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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 4

QUALITY AND REGULATORY AFFAIRS AND SOURCES OF REGULATORY INFORMATION

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1 Introduction to the chapter

Regulation of clinical research contributes to the quality of research, ensures the objectivity and credibility of data and safety of patients or healthy volunteers, which participate in clinical studies. As you might know, it is a complex issue, as evidenced by the rise of Regulatory sciences in the field of pharmaceutical medicine and by the existence of regulatory experts who are deeply knowledgeable in this area. As a PhD student or a junior researcher, you probably do not aim to become a regulatory expert, nor it is the aim of this chapter to educate you in this way. Whether you will evaluate a new chemical substance, vaccine, product of gene therapy, tissue-engineered product, a medical device for wound healing, a diagnostic software, or you will monitor the post-authorisation safety or effectiveness of the drug, all these have their regulatory specifics. This chapter should facilitate to you navigation within the regulatory framework, databases of clinical trials, and introduce the systems to manage the quality of clinical studies.

This chapter refers to a large number of legal acts, guidelines, or websites on clinical research regulatory affairs. It is not important to go through every link and study all information but use the chapter as an overview and a source of that information.

2 Regulatory framework

When talking about the regulatory framework concerning clinical trials, the documents covering the protection of human rights regarding the application of biology and medicine need to be mentioned in the first place. The **Oviedo Convention** is the only international legally binding instrument on the protection of human rights in the biomedical field. Others from international guidelines (listed in Table 1) are generally non-binding and not every country recognizes them in full.

Table 1: International guidance and conventions on clinical research

International convention	developed by...
Convention on Human Rights and Biomedicine (Oviedo Convention)[1]	Council of Europe, Strasbourg
International guidelines	
Declaration of Helsinki[2]	World Medical Association
Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants[3]	World Health Organisation
Guideline for Good Clinical Practice E6(R2)[4]	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

[1] https://www.coe.int/en/web/bioethics/oviedo-convention
[2] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[3] https://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf
[4] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Guideline for Good Clinical Practice E6 (amended with an integrated Addendum as E6(R2), hereinafter referred to as ICH GCP) was developed by the International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). The objective was to provide a unified standard for the European Union (EU), Japan, and the United States (US) to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. Currently (June 2023), the ICH GCP is implemented by 13 countries and the EU. The guideline serves as an international quality standard for clinical trials. In the field of medical devices, the so-called ISO-GCP (ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice[5]) is required by European law and recognized by the US among others.

Clinical research is further governed by national/multinational legal acts complemented by a number of guidelines and recommendations.

Regulatory requirements differ across the world. Clinical research-active countries, like the EU Member States, the US, Canada, Japan, Australia, and China have very well-developed robust regulatory frameworks. Setting clinical trials in countries with less stringent legal requirements and lower research costs is a common approach. However, low-income countries are implementing more robust and more complex regulatory frameworks for the protection of clinical research participants.

2.1 Regulatory authorities

In the EU, the European Medicines Agency (EMA) plays a key role in ensuring that the standards of GCP are applied across the European Economic Area (EEA) in cooperation with the Member States. EMA does not evaluate applications for the authorisation of clinical trials but manages a database of clinical trials carried out in the EU. The authorisation of clinical trials occurs at the national level by national competent agencies (NCAs) in cooperation with ethics committees. EMA published a list of NCAs with contact details e.g., on the EudraCT website.[6]

2.2 European legislation, recommendations, and guidelines

Currently, two main legislative acts govern **clinical trials with medicinal products**, **Regulation (EU) No 536/2014** and **Directive 2001/20/EC**. A "directive" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals. Whereas a "regulation" is a binding legislative act. It must be applied in its entirety across the EU. Clinical Trials Regulation (hereinafter “CTR”, Regulation (EU) No 536/2014) came into force on 31 January 2022 and repealed the Directive 2001/20/EC (hereinafter “Directive”). The legal form of a Regulation instead of a Directive will ensure that the rules for assessing clinical trial applications and for conducting clinical trials are identical throughout the EU/EEA.

[5] https://www.iso.org/standard/71690.html
[6] https://eudract.ema.europa.eu/nca_contacts.html

QUIZ
Watch the video from EMA to learn more about the transition from Directive to CTR.[7] Fill in the missing dates (YYYY) in the following paragraph:

- ✓ From January YYYY, all new clinical trial applications have to be submitted according to the CTR, however until January YYYY, ongoing clinical trials may continue to proceed according to the Directive.
- ✓ Be aware that the whole system of clinical trials changes significantly and many published documents may no longer be valid. Therefore, it is necessary to track which act they relate to.

At the end of the transition period (31 January 2025), also other legislative documents governing clinical trials will be repealed by new ones (See Table 2).

Table 2: Transition to new European law governing clinical trials

Original	→ will be repealed by…
Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use	**Regulation (EU) No 536/2014** on clinical trials on medicinal products for human use ✓ *transition period applicable*
Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products	**Commission Implementing Regulation (EU) 2017/556** on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 ✓ *transition period applicable*
Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	**Commission Delegated Regulation (EU) 2017/1569** supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections ! *applicable to all clinical trials as 31/1/2022 or according to national law until the end of the transition period*

The useful information about the transition from Directive to CTR can be found in the Regulation (EU) No 536/2014 Questions & Answers Document.[8]

The General Data Protection **Regulation (EU) 2016/679** (GDPR), which applies to the processing of personal data carried out by organisations and bodies operating within the EU, is the other relevant legislation.

[7] https://www.youtube.com/watch?v=0nQ2ABHa9L0
[8] https://health.ec.europa.eu/latest-updates/questions-and-answers-document-regulation-eu-5362014-version-5-january-2022-2022-02-01_en

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In the case that the clinical trial is aimed to support the marketing authorisation of medicinal product, it is important to get acquainted with the **Directive 2001/83/EC** *on the Community code relating to medicinal products for human use* as well, specifically with Annex I: Analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products. In Part 4, the requirements for clinical documentation as part of the application for marketing authorisation can be found.

The complete list of key documents for clinical trials (legislation, guidelines, recommendations) is presented on the official website of the European Commission[9] and in **EudraLex** (The rules governing medicinal products in the European Union) – **Volume 10: Clinical trials guidelines**.[10] The lists of documents published are extensive, therefore you can understand them as a comprehensive overview of the information sources. In EudraLex can be currently found two sets of documents according to applicable legislation (CTR vs. Directive), which are divided into Chapters: Application and application documents, Safety reporting, Quality, Inspections, Additional documents, and Legislation.

Neither the CTR nor the Directive applies to the non-interventional studies, that are governed by the national legislation of the Member States. To verify whether a study is a clinical trial or a non-interventional study, reference should be made to the table in Annex I of the Regulation (EU) No 536/2014 Questions & Answers Document.[11] Sponsors are also advised to consult with national authorities when planning studies under these conditions. Table 3 includes the EU regulations and guidelines, which should be followed.

Table 3: EU regulations and guidelines regarding non-interventional studies

Including, but not limited to:
General Data Protection Regulation (EU) 2016/679
Directive 2010/84/EU on pharmacovigilance (Article 107)
Directive 2001/83/EC
EMA GVP Module VIII (specific to post-authorisation safety studies, PASS)[12]
ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Standards and Guidance[13]
Guidelines for good pharmacoepidemiology practice[14]
Applicable legislation and guidance issued by the EU Member States

All the European legislation can be accessed at the official website of the European Union: **EUR-Lex**.[15]

[9] https://health.ec.europa.eu/medicinal-products/clinical-trials_en
[10] https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en
[11] https://health.ec.europa.eu/latest-updates/questions-and-answers-document-regulation-eu-5362014-version-5-january-2022-2022-02-01_en
[12] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
[13] https://encepp.europa.eu/encepp-toolkit_en
[14] https://www.pharmacoepi.org/resources/policies/guidelines-08027/
[15] https://eur-lex.europa.eu/

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Practical exercise

- ✓ Watch the tutorial introducing EUR-Lex.
- ✓ Search the Regulation (EU) No 536/2014 at EUR-Lex a go through the table of its content to get an overview of what it governs.
- ✓ Then, search in CTR for information about the informed consent procedure submitted as part of the application dossier. Notice the phrase "information per Member State concerned" and find other parts of the application dossier with that type of note. Write these in the text field below. These parts will be evaluated by each Member State where the trial is planned to be performed.

Information per Member State concerned according to the Regulation (EU) 536/2014:

_____

_____

_____

_____

So far described information is related to clinical trials with all medicinal products in general. Moreover, medicinal products include specific groups of products, to which the additional provisions for clinical trials may be applied. We selected as examples: for vaccines and serums, the immunological status of the trial population should be monitored (Directive 2001/83/EC); for products containing genetically modified organisms (GMOs), an environmental risk assessment is required (Directive 2001/18/EC); for products containing human cells or tissues, the traceability system shall be established and data should be kept for 30 years after the expiry date of the product (Regulation (EC) No 1394/2007). The specific requirements for special groups of products are described in the yellow box below to simplify searching for particular information if interested.

Regulatory framework specific to clinical trials with advanced therapies

ATMPs (Advanced Therapy Medicinal Products) according to **Regulation (EC) No 1394/2007** *on advanced therapy medicinal products* are defined as a gene therapy medicinal product, a somatic cell therapy medicinal product, or a tissue-engineered product. If the investigational medicinal product (IMP) contains or consists of GMOs, besides the legislation governing the clinical trials, the clinical trials need also comply with the requirements under **Directive 2001/18/EC** *on the deliberate release into the environment of genetically modified organisms* and/or under **Directive 2009/41/EC** *on the contained use of genetically modified micro-organisms*. The application for a clinical trial with IMPs that contain or consist of GMOs needs to include an environmental risk assessment and technical documentation. Such clinical trials are also published in the GMO register at the Joint Research Center of the European Commission.[16] The European Commission website brings an overview of national regulatory requirements for medicinal products containing GMOs.[17]

Where an ATMP contains human cells or tissues, it should be confirmed that the donation, procurement and testing of the cells and tissues used as starting materials are in accordance with

[16] https://webgate.ec.europa.eu/fip/GMO_Registers/
[17] https://ec.europa.eu/health/medicinal-products/advanced-therapies/genetically-modified-organism-gmo-aspects-investigational-medicinal-products_en

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Directive 2004/23/EC *on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells* or **Directive 2002/98/EC** *setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components*. The further aspects are covered by ATMP Regulation.

European Commission published detailed information on advanced therapies on its website.[18] Several documents regarding GMO requirements for IMP including application forms can be found there as well. The European Commission adopted **Guidelines on Good Clinical Practice specific for Advanced Therapy Medicinal Products**.[19] EMA created a **Guideline on ATMP Clinical development**[20] to help navigate the most important regulatory requirements during the clinical development phase, other relevant EMA guidelines can be found on its website.[21]

Regulatory framework specific to clinical trials with vaccines

Documents specifically targeted to clinical evaluation of vaccines were published by WHO[22] and EMA.[23, 24] Considering the Directive 2001/83/EC, vaccines correspond with the definition of an immunological medicinal product, however, the term "vaccine" is not fully specified by legislation. Newly produced so-called "therapeutic vaccines" meet the definition of ATMP and then, the regulation corresponds with previously described, including GMO and Tissues and cells Directives.

Clinical trials with other "special groups" of medicinal products

If the clinical trial investigates the medicinal product containing narcotic or psychotropic substances, the application of the national law is additionally required. In the case of radiopharmaceuticals, the CTR detached the radiopharmaceuticals used as diagnostic medicinal products (Article 61.5.b). The national law should be followed as well (such as approval of the national competent agency for nuclear safety). For clinical trials with IMP for an orphan condition, the sponsor declares that he has obtained the orphan designation according to Regulation (EC) No 141/2000 on orphan medicinal products. The clinical research relevant to the development of medicines for children will be the subject of Chapter 8.[25]

In relation to the COVID-19 pandemic situation, the **Regulation (EU) 2020/1043** *on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19)* was adopted to facilitate and speed up the development and marketing authorisation of treatments and vaccines. In Chapter 7,[26] you can read about the effect of COVID-19 pandemic on clinical trials and the marketing authorization process. Another example of such an accelerating process was seen in the 1990s when the FDA granted permission for studies involving more than 80 different AIDS-related antiviral or immunomodulating drugs.[27]

[18] https://ec.europa.eu/health/medicinal-products/advanced-therapies_en
[19] https://ec.europa.eu/health/system/files/2019-10/atmp_guidelines_en_0.pdf
[20] https://www.ema.europa.eu/en/documents/other/guide-advanced-therapy-medicinal-products-clinical-development-flowchart_en.pdf
[21] https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products
[22] https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9
[23] https://www.ema.europa.eu/en/clinical-evaluation-new-vaccines
[24] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-vaccines
[25] Chapter 8, Paediatric clinical trials; https://www.conscious2.eu/
[26] Chapter 7, Early phase trials; https://www.conscious2.eu/
[27] https://www.ncbi.nlm.nih.gov/books/NBK234129/

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Regulatory framework specific to clinical investigation of medical devices
In order to sell a medical device in the EU market, manufacturers are required to perform the clinical/performance evaluation as part of the CE marking process (conformity assessment) to prove its safety and/or efficacy, whether it is an electrocardiograph, pacemaker, joint replacement, wheelchair, thermometer, medical devices software, pregnant test, bandage or even examination gloves. Whereas the clinical evaluation is compulsory, it can lead only in some cases to a **clinical investigation**, which means that an assessment of the safety and/or efficacy of the device involves human subjects. The clinical evaluation of medical devices is governed by the **Regulation (EU) 2014/745** *on medical devices*, performance evaluation of *in vitro* diagnostic medical devices by the **Regulation (EU) 2017/746** *on in vitro diagnostic medical devices*. Clinical investigations which are not intended to support the conformity assessment may fall under relevant national regulation of the Member State concerned.

The European Commission published a range of documents and guidelines endorsed by the Medical Device Coordination Group (MDCG).[28] Besides documents about **Clinical investigation and evaluation**, documents about **Borderline and Classification** are important as well because the proper classification of the medical device is necessary to understand if the clinical investigation is applicable. A drug-device combination and a combination of the device with tissues or cells of human or animal origin are other special categories from a regulatory perspective and firstly the regulatory status of this product needs to be determined to set up the next activities. Specifics of clinical investigation of medical devices will be the subject of Chapter 9.[29]

2.3 Compliance with legislation: practical aspects for investigators

In most academic clinical trials (also referred to as non-commercial, investigator-initiated trials, IIT), there is a sponsor (e.g., university, hospital, research institution, etc.) who is responsible for all the GCP and regulatory requirements associated with both the management and conduct of the clinical trial. In some cases, the role of the sponsor is held by the investigator, which means, that that person complies with the responsibilities of both actors. This part of the chapter does not aim to describe all the tasks and responsibilities of the sponsor. It is advisable to study Chapter 3 “Trial management”[30], ICH GCP Section 5. Sponsor[31] and follow the EudraLex Volume 10.[32] This part of the chapter provides an overview of the activities and responsibilities of the investigator. We recommend self-study ***ICH GCP Section 4. Investigator***.[33]

Find out more about the responsibilities of the investigator from another perspective in CONSCIOUS Chapter 12, Trial Management, 12.1 Key Players in Clinical Trials.[34]

[28] https://ec.europa.eu/health/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en
[29] Chapter 9, Clinical evaluation and clinical investigations of medical devices; https://www.conscious2.eu/
[30] Chapter 3, Trial management; https://www.conscious2.eu/
[31] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
[32] https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-10_en
[33] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
[34] CONSCIOUS: Chapter 12, Trial Management; http://conscious.novaims.unl.pt/my/

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The following text covers the clinical trials with medicinal products (not medical devices), not the non-interventional studies, which are governed by the national legislation of Member States. In addition, it considers the CTR, the Directive was not included, as practically no longer applicable.

2.3.1 Planning, authorisation procedure, before the trial initiation

The investigator may be consulted by the sponsor during protocol design or, in some cases, may personally contribute to the design of the protocol. The investigator may also be consulted to deal with the comments of the NCA or the ethics committee on the application concerning the medical issues. To get the trial authorized, the sponsor must ensure that the investigators are suitable. The suitability of an investigator for a clinical trial is defined in Article 49 of CTR, and the required information for the Application dossier is covered in Annex I Section M. EudraLex Volume 10 provides an Investigator Curriculum Vitae template and Declaration of interest template used by the sponsor as a part of the application dossier. The up-to-date CV is then stored by the investigator at the trial site.

For multicentre trials, the coordinating investigator is usually appointed, mostly from among the participating investigators. In the case of multinational trials, a national coordinating investigator can be chosen in each country. He mediates communication between investigators (and, consequently, trial sites, even potential ones) and the sponsor.

The investigator signs the agreement with the sponsor to conduct the trial (ICH GCP 5.6.2, 5.6.3 Investigator Selection). Before initiating the trial, the investigator should be thoroughly acquainted with the protocol, Investigator's Brochure, and informed consent. The investigator attends a Site Initiation Visit prior to study enrollment.

2.3.2 During the clinical trial

The main tasks and responsibilities of the investigator are summarized in Table 4 with reference to the applicable parts of the documents recommended for self-study. The investigator should conduct the trial in compliance with the approved protocol (ICH GCP 4.5. Compliance with Protocol). The investigator usually delegates many of his trial-related duties to other appropriately qualified persons (members of the study team), however, he is responsible for supervising them. Such a delegation of responsibilities is properly recorded and kept up to date as a "Delegation log" by the investigator, as well as the CV of every person delegated. Handling with study medication (receipt, storage, records of storage conditions, preparation, dispensing) is typical accountability that is usually delegated to an appropriate pharmacist. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the IMP, and their trial-related duties and functions.

Table 4: Investigator's responsibilities and tasks

Activity	Regulatory reference
Screening/recruiting of study participants The investigator should follow the recruitment procedure and inclusion/exclusion criteria in accordance with protocol. The investigator keeps the *Subject screening log* to document the identification of subjects who entered pre-trial screening.	✓ CTR Annex I Section D. Protocol 17. (v), (z) ✓ CTR Annex I Section K. Recruitment arrangements

Informed consent obtaining, informing subjects about study progress The subject voluntarily confirms willingness to participate in a trial, after having been informed of all aspects of the trial that are relevant to the decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. The subject should be informed if new information becomes available that may affect the willingness to continue participation.	✓ CTR Preamble (27), (30–33), (36) ✓ CTR Chapter V: Protection of subjects and informed consent ✓ CTR Annex I Section L. Subject information, informed consent form and informed consent procedure ✓ CTR Q&A Document, Chapter 9. Informed consent and other substantial requirements for conducting clinical trials ✓ ICH GCP 4.8. Informed Consent of Trial Subjects ✓ ICH GCP 4.3.4: withdrawing prematurely
Confirmation of eligibility, enrollment of the subjects The investigator obtains the medical history, performs the physical examination, and confirms the eligibility for inclusion in the trial. The investigator keeps the *Subject enrollment log* to document the chronological enrollment of subjects by trial number and the *Subject identification code list* to reveal the identity of any subject.	✓ CTR Annex I Section D. Protocol 17. (v) ✓ ICH GCP 4.3.3: recommendation to inform the subject's primary physician
Randomization and event. unblinding The investigator should follow the trial's randomization procedures in accordance with protocol. Unblinding by the investigator is possible only if it is relevant to the safety of the subject.	✓ ICH GCP 4.7. Randomization Procedures and Unblinding ✓ CTR Annex I Section D. Protocol 17. (m), (q) ✓ CTR Annex III, 2.5. Unblinding treatment allocation ✓ CTR Q&A Document, Question 7.22
Coordination and conduction of subjects' study visits The investigator ensures the planning of study visits according to the protocol (using a flowchart), performs/provides the examination and the study visit procedures, and evaluates the results of the study-related tests.	✓ CTR Annex I Section D. Protocol 17. ✓ ICH GCP 4.5. Compliance with Protocol
Handling laboratory samples The investigator follows the protocol for the collection, processing, storage, or shipping of biological samples. The investigator keeps the *Record of retained body fluids/tissue samples* if assays need to be repeated.	✓ CTR Annex I Section D. Protocol 17. (s)
Data entry into (e)CRF, event. correction The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data in the CRFs. The sponsor should provide guidance to the investigator on making corrections. The investigator is responsible for resolving data queries.	✓ ICH GCP 4.9. Records and Reports ✓ CTR Article 56 (Recording, processing, handling and storage of information)

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Handling with study medication The investigator is responsible for the study medication at the site (receipt, preparation, dispensing, records maintenance, storage conditions). The investigator should explain the correct use of study medication to each subject and control the treatment compliance. This accountability is usually delegated to an appropriate pharmacist. The pharmacy personnel can also have access to the treatment assignment in blind study to facilitate the preparation of study intervention.	✓ CTR Preamble (46) and (57), Article 51 (Traceability, storage, return and destruction of investigational medicinal products) ✓ ICH GCP 4.6. Investigational Product(s) ✓ CTR Annex I Section D. Protocol 17. (t), (ab, ac)
Safety monitoring and reporting The investigator shall record, assess and document all adverse events. He should report all serious adverse events to the sponsor within 24 hours and provide the causality assessment.	✓ CTR Article 41 (Reporting of adverse events and serious adverse events by the investigator to the sponsor), Annex III (Safety reporting) ✓ ICH GCP 4.11. Safety reporting
Maintenance of essential documents All clinical trial information shall be recorded, processed, handled, and stored by the sponsor and investigator. The sponsor and the investigator shall keep a clinical trial master file (for the investigator usually referred to as an Investigator site file). Information and personal data processed shall be protected against unauthorized or unlawful access.	✓ CTR Article 56 (Recording, processing, handling and storage of information), Article 57 (Clinical trial master file), Article 58 (Archiving of the clinical trial master file) ✓ EudraLex Volume 10, Chapter V: Recommendation on the content of the trial master file and archiving ✓ ICH GCP 4.9. Records and Reports ✓ ICH GCP 8. Essential documents for the conduct of a clinical trial
Monitoring, auditing, inspection The investigator should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.	✓ CTR Annex I Section D. Protocol 17. (ah) ✓ ICH GCP 4.9.7 ✓ EudraLex Volume 10, Chapter IV – Inspections

One of the other responsibilities of the investigator may be communication with the ethics committee. However, that is especially applicable in the case of IIT, where the difference between sponsor and investigator blurs. When the roles are separated, the investigator has responsibilities only to the sponsor, and the communication between the sponsor (or him designated person), regulatory authorities and EC is ensured through the Clinical Trial Information System (CTIS) for authorisations, review, and reporting (CTR Preamble (18), Article 4, Article 44; ICH GCP 4.4. Communication with IRB/IEC).

2.3.3 After the termination of the clinical trial

After the trial is completed, the investigator ensures that any unused IMP is returned to the sponsor or the alternative disposition in accordance with the protocol was used (ICH GCP 4.6. Investigational Product). The investigator should report to the sponsor any serious adverse event with a suspected causal relationship to IMP he becomes aware of (CTR Article 41). Further, he shall archive the content of the clinical trial master file (in that case meant investigator site file) for at least 25 years after the end of the clinical trial. The medical files of subjects shall be archived in accordance with national law (CTR Article 58).

2.4 Databases of regulatory information

So far, the regulatory framework was presented on the European level, and you were introduced to options of how to get to key documents and information. If you need to follow the national requirements, e.g. in the case of non-interventional study, clinical investigation of medical devices not intended to support the conformity assessment, specific requirements for IMP with GMOs, and more, it is necessary to get this information on the level of the country concerned. Start with searching for particular information on websites of national competent agencies and in national legislation (almost every European country has legislation freely available also online).

This part of the chapter introduces you to different freely accessible databases where national regulatory information can be found. While some of them display basic information about clinical studies regulations worldwide (REGTRAC), some of them aim at a specific region and provide more details (CAMPUS ECRIN, ClinRegs). Another database describes regulatory information about different products and the regulation of clinical research is one of their parts (EATRIS).

Practical exercise

- ✓ Watch tutorials on each database to get an overview of the information available there. **REGTRAC**,[35] **ClinRegs**,[36] **CAMPUS Database**,[37] and **EATRIS Regulatory Database**[38]

Practical notes while working with databases and legislation

- ✓ Select the proper database according to the country and type of information you are searching for.
- ✓ The information in databases may not be updated regularly. Keep in mind, that these databases are not the official source of national legislative requirements.
- ✓ Regulations often change, they are amended. The amendments result in consolidated texts. See if the version of regulation displayed is in force or repealed.

Task

- ✓ Search for a competent agency that will assess the application for your clinical trial in the following countries using one of the databases listed above and fill in the table.

Country	NCA
Czech Republic	
France	
Hungary	
Ireland	
Portugal	
(your country, if it is not listed above)	

- ✓ Find basic information about the authorisation of a non-interventional study in your country. Use the databases and/or the website of the NCA. Go to the discussion board and write there the country selected, the relevant legislation, and a useful link when appropriate.

[35] https://trialsearch.who.int/regtrac.aspx
[36] https://clinregs.niaid.nih.gov/
[37] http://campus.ecrin.org/
[38] https://eatris.eu/services/regulatory-services/

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QUIZ

Select one of the possible answers:

1. The only international legally binding document covering the protection of human rights in the biomedical field is:
   a) Declaration of Helsinki
   b) Directive 2001/20/EC
   c) ICH GCP
   d) Oviedo Convention

2. Fill in the statement about the European law: A "_____" is a binding legislative act. It must be applied in its entirety across the EU.

3. Is an mRNA vaccine subject to the regulation of Directive 2001/18/EC among others?
   Yes/No

4. The non-interventional post-authorisation safety study should follow:
   a) National legislation of the Member State concerned
   b) Regulation (EU) 536/2014
   c) Directive 2001/20/EC
   d) Commission Directive 2005/28/EC

5. The ultimate responsibility for investigational product(s) accountability at the trial site rests with the:
   a) Pharmacist
   b) Investigator
   c) Sponsor
   d) Project manager

6 Select the official source of EU legal documents:
   a) EATRIS
   b) EudraLex
   c) EUR-Lex
   d) REGTRAC

3 Databases of clinical trials

The Declaration of Helsinki states that every research study involving human subjects must be registered in a publicly accessible database before the recruitment of the first subject. The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility and helps to improve research transparency and data validity.

The International Committee of Medical Journal Editors (ICJME) announced a policy in 2004 that as a condition of publication, clinical trials would be required to be listed in a public registry. Subsequently, this was reflected in the legislative requirements of different countries, as well as the scope of requirements for the registration has been extended. The prospective registration of clinical

trials is required by law in some countries. The WHO manages the International Clinical Trials Registry Platform (ICTRP), the global initiative connecting at this time (June 2023) 17 primary registries which meet the specific criteria defined by WHO and ICJME.

Clinical trial registries are set up and managed by governmental and non-governmental organisations, universities, as well as commercial and non-profit entities (pharmaceutical companies, international organisations, health organisations). They can be divided into **primary registries** where the clinical trials are registered directly by the sponsor and **meta-registries** that collect the registered trials from primary registries. The national and international registries provide access to data on planned, ongoing and completed research for both professionals and the lay public.

Different registries include different kinds of clinical research and have different scopes and requirements for registration. Registries can be medicinal product-, device-, procedure- or country-specific, on the contrary, some registries accept all studies involving human subjects, e.g., ISRCTN[39] includes studies in education, workplace safety, economic development as well.

3.1 European databases

3.1.1 EudraCT and EU Clinical Trials Register (EU CTR)

EudraCT (European Union Drug Regulating Authorities Clinical Trials Database)[40] is the European database for all interventional clinical trials on medicinal products authorized in the EU/EEA and outside the EU/EEA if they are part of a Paediatric Investigation Plan from 1 May 2004 until January 2023. This has been established in accordance with Directive 2001/20/EC. National competent authorities used EudraCT to enter clinical trial data from clinical trial sponsors and paediatric investigation plan addressees. A subset of this data (protocol and results information) is made publicly available through the European Union Clinical Trials Register (EU CTR)[41] since September 2011, with exception of phase I adult trials. It had been mandatory for sponsors to post clinical trial summary results in the EudraCT database since July 2014. The EU CTR has been a primary registry in the WHO Registry Network.

As of 31 January 2023, all initial clinical trial applications in the EU/EEA must be submitted through the **Clinical Trials Information System (CTIS)**. All ongoing clinical trials in the EU must be transitioned to the CTIS by 31 January 2025. EU CTR still continues to display information on EudraCT trials.

