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Position Paper
A European Approach to Clinical Investigator Training

CONTENT

1. The need for improved and harmonised investigator training in Europe

Planning, preparing and organising clinical trials at the investigator site has become a highly complex task taking into consideration the need to protect the patients, to generate reliable data, to perform the trials efficiently, with increasingly short timelines, and to fulfill all quality requirements according to the current legislation and inspection requirements. Obviously, it is important that European sites are able to perform clinical trials according to the required standards. While the number of performed clinical trials has only slightly decreased in the last years, other regions like Eastern Europe, Asia and South America have become more attractive to biopharmaceutical industry sponsors, leading to a decreased number of studies they initiate in Western- and Central Europe. Overall, the number of clinical trials in Europe has decreased by 20% in the last 3 years. The complexity of clinical trials and the regulatory requirements have increased significantly in the last few years, requiring an increasing level of scientific, methodological, regulatory and organisational know-how to be able to perform clinical trials efficiently. Despite pharmaceutical industry's increase of the percentage of multi-national trials and the number of sites involved, the number of enrolled patients per year has not increased (EUdraCT database), making the

planning and execution of clinical trials difficult and costly. In Europe, clinical research (clinical trials science and methodology) is often not highly regarded academically and collaboration with pharmaceutical industry in performing the trials is still subject to suspicