time points? Is the trial already running in other countries? What is the recruitment period (6 months / 2 years)? General timelines of the trial. Electronic ISF? Or paper?
Adequate Resources Sufficient time to run the clinical study, Adequate staff to perform the clinical study, Certification in GCP. Staff´s experience in clinical trials. Assess to patient/subject population.	**Adequate Resources** Is the trial complex and feasible? Who will be the research team? Where can we find patient/subject population? Working subjects (missing work) / pediatric?
Adequate Facilities Exam rooms. Special testing areas (x-rays, MRIs, CT scans, etc.). Availability of required equipment (certification, calibrated?) Emergency room available? Archival facilities.	**Adequate Facilities** Ambulatory or hospitalization? Special exams and frequency?
Financial Aspects Existing fees (submission, archival, etc). Participant fee. Contract negotiation: Who? How long? Timelines?	**Financial Aspects** Participants expenses reimbursement (travel, food, work absences).
Laboratory Central / local, or both? Local lab certification. Local lab ranges. CV lab head.	**Laboratory** Collection, processing, storage procedures and equipment. Shipping times.
Investigational Product Secure investigational product storage area. Is it locked? How is temperature and humidity maintained? Does the monitoring system generates alerts? Who receives them? IP dispensing and administration circuit.	**Investigational Product** Room temperature, 4ºC, -20ºC? Required space (bottles, flasks, systems) Needs preparation? When it will be available at the site (after SIV, recruitment of first subject?)
Principal Investigator (PI) Qualifications Up-to-date CV. Certification in GCP. PI´s expertise in the field. PI's experience in conducting a trial.	
Source documents Medical records, lab reports, all patient records. Paper, electronic or both.	
Data verification	**Monitoring plan** Frequency?

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How the data will be available to CRAs, auditors, inspectors, and sponsor personnel.	Remote or on-site?
SOPs Does the site have any SOPs? When was last revision?	
Audits Where previous regulatory audits? Any findings? Implemented measures.	

Site Initiation Visit

Once a clinical study has all the ethical and regulatory approvals, Site Initiation Visit (SIV) takes place before recruitment can start to provide study-specific training to investigators and staff. The Monitor/CRA will present the protocol, the process of informed consent, patient inclusion and retention, study-specific procedures, GCP, adverse events identification and reporting, as represented in **Figure 5**.

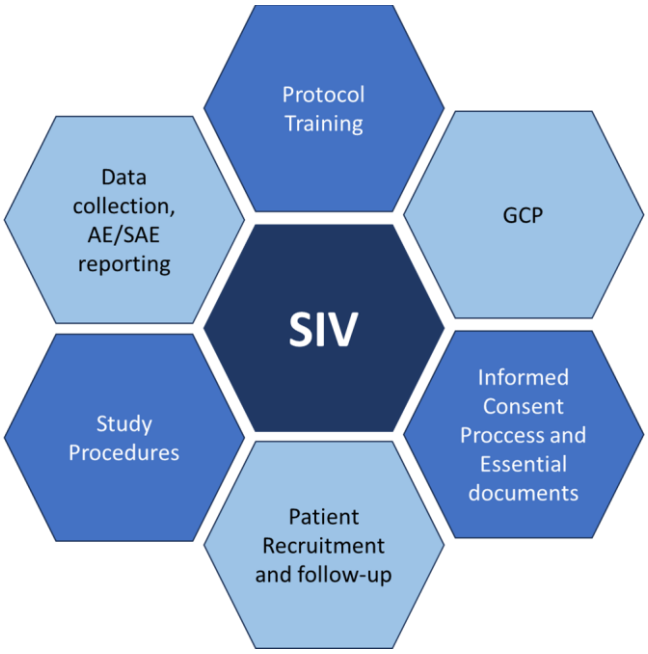

Figure 5: Main aspects discussed at a Site Initiation Visit

The SIV ensures that the principal investigator is aware of his/her responsibilities with the clinical trial protocol and that the research team is familiar with protocol, study documentation, investigational product management, study procedures and administrative procedures. After the SIV, the sponsor ensures the research team has all the resources necessary and is ready to start enrolling subjects and conduct the clinical trial.

The Monitor/CRA and the site should agree on a mutually convenient meeting date and time. Ensure the key members of the team are available to attend. The site should schedule a meeting room and key members of the team should reserve sufficient time for SIV.

The SIV typically occurs once the site has completed their regulatory requirements (upon IRB approval and contract execution). Nevertheless, SIVs may take place prior to IRB approval. If this is the case, it should be documented that study product will not be released to the site until IRB approval is granted.

SIVs can be on-site or remote, depending on the monitoring plan, complexity of the protocol and study product.

The **sponsor** should send the SIV agenda prior meeting and should send study binders and study related material, as well as laboratory kits, specific-study equipment's (eg tablets, phones, ECG machines, etc.). **Site** should review protocol and any other documents sent by sponsor (CRFs, Investigator Brochure), annotate questions that they may have, and confirm that supplies have arrived.

After the visit the site should send all the missing documents that were not collected during SIV. Any follow-up actions that were identified during the SIV must be completed in a timely manner. The Monitor/CRA will complete the SIV report and will add this report to the appropriate site binder section of the TMF. This report will also be sent to the site and that should be filed in the proper section of the ISF. Site activation will happen after all issue have been solve, usually sponsor send an email confirming that the site can start recruiting (Green Light).

Here you can find detailed information regarding the topics usually discussed at SIVs.

- Background and purpose of the study, including study objectives and design;
- Inclusion and exclusion criteria;
- Study procedures;
- Subject recruitment and screening;
- Subject consent procedures;
- Drug or device requirements (description, packaging, dispensing, administration, storage, accountability);
- Review AE and expedited AE reporting requirements;
- Review sponsor and PI responsibilities;
- Review study documentation;
    - Drug accountability forms;
    - CRFs;
    - Logs (training, delegation, subject screening and enrollment, biological samples, etc.);
    - Informed consent forms (main, optional);
- Review regulatory binder;
- Review regulatory obligations;
- Data management plan;
- Monitoring plan;
- Data collection and record keeping, expected metrics;

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CRA

- Obtain staff signatures on training and delegation logs;
- Collect all CVs, GCPs, and trial specific documentation from research team;
- Obtain signatures for monitoring log;

Periodic Monitoring Visits

The objective of the Periodic Monitoring Visits (on site, remote or centralized) is to ensure that all clinical trial activities are performed according to protocol, GCP guidelines and regulatory requirements. Additionally, these visits are also performed to ensure that participant safety is being properly evaluated by the research site. In summary, these visits have the following main objectives:

- Review the progress of a clinical study,
- Assure safety of subjects,
- Ensure protocol adherence,
- Assure accuracy of data,
- Assure regulatory compliance (code federal regulations – CFR and GCP).

The frequency of monitoring visits depends on:

- Disease being studied,
- Protocol complexity,
- Recruitment rate,
- PI/research team experience in conducting clinical trials
- Site performance,
- Sponsors SOPs.

The regular monitoring visits can be divided in 3 phases: preparation, conducting and post-visit, following the monitoring plan prepared by the sponsor/CRO/CTU.

Close Out Visit

The objective of a Close Out Visit (COV) is to ensure that all clinical trial related activities are reviewed, reconciled, recorded, and reported at the end of the study in accordance with protocol, GCP, SOPs and applicable regulatory requirements. This visit will only occur when the participation of the patients in the clinical study is already completed and all data is collected, reviewed, database-lock has occurred, and data is ready for statistical analysis.

This is the final visit of the monitor to the center and the points described in Figure 6 should be verified and addressed:

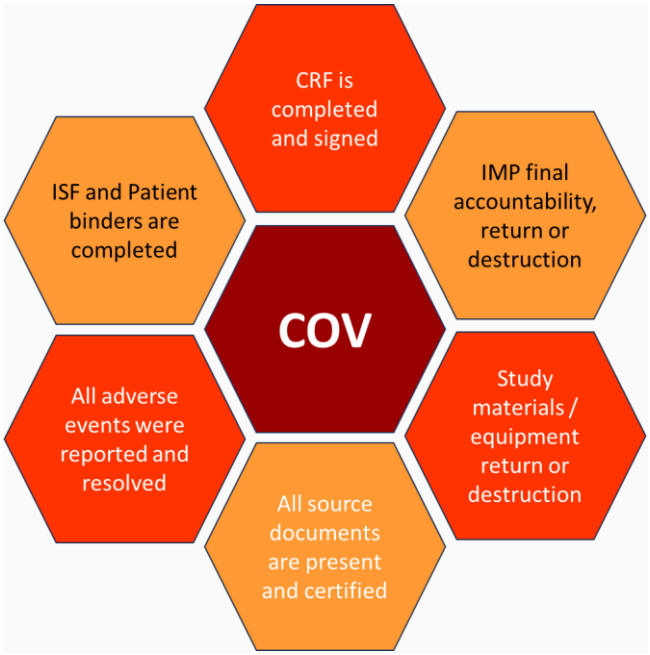

Figure 6: Main aspects discussed at a Close-Out Visit

QUIZ

1. What meant “risk-based approach” to monitoring?
   a) Monitoring is no longer a requirement.
   b) Less monitoring visits
   c) More monitoring vistis
   d) Adapted monitoring according to the risks posed by a trial

2. According to ICH GCP E6 (R2) guideline, the document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial is what?
   a) SOPs
   b) Monitoring Plan
   c) Safety Manual Plan
   d) Data Management Plan

3. Which type of monitoring visit is described here: "To ensure that a potential investigator has the necessary training, experience and adequate resources to properly conduct the trial"
   a) Site Qualification Visit (SQV).
   b) Site Initiation Visit (SIV)
   c) Monitoring Vist (MOV)
   d) Close Out Visit (COV)

4. Which of the following procedures are the responsibility of the monitor on a monitoring visit?
   a) Preparing for the visit in order to identify the objectives and tasks inherent to the visit
   b) Scheduling and confirming the monitoring visit with the research team
   c) Send a report to the sponsor/CTU/CRO describing the activities undertaken and the points of discrepancy found
   d) All of them

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Here you can find specific videos explaining each type of monitoring visit and templates that you can adapt to prepare your one visit:

Visit	Videos and Templates
SQV	key features of a SQV: CRA Basics: Good To Know About Visits - Pre-Study Visit PSV - Part 2[46]
SIV	key features of a SIV: CRA Basics: Good To Know About Visits - Site Initiation Visit SIV - Part 3[47]
MOV	how to prepare a MOV: CRA Basics: Good To Know About Visits - Questions on Preparing the Monitoring Visits - Part 6[48] CRA Basics: Good To Know About Visits - Source Documents and Source Data - Part 7[49] key features of regular monitoring visits: CRA Basics: Good To Know About Visits - Preparing the Monitoring Visits - Part 5[50] which documents should be verified during a MOV: CRA Basics: Good To Know About Visits - Checking the Investigator's Folder - Part 12[51] CRA Basics: Good To Know About Visits - Source Documents and Source Data - Part 7[52] SOPs, and document templates that you can use to prepare and conduct a MOV: The King's Health Partners Clinical Trials Office[53] SCTO Platforms[54]
COV	key features of a COV: CRA Basics: Good To Know About Visits - The Close-Out Visit - Part 14[55] SOPs, and document templates that you can use to prepare and conduct a COV: SCTO Platforms[56] The King's Health Partners Clinical Trials Office[57] Global Health Training Centre[58] The University of Mississippi Medical Center[59]

2.5.5 Monitoring Reports

After each visit to the research site the sponsor should write and send a follow-up letter to the site and a report that summarizes the visit performed. This report should cover the following topics:

[46] https://www.youtube.com/watch?v=if3TceXgkkk
[47] https://www.youtube.com/watch?v=qFyMealyKYc
[48] https://www.youtube.com/watch?v=ehz6tN5MSiM
[49] https://www.youtube.com/watch?v=8xqJnKY9ahU
[50] https://www.youtube.com/watch?v=dwCteiZpDRA
[51] https://www.youtube.com/watch?v=wW6-PnmERXk
[52] https://www.youtube.com/watch?v=8xqJnKY9ahU&t=5s
[53] https://khpcto.co.uk/SOPs/03_MonitoringSOP.php
[54] https://www.sctoplatforms.ch/en/tools/monitoring-visit-report-template-27.html
[55] https://www.youtube.com/watch?v=sJNh8acDRDg
[56] https://www.sctoplatforms.ch/en/tools/monitoring-visit-report-template-27.html
[57] https://khpcto.co.uk/SOPs/16_siteCloseOutSOP.php
[58] https://globalhealthtrainingcentre.tghn.org/
[59] https://www.umc.edu/Research/Research-Offices/Clinical-Trials/Researchers/Road-Map/Study-Closure/Study-Close-Out-Visit.html

- Who was present at the monitoring visit,
- Detailed activities performed by the CRA,
- Site adherence to study protocol / Protocol Deviation,
- Points discussed with the research team,
- Points that will need to be addressed by the research team or the monitor/sponsor.

To find more on the content of a monitoring reports you can watch this video "CRA Basics: Good To Know About Visits - The Monitoring Visit Report - Part 13"[60] and you will find templates of the different reports on the following additional content.

Visit	Reports
SQV	Pre-Study Qualification Visit Report[61] Pre-Site Selection Visit Checklist[62]
SIV	Monitoring Site Initiation Visit (SIV) Report Template[63]
MOV	Monitoring Visit Report Template[64]
COV	Monitoring Close-Out Visit (COV) Report Template[65]

2.5.6 Safety Reports

Safety reports (Chapter 5)[66] are essential to ensure the correct safety evaluation of the Investigational Medicinal Products (IMPs) or devices. In accordance to ICH guidelines, clinical trial sponsors should develop written processes for the evaluation and management of adverse events that may occur on a clinical trial and must report information on the safety of trial participants to the regulatory agencies.

You can discover more about safety monitoring in clinical trials and sponsor responsibilities by watching the following video "Safety monitoring in Clinical Trials - Responsibilities of the Investigators and Sponsor".[67]

There are 3 types of safety reports:

- Individual Case Study Report (ICSR),
- Development Safety Update Report (DSUR),
- Periodic Safety Update Report (PSUR).

2.5.7 Management of deviations/breaches

Protocol deviations occur when a clinical research member is not compliant to the protocol approved by IRB. According to GCP a **Protocol Deviation** is any change, divergence, or departure from the study design or procedures defined in the approved protocol, consent document, recruitment process, or study materials (e.g. questionnaires) originally approved by

[60] https://www.youtube.com/watch?v=GM_Gt0s8wfI
[61] https://researchhow2.uc.edu/docs/default-source/default-document-library/mon-form-003-pre-study-qualification-visit-report.pdf?sfvrsn=4d627447_0
[62] https://www.smartsheet.com/sites/default/files/IC-Pre-Site-Selection-Visit-Checklist-Report-Template-10628_PDF.pdf
[63] https://www.sctoplatforms.ch/en/tools/monitoring-site-initiation-visit-(siv)-report-template-63.html
[64] https://www.sctoplatforms.ch/en/tools/monitoring-visit-report-template-27.html
[65] https://www.sctoplatforms.ch/monitoring-close-out-visit-(cov)-template-158.html
[66] CONSCIOUS II: Chapter 5; Pharmacovigilance and study medication; https://www.conscious2.eu/
[67] https://www.youtube.com/watch?v=bgFpw7auPEo

the IRB or Ethics Committee. These deviations might occur due to several issues and must be reported to IRB.

There are several types of deviations:

- **Emergency deviations** – occur in an emergency situation. For instance is necessary to deviate from protocol to protect the life of physical-well being of a participant. These situations are always considered as unanticipated problems. IRB approval is done after deviation occurs.
- **Serious breaches –** any deviation to the approved version of the protocol clinical trial that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial. The sponsor is responsible to perform a root cause analysis to identify the cause of the serious breach and to assess the impact of the breach on the reliability and robustness of the trial data as well as the impact on a trial participant's safety and/or rights. The assessment and subsequent decisions and actions should be documented and reported to the medicines and healthcare products regulatory agencies and ethics committees within 7 calendar days of becoming aware of a serious breach.
- **Major, non-emergent deviations** – planned deviations that are non-emergent and are a major alteration to the protocol initially approved by the IRB. They can only occur after a new IRB approval is in place. For instance: schedule of administration of an IMP, exceptions to the manner of obtaining informed consent (before was only face to face, after IRB approval can be forms sent home after telephone explanation).
- **Minor or administrative deviations** – deviations that do not affect the scientific value of the protocol, or the rights, safety or well-being of the participants. Examples include: visits occurring after the planned visit schedule due to participants time constraints or blood samples collection time not exactly the one described in the protocol (some minutes difference)

Here you can find extra information regarding Protocol Deviation identification and how to manage them:

- Protocol Deviation & Violation[68]
- Management of Protocol Deviations, violations and Urgent Safety Measures[69]
- EMA: Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol[70]

2.6 Clinical Study Reports (CSR) and trial´s result dissemination and publications to the wider public

When a clinical trial ends the sponsor has to notify all Member States concerned and all third countries in which the clinical trial has been conducted through the CTIS portal, Notification

[68] https://www.protocoldeviation.com/
[69] https://www.imperial.ac.uk/media/imperial-college/research-and-innovation/research-office/public/RGIT_SOP_037_Deviations_Violations_USM_V6.0_02-Nov-2021.pdf
[70] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

shall be made within 15 days from the end of the clinical trial in the last Member State concerned[31].

The article 37(4) of the Clinical Trials Regulation (EU CTR) 536/2014[Chyba! Záložka není definována.] describes that irrespective of the outcome of a clinical trial, the sponsor will have to submit within one year from the end of a clinical trial in all Member States concerned or within six months for a trial in paediatric population, a **summary of the results of the clinical trial**.

The summary of results shall be accompanied by a lay summary report written in a manner that is understandable to lay persons, written for members of the public, rather than researchers or professionals.

The EFGCP[71] in collaboration with EFPIA[72] set up Roadmap Initiative to Good Lay Summary Practice Group with members from academia, pharmaceutical industry, patient organisations, and not-for-profit organisations and established the Good Lay Summary Practice (GLSP)[73] Recommendations published on 2021 in EudraLex Volume 10. The GLSP provides recommendations on how to prepare, write, translate, and disseminate summaries of clinical trial results in lay language.

The summary of the results should also be published in the clinical trials registries/ databases like EU CTR, WHO-Clinical Trials Registry Platform, ClinicalTrials.gov described in Chapter 4[22].

Dissemination of clinical studies/trial results is important for scientific progress as increases the credibility of scientific research, can minimize the redundancies of duplicative experimentation, in turn reducing research costs and maximizing the contributions of human subjects who participate in studies. It is good practice to disseminate the clinical studies/trial results to participants and other interested groups, or communities independent of the outcome. However, unfortunately 25% - 50% of clinical trials are still not published.

In addition, marketing authorisation holders have to submit to the EU database the clinical study report (CSR) within 30 days after the day the marketing authorisation has been granted.

A CSR is a comprehensive regulatory document that gathers all aspects and data produced during a clinical trial. A CSR is a written description of a clinical study or trial, of any therapeutic, prophylactic, or diagnostic agent conducted in human participants, in which the clinical and statistical description, analyses and results, including efficacy and safety data are fully integrated into a single report.

The CSRs are to be submitted by the Marketing Authorisation Holders to regulatory agencies (FDA/EMA) if the clinical trial was intended to be used for obtaining a marketing authorisation of the investigational medicinal product or to support the information in the product label.

[71] https://efgcp.eu/
[72] https://www.efpia.eu/
[73] https://health.ec.europa.eu/system/files/2021-10/glsp_en_0.pdf

The structure and content of CSRs is specified in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 guideline.[74] It includes:

- Title page,
- Synopsis,
- Table of contents for the CSR,
- List of abbreviations and definitions of terms,
- Ethics of the clinical study,
- Study administrative structure,
- Introduction,
- Study objectives,
- Investigational plan,
- Study participants,
- Efficacy evaluation,
- Safety evaluation,
- Discussion & overall conclusions,
- End of Text Tables and Figures,
- References,
- Appendices.

Here you can watch a video "What is a Clinical Study Report (CSR)?"[75] that summarizes CSR purpose, its structure, and the components of a CSR.

Over the past decade, several measures/initiatives, such as those mentioned above, have been implemented with the aim of increasing the dissemination of clinical studies/trial results, with the ultimate goal to increase transparency and the ability of patients, physicians, researchers and policy makers to make informed decisions.