3.1.2 Clinical Trials Information System (CTIS)

The Clinical Trial Regulation gave rise to CTIS (in CTR referred as “EU portal” and “EU database”) which should facilitate the submission of clinical trial applications including those for multi-national trials.

CTIS is the single entry point for clinical trials information in the EU/EEA. This includes a single clinical trial application dossier, covering clinical trial applications submitted to EU/EEA

[39] https://www.isrctn.com/
[40] https://eudract.ema.europa.eu/index.html
[41] https://www.clinicaltrialsregister.eu/ctr-search/search

Member States (including submission to national competent authorities and ethics committees) and registration of the clinical trial in a public register; all in one integrated submission. Each clinical trial is identified by a unique EU trial number. The exchange of information between sponsors and the Member States is fully electronic. The Member States collaborate and coordinate amongst themselves for the evaluation and supervision of clinical trials resulting in one single decision per Member State concerned. CTIS also interacts with the EudraVigilance system, connects the electronic reporting of suspected adverse reactions, and provides an electronic Annual Safety Reports repository.

CTIS is structured in two restricted and secured workspaces (Sponsor and Authority),[42] only accessible to registered users, and a website openly accessible to the general public,[43] where the clinical trial information and results are available, results both as a technical summary and in lay language. Sponsors are legally obliged to make the results of drug trials public within one year from the end of the clinical trial. The content of the summary of the results is defined by CTR in Annex IV and V.

CTIS: Online modular training programme
EMA developed the training programme for CTIS consisting of e-learning courses, guides, infographics, videos, and frequently asked questions. Training materials are available on the EMA's website.[44] The training videos can also be found on the EMA's YouTube channel.[45]

3.1.3 Registration of non-interventional studies

The **HMA-EMA Catalogue of real-world data studies**[46] (previously EU PAS Register) serves as a register of non-interventional post-authorisation studies, that should support the transparency of observational research and ensure compliance with the requirements of EU pharmacovigilance legislation (obligation for marketing authorisation in accordance with Regulation (EC) 726/2004 and Directive 2001/83/EC). Details about the requirements for the registration of post-authorisation safety studies (PASS) are available in the **Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII**.[47] Any other real-world data studies, that are not clinical trials, should also be entered in here.[48]

Discussion board
- ✓ Read a paragraph about the Publication of study results (VIII.B.5) in Guideline on GVP – Module VIII, p. 17 to understand the publication policy (investigator vs. marketing authorisation holder).[49]
- ✓ Do you plan a study with a medicinal product that is already placed on the market? What is your relation to the marketing authorisation holder? Leave your comment on the discussion board/discuss it with the teacher.

[42] https://euclinicaltrials.eu/ctis-for-sponsors
[43] https://euclinicaltrials.eu/search-for-clinical-trials
[44] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme
[45] https://youtube.com/playlist?list=PL7K5dNgKnawZC5W6okujD6ic0tOMsmtsg
[46] https://catalogues.ema.europa.eu/
[47] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
[48] https://catalogues.ema.europa.eu/catalogue-rwd-studies
[49] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf

Other European registries
In Europe, other clinical trial registries are available so far. From EU countries, it is the German Clinical Trials Register (Deutschen Register Klinischer Studien, DRKS) and the Netherlands Trial Register, both included in WHO Registry Network, however, the latter one is now permanently closed for new study registration. The National Registry for Clinical Studies (Registo Nacional de Estudos Clínicos, RNEC) serves as a tool for the registry and publication of all clinical studies undergoing in Portugal, including cosmetic products. Outside the EU, the Swiss National Clinical Trials Portal (Koordinationsstelle Forschung am Menschen, kofam) publishes the clinical trials conducted in Switzerland, ISRCTN (originally stood for International Standard Randomised Controlled Trial Number) in the United Kingdom. Furthermore, on the websites of some national competent authorities, information about the clinical studies conducted in that country can be found.

The registration of clinical investigation of medical devices in Europe is so far scattered in multiple registries recognized by WHO. “Clinical Investigations and performance studies” is one of the planned modules of the new European Databank on Medical Devices (**EUDAMED**) to be used as an entry point for the submission of all applications, notifications, and reporting and to enable the public to be adequately informed about clinical investigations, however, it is not in the plan to integrate it into WHO Registry Network, unlike EU CTR.

3.2 ICTRP, ClinicalTrials.gov, others

3.2.1 International Clinical Trials Registry Platform (ICTRP)[50]

The ICTRP is the publicly accessible search portal/database managed by WHO. It is a meta-register, i.e., the trial cannot be registered in this WHO ICTRP, but need to be submitted to any of the Primary Registries in the WHO Registry Network. WHO considers trial registration as the publication of the set of information about the design, conduct and administration of clinical trials. The minimum amount of trial information represents 24 items agreed by representatives of regulatory authorities, the pharmaceutical industry, research organisations, registry administrators, and editors of scientific journals as the WHO Trial Registration Data Set.[51] WHO also published the International Standards for Clinical Trials Registries.[52]

WHO has established a system of assigning a number, Universal Trial Number (UTN), to each clinical trial to make it easier to uniquely identify trials through ICTRP, because several registration numbers are assigned by different registries.

3.2.2 ClinicalTrials.gov[53]

ClinicalTrials.gov is a registry and a public database of clinical studies maintained by the US National Library of Medicine. It allows the registration of clinical studies conducted around the world with human subjects that assess biomedical and/or health outcomes. Listing a study does not mean it has been evaluated by the U.S. Federal Government, information on ClinicalTrials.gov is provided by study sponsors and investigators who ensure that the studies follow all applicable laws and regulations.

[50] https://www.who.int/clinical-trials-registry-platform
[51] https://www.who.int/clinical-trials-registry-platform/network/who-data-set
[52] https://apps.who.int/iris/bitstream/handle/10665/274994/9789241514743-eng.pdf
[53] https://clinicaltrials.gov/

In the US, U.S. Food and Drug Administration (FDA) requires prospective registration and the reporting of results no later than 1 year after their completion date for phase II–IV of a clinical trial with medicinal products and clinical investigation of medical devices. Retrospective registration is allowed as well for voluntarily registered studies.

Discussion board, practical exercise

- ✓ The use of databases/registries in the planning phase of clinical trials is especially important and necessary. If you want to get an overview of clinical research with a certain product, is it sufficient to search in only one database/register? Discuss the reasons and the choice of database(s) on the discussion board/with the teacher.

- ✓ To find out what the study registration entails, you can go through the instructions on How to Register Your Study[54] at ClinicalTrials.gov, which contain comprehensive tutorials and study protocol registration templates. You can also check instructions on How to Submit Your Results[55] with useful tutorials, checklists, and templates. Do you have any experience with study registration or results submission? Which register did you use and why? How much time did it take? Was the submission process reviewed? Did you have any issues? Leave your comment on the discussion board/discuss it with the teacher.

3.3 Trials registration vs. patient registries

Patient registries are organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time. More information about patient registries can be found on the EMA's website.[56] Patient registries can serve as a source of data for **registry-based studies**. A registry-based study is either a clinical trial or a non-interventional study. The patient registry itself does not serve as a trial registration. The registry-based study is subject to the same regulatory requirements just as any other clinical study, depending on the type of study (clinical trial/non-interventional study).

EMA has published the **Guideline on registry-based studies**,[57] which focuses on studies involving disease registries or condition registries to evaluate the benefit-risk of medicines prescribed to or consumed by patients. This guideline explains the differences between a registry based-study and a patient registry, describes how to plan a registry-based study, specifics of the study protocol, informed consent, data collection, data quality management, data analysis, and data reporting. In addition, it introduces how to establish and manage a patient registry to be eligible for regulatory purposes.

As a specific example of a patient register, a European volunteer registry to register persons interested to participate in the coronavirus vaccination study, may be mentioned. It was established under the clinical research network VACCELERATE and its aim is to provide fast and efficient recruitment of trial participants and speed up with it the COVID-19 vaccine development.

[54] https://www.clinicaltrials.gov/ct2/manage-recs/how-register
[55] https://clinicaltrials.gov/ct2/manage-recs/how-report
[56] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/patient-registries
[57] https://www.ema.europa.eu/en/guideline-registry-based-studies-0

Practical exercise

- ✓ Think about the possible utilization of registry-based studies in clinical research and write down your ideas. After that, go through Chapter "3.2. Use of registry-based studies for evidence generation" of the Guideline on registry-based studies[58] to get more details. You can compare the information obtained with those you wrote.
- ✓ Search for patient registries active in your country and write some of them on the discussion board mentioning the relevant country.

4 Quality

4.1 Concept of quality in clinical research

The 13th principle of ICH GCP states that "Systems with procedures that assure the **quality** of every aspect of the trial should be implemented." The sponsor should implement a **system to manage quality** throughout all stages of the trial process to ensure human subject protection and the reliability of trial results. ICH GCP is considered an ethical and scientific standard of quality. You can read the CONSCIOUS Chapter 4.2 to get an overview about ICH GCP and its principles.[59]

The Clinical Trials Transformation Initiative (CTTI) has characterized quality as, "the ability to effectively answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure while assuring protection of human subjects".

According to the ISO 9000, quality is "the degree to which a set of inherent characteristics of an object fulfils requirements". The standard defines a requirement as a need or expectation that is stated, generally implied, or obligatory. In other definition, quality is a set of characteristics that a product and service have to satisfy the requirements of the customers. In the context of clinical research, we can understand the product as information from the clinical research process; the service as a medical service provided to research subjects; the requirements as law and regulations, GCP, ethical standards, study protocol, budget, and timeline; and the customers as research subjects, sponsors, regulatory authorities, hospitals, institutional review boards/independent ethics committees.[60]

Quality in clinical studies should be used as a tool to build trust, especially trust of the research subject and public. We can find several serious ethical issues concerning human research in history. To read more about Nazi medical experiments, Tuskegee Syphilis Study, or Willowbrook hepatitis study we recommend you study CONSCIOUS Chapter 4, Ethics in Clinical Trials.[61] In response to these affairs, several documents laying the modern ethical foundation of medicine have been developed: from the Nuremberg Code, through the Declaration of Helsinki, Belmond Report, to the ICH GCP.

[58] https://www.ema.europa.eu/en/guideline-registry-based-studies-0
[59] CONSCIOUS: Chapter 4, Ethics in Clinical Trials; http://conscious.novaims.unl.pt/my/
[60] https://www.researchgate.net/publication/293597898_Quality_management_system_of_clinical_research
[61] CONSCIOUS: Chapter 4, Ethics in Clinical Trials; http://conscious.novaims.unl.pt/my/

4.2 Quality management system, risk-based management

Quality Management System (QMS) is a set of tools to ensure, control, maintain, and improve quality. This concept was adapted and applied for clinical research as **Clinical Quality Management System** (CQMS). The QMS usually consists of formal controlled procedural documents, such as policies, **standard operating procedures** (SOPs), work instructions, forms, and templates. A properly set up QMS should include the distribution of such documents to any team member and their systematic training as well. In other words, QMS applies similar elements as our immune system: recognizes, learns, remembers, and acts.

Discussion board

- ✓ Read more about SOPs in WHO Handbook for GCP, on p. 8–10, part 2. Development of standard operating procedures (SOPs).[62]
- ✓ Think about the following questions and write down the answers:
  1. Who should consider preparing SOP?
  2. Can you repeat some of the study-related activities?
  3. The number and elaboration of documents vary significantly depending on the sponsor of the study. Try to think of why.
- ✓ More about SOPs can be found in Chapter 3.[63]

There are no exact or legislatively binding instructions on how to develop and manage quality. It depends especially on the possibilities of sponsors. In IITs, the role of sponsor and investigator is held by one party/subject and other roles and responsibilities are cumulated by individuals. However, precisely because of the overlap of parties, optimal management should be secured in the area of conflict of interest, separation of responsibilities, and adjustment of personnel capacity.

The QMS includes quality planning, quality assurance, quality control, and quality improvement.

4.2.1 Planning

We need to focus on quality when planning clinical studies. We need to be able to maintain and control the whole system we set up. Designing quality into clinical studies and focusing on those factors critical to the quality of the studies and their management using a risk-proportionate approach is described in detail in ICH guidelines E6 and E8. This approach is often referred as Quality by Design and uses **risk-based quality management (RBQM)** as a key tool. The basic idea of RBQM is the continuous identification of risks for risk-bearing activities of clinical trials to reduce and manage these significant risks to participants, as well as the reliability of trial data. The application of RBQM approaches to clinical trials can also facilitate decision-making for better utilization of the available resources. Risk management should be appropriately documented and integrated within existing quality systems. The process can be clearly described by the following Figure.

[62] https://apps.who.int/iris/bitstream/handle/10665/43392/924159392X_eng.pdf
[63] Chapter 3, Trial management; https://www.conscious2.eu/

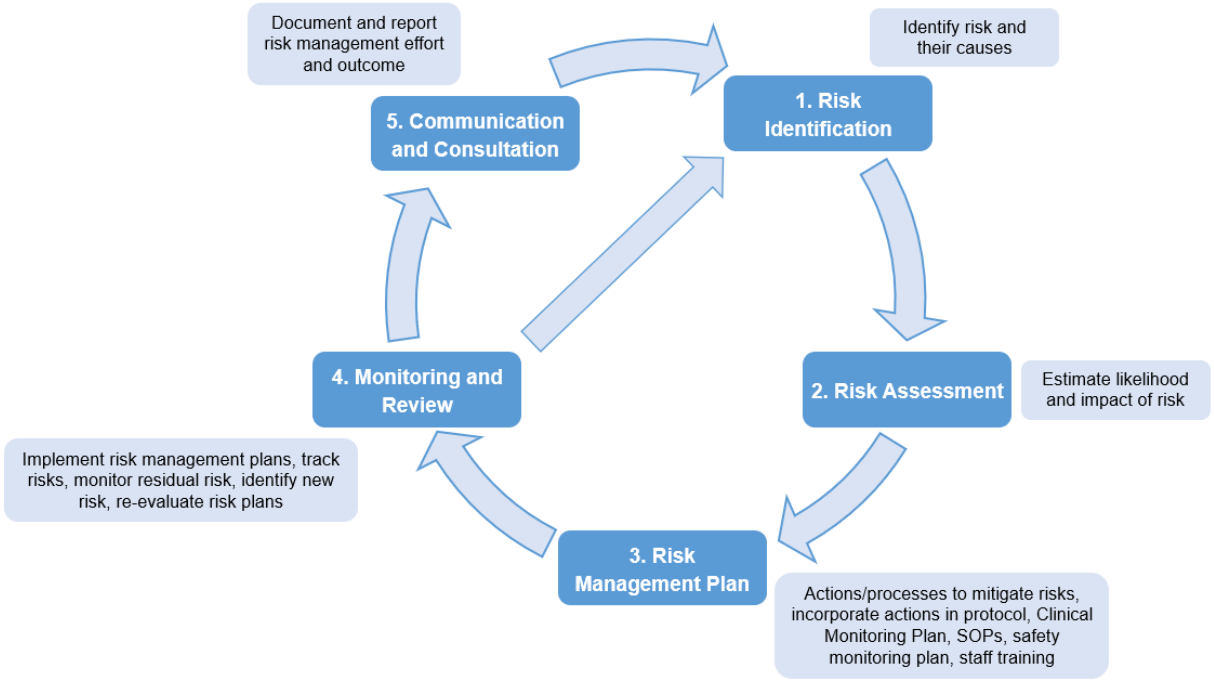

Figure 1: Risk management process[64]