The classic way to disseminate clinical studies/trials results is in the form of a peer-reviewed paper in specialist medical journals and presentation of results at international medical conferences, typically, by introducing the trial and its methodology and discussing some of the results. Nevertheless, access to this information is often restricted to scientific or medical community rather than the general public and publishing negative results is not so appealing, which makes that in the scientific literature, clinical trials with positive results tend to be over-represented. Negative results are just as important for the knowledge base, and journals are increasingly encouraging their publication. To further explore this topic, you can consult Chapter 11[76] dedicated to scientific publishing and open research.

It is also important to understand that clinical studies can generate a huge amount of information, including raw study data, summary level data/ meta data (e.g. protocols, clinical study reports, and publications), and study documentation (e.g. ICFs, data specifications). Numerous medical organizations and funders have made data sharing recommendations or

[74] CH Topic E 3 Structure and Content of Clinical Study Reports, July 1996, European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-content-clinical-study-reports-step5_en.pdf
[75] https://www.youtube.com/watch?v=ozRJBMJOWBI
[76] CONSCIOUS II:Chapter 11: *Open Research and Scientific Publishing; https://www.conscious2.eu/*

policies, including the World Health Organization,[77] the US National Academy of Medicine,[78] ECRIN,[Chyba! Záložka není definována.] NIH.[79]

Journals have also recognized the importance of data sharing, and some journals, e.g. PLOS Medicine and BMJ, have implemented more stringent policies, requiring data sharing as a condition for publication of randomized controlled trials. Data can also be published or shared in repositories for researchers to access and analyze without the need for a full peer-reviewed article.

Although debates on the key potential benefits and risks of data sharing continues and the challenges of the data sharing process to be clear, transparent, and accountable there has been growing support for data sharing, among patients, researchers, and research institutions.

ecrin

The ECRIN Clinical Research Metadata Repository[80] is the online tool freely available to help scientific researchers find documents and data linked to a clinical research study, and to obtain information on the accessibility of those results. It is updated regularly through collection of data from the most important sources of information worldwide, from New Zealand to Italy and from Japan to Lebanon.

3 Conclusion

This chapter offers you a comprehensive overview why clinical trials of whatever size and complexity, require efficient trial management. Here the most important aspects of clinical trial management from the implementation phase to the end of trial are covered. In particular the oversight and monitoring of the trial progress ensuring the rights and safety of the participants and guaranteeing high-quality data. This chapter is focused on the management of practical aspects, such as tools, infrastructures and available resources to support academic sponsors and clinical researchers to carefully plan, implement, manage and monitor effective and successful investigator initiated clinical studies.

[77] The World Health Organization. *Developing Global Norms for Sharing Data and Results during Public Health Emergencies*. (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001935)
[78] Committee on Strategies for Responsible Sharing of Clinical Trial Data; Board on Health Sciences Policy; Institute of Medicine. Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk. Washington (DC): National Academies Press (US); 2015 Apr 20. (https://pubmed.ncbi.nlm.nih.gov/25590113/)
[79] Hudson KL and Collins FS. Sharing and reporting the results of clinical trials. *JAMA* 2015; 313(4): 355–356. https://jamanetwork.com/journals/jama/fullarticle/1939045
[80] https://ecrin.org/clinical-research-metadata-repository

Practical exercise

According to what you have learned throughout this chapter, match each definition in Column A with the name in Column B.

Column A	Column B
A. a measure or set of measures taken by a project manager to reduce or eliminate the risks associated with a project	1. Slack
B. an individual responsible for the planning, implementation and tracking the day-to-day processes and the clinical trial progress	2. Project Stakeholder
C. the amount of time that a task can be delayed without affecting the deadlines of other subsequent tasks, or the projects final delivery date	3. Sponsor
D. an individual, group, or organisation, who may affect, be affected by, or perceive itself to be affected by a decision, activity, or outcome of a project	4. Risk Mitigation
E. an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial	5. Trial Management Plan
F. defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs and regulatory requirements	6. Monitoring
G. outline a strategy that combines project management and clinical trial processes	7. Clinical trial Manager