It is essential to **assess the risk** of a clinical trial at the very beginning. This can already be done on the basis of a research proposal and re-evaluated once the protocol has been drafted. Risk assessment should be performed also at the level of the trial site. Sites can differ significantly in levels of experience with GCP and specific procedures under the study, available equipment and technology, personnel workload, site performance, rate of enrollment, etc. Risk assessment of the proposed project can help to set up the appropriate QMS as a tool to reduce risks (adjustment of monitoring activities, frequency of internal audits, external audits, etc.).

[64] Adapted from: https://vcccalliance.org.au/assets/What-we-do/Clinical-Trials-Expansion/IIT/Documents/c52dfd4dad/Risk-overview.pdf

Risk assessment process with examples

Risk assessment is the process of risk identification, risk analysis, and risk evaluation. As an example, to understand this process in practice we recommend seeing the Risk Assessment and Categorization Tool (RACT) Template published as part of TransCelerate's Risk Based Monitoring Initiative.[65]

This Tool provides a comprehensive assessment of the proposed project and you probably meet a wide variety of different versions/tools. Go through the columns in the table and observe the risk assessment process:

1) risk identification: "What might go wrong?" to identify a protocol's/site inherent scientific and operational risk factors
2) risk analysis = understanding of the risk: cause analysis (nature and type of causes), consequence analysis (nature and type of impact), and **quantification** (to quantify the risk to facilitate further decision making):
    - based on the risk's probability (likelihood), detectability, impact (severity, gravity)
    - usually graded as low/medium/high and easy/medium/difficult to detect
3) risk evaluation: It is important to decide which risks to reduce and which risks to accept. Risk reduction activities may be incorporated into the protocol, monitoring plans, by defining roles and responsibilities, etc. The decision is made according to the level of risk score (tolerance threshold), event. to risk matrix ("traffic light system", an example below).

	severity		
likelihood	**minor**	**moderate**	**major**
likely	acceptable add controls		unacceptable don't go
possible		acceptable add controls	
unlikely	acceptable routine procedure		acceptable add controls

As another example see the Risk Assessment Tool (UKCRF Network) based on Risk Significance Score (assigned score for the individual question-answer).[66]

Risk assessment is not limited to assessing the project or site during the planning stage, but it takes place also during the conduct and closing phases of a trial. A **key risk indicator** is a metric that provides information on the level of exposure to a given risk that the organization has at a particular time point. Controls need to be implemented to reduce/mitigate given risk exposure. Periodic review is needed, because new or anticipated issues may arise once the study has begun and the relative risk importance changes as the study progresses.

[65] https://www.transceleratebiopharmainc.com/wp-content/uploads/2021/07/RACT_FINAL.xlsx
[66] https://twitter.com/nihr_ukcrfn/status/1029305840405233665

Reading

Read the snippet of the article "Beauregard, A., Labrie, F., Tantsyura, V. (2018). The Basics of Clinical Trial Centralized Monitoring. *Applied Clinical Trials.* 27(11): 11-01-2018."[67] about the changing risk importance in the study progress:

"The enrollment rate at the beginning of a study is an important indicator of trial viability, but after the enrollment is closed, it becomes only an indicator of high enrollers, which does not directly impact trial integrity. In comparison, a high query rate at the beginning of a study might be addressed by retraining research coordinators without significant consequences. But at the end of the study, it may directly impact study quality and the time to database lock. Accordingly, risk assessment should evaluate a study at different phases and the focus of risk management should change with time."

Risk Assessment Output

KEY RISK INDICATORS	RISK CATEGORY			IMPORTANCE BY PHASE*		
	SUBJECT SAFETY	DATA QUALITY	TRIAL INTEGRITY	START-UP	EXECUTION	CLOSE-OUT
Enrollment Rate			✓	H	M	L
Screen Failure Rate			✓	M	M	L
Early Termination Rate	✓		✓	L	M	L
Out of Range Visit Rate			✓	L	M	M
Missed Dose Rate			✓	N/E	H	H
Missing Data Rate		✓	✓	H	H	M
Time to Data Entry		✓		M	H	M
Query Rate		✓	✓	L	H	H
Time to Query Resolution		✓		L	H	H
Error Rate		✓	✓	H	H	H
Deviation Rate	✓		✓	M	H	H
Adverse Event Rate	✓		✓	L	H	M
Site Appreciation Survey Score			✓	H	H	H

*L: Low, M: Medium, H: High, N/E: Not Evaluated

Source: Beauregard et al.

Table 1. Common key risk indicators and the typical output of a phase-relative risk assessment.

4.2.2 Quality assurance (QA) and Quality control (QC)

QA and QC are two aspects of quality management. Although they are interrelated and they have similar intentions, there is a difference between them. They are defined by ICH GCP following:

Quality assurance: All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements.

Quality control: The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

QA focuses on providing confidence, that the quality requirements are fulfilled; QC focuses on fulfilling quality requirements. QA verifies through systematic, independent audits that existing quality control systems (e.g., study monitoring, data management systems, or also the control of drug expiration, the calibration of diagnostic tests before initiation of the study, etc.) are working and effective. We can understand the QC as a subset of QA. QA is in the competency of the quality manager and uses auditing, whereas QC is supervised by the project manager

[67] https://www.appliedclinicaltrialsonline.com/view/basics-clinical-trial-centralized-monitoring

with monitoring as the main tool. Tools of QC and QA are described more in detail in Chapter 3.[68]

QC is an integral part of the everyday activities of every project/study team member. Each person involved in the clinical study should know and understand the roles and responsibilities of himself and the others. QC should start by controlling own work and tasks.

4.2.3 Quality improvement

Non-compliance with the protocol, SOPs, GCP, or regulatory requirements should lead to prompt action by the sponsor to secure compliance. Non-compliance can be noticed by auditors, monitors, or any team member. If non-compliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate **corrective and preventive actions** (ICH GCP, Section 5.20). Corrective action is taken to eliminate the cause of non-compliance to prevent a recurrence. Preventive action is taken to prevent the occurrence of such non-compliance. The purpose of corrective and preventive actions (**CAPA**) processes is to ensure that the identified non-compliance is visible and tracked and that the root cause is determined and resolved.

What that means in practice: Such a non-compliance is called Protocol Deviation (PD). PD is a general term further classified usually as minor/major/critical and also includes terms Protocol exception and Protocol Violation. A non-compliance initiates a protocol deviation procedure (identifying, recording, documenting, and reporting a PD) followed by a correction. The sponsor has a developed SOP for the Protocol deviation reporting (see example)[69] to guide the classification of PD and the following activity. A Protocol Deviation Form (see example)[70] is a part of it. In some cases, the trial site and/or sponsor may need to initiate a series of actions to correct the effects of the PD and prevent any further repeats (CAPA). The sponsor may have the developed SOP for CAPA and the CAPA template (see the example).[71]

CAPA process should be integrated into the CQMS. All steps of the process should be well documented and available for an audit or inspection.

To construct and apply a **CAPA plan** for a specific non-compliance/non-conformance it can be proceeded according to the following points:

1) *Identify the issue*: What happened, who discovered it, and who is involved.
2) *Evaluate the severity of the issue and its impact* on the quality by risk assessment (e.g., ok/minor/major/critical). Not every non-compliance should activate the CAPA process, because it would lead to overwhelming the system and delaying the solution of significant non-compliance. If the problem is minor, it can be solved with an effective correction, event. corrective action.
3) *Investigate the root cause*: person(s), process, system, external factor. Identifying root causes can be intimidating because there could be many potential causes and it's tough to be certain that one cause is more responsible than another. Different tools of

[68] Chapter 3, Trial management; https://www.conscious2.eu/
[69] https://www.ed.ac.uk/files/atoms/files/ectu_sop_op_11_recording_and_reporting_protocol_devations_and_violations_v2.0.pdf
[70] https://ukstar.octru.ox.ac.uk/sites/wot.octru.ox.ac.uk/files/UKSTAR:%20UK%20Study%20of%20Tendo%20Achilles%20Rehabilitation/files/UKSTAR_CRF_Form7_ProtocolDeviation_V1.0_17Jun2016.pdf
[71] https://www.uhhospitals.org/-/media/Files/For-Clinicians/Research/qa-503-capa-sop.pdf

root cause analysis are available (e.g., 5 Whys, Fishbone Diagram), but always is necessary to proceed systematically and a team effort is usually required.

4) *Determine resolution options*: corrections, corrective actions, or preventive actions are determined.
5) *Implement corrective actions.*
6) *Implement preventive actions.*
7) *Monitor efficacy of actions*: the most important step to ensure the action was appropriate and the issue was resolved and stop occurring.
8) *Close CAPA/Modify the procedures.*[72]

Practical exercise

A non-compliance was detected by the monitor during the monitor's visit. How to solve it?

- ✓ Firstly, watch the video "CAPA Case Study"[73] and discuss the described solution of non-compliance on the discussion board/with the teacher.
- ✓ Suggest a plan by yourself for: "the lab tests for the 2nd visit are not complete for 3 study participants". That information is not sufficient to construct a single CAPA plan, it offers several possible root causes, as well as the evaluation severity of that non-compliance can differ according to the type of test missing. Discuss your suggested solution on the discussion board/with the teacher. How many root causes can we get? Explore the discussion board.

4.3 International quality guidelines for clinical trials

Besides the many times mentioned the ICH GCP guideline, many other guidelines, and recommendations from different organisations were published to help to ensure the highest quality of clinical trials. The following table (Table 5) provides a basic list of them, which or their parts are relevant to the quality. Because quality management is a complex system affected by a number of documents and the table includes the whole scale of them, it is necessary to understand, that the ICH GCP guideline is the fundamental document. Investigators and all personnel involved in the conduct of clinical trials are required to be trained in GCP. Other documents can offer you an insight into the quality and detailed knowledge from different perspectives if you are interested.

These documents presented, were published by the ICH, EMA, WHO, FDA, International Organisation for Standardisation (ISO), Organisation for Economic Co-operation and Development (OECD), European Clinical Research Infrastructure Network (ECRIN), or CTTI.

Table 5: Guidance and documents on quality of clinical studies

Guideline for Good Clinical Practice E6(R2)[74]
ICH guideline E8 (R1) on general consideration for clinical studies[75] Section 3: Designing quality into clinical studies, Section 7: Considerations in identifying critical to quality factors

[72] https://www.i-sight.com/resources/building-an-effective-capa-plan-your-8-step-guide/
[73] https://www.youtube.com/watch?v=SaCARnvBo7o&ab_channel=USCDepartmentofRegulatoryandQualitySciences
[74] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
[75] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-e8-r1-general-considerations-clinical-studies_en.pdf

ICH guideline Q8 (R2) on pharmaceutical development[76]
ICH guideline Q9 on quality risk management[77]
ICH guideline Q10 on pharmaceutical quality system[78]
WHO: Handbook for good clinical practice (GCP)[79] Principle 14: Quality systems
EMA: Reflection paper on risk-based quality management in clinical trials[80]
FDA: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, Guidance for Industry [81]
ISO 9000 family – Quality management[82]
ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice[83]
ECRIN: Risk-based monitoring Toolbox[84] Risk Assessment Tools, Risk-Adapted Monitoring Tools
CTTI: Quality by design[85] Recommendations for Quality by Design, Recommendations for Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials

QUIZ

Select one of the possible answers:

1. Who is responsible for setting up the quality management system?
   a) Sponsor
   b) Investigator
   c) Project manager
   d) Monitor

2. Fill in the following terms in the left column of the table: Risk Management Plan, Monitoring and review, Risk identification, Communication and consultation, Risk assessment

	Identify risk and their causes
	Estimate likelihood and impact of risk
	Action/processes to mitigate risk, incorporate actions in protocol, clinical monitoring plan, SOPs, safety monitoring plan, staff training

[76] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-11.pdf
[77] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-3.pdf
[78] https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf
[79] https://apps.who.int/iris/bitstream/handle/10665/43392/924159392X_eng.pdf
[80] https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf
[81] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring
[82] https://www.iso.org/iso-9001-quality-management.html
[83] https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-3:v1:en
[84] https://ecrin.org/tools/risk-based-monitoring-toolbox
[85] https://ctti-clinicaltrials.org/our-work/quality/quality-by-design/

	Implement risk management plans, tracks risks, monitor residual risk, identify new risk, re-evaluate risk plans
	Document and report risk management effort and outcome

3. Assign the following terms to the correct column: Project manager, Audit, Data management system, Monitoring, Quality manager

Quality assurance	Quality control

5 Conclusion

For the investigator-initiated trials, generally, the same rules are applicable as for industry-initiated ones. The crucial issue in both types of trials is the credibility of the research and safety and well-being of subjects, which is always personnel/financially demanding and also requires a good understanding of and orientation in regulatory affairs. However, ensuring the credibility of the research and the safety of subjects are exactly the key responsibilities of every person working in clinical research, no matter what position holds. Be mindful of these responsibilities and adapt your work according to them.

Should you conduct/plan to conduct an investigator-initiated trial, keep in mind that supportive infrastructures with extensive expertise in clinical trial preparation and management are operated in many European countries (e.g., ECRIN) and you can take advantage of these services to simplify your research path and its implementation.

We hope that this chapter gave you a general idea of what it means and entails to perform a clinical trial from a legislative and qualitative perspective, and it will facilitate your future work.

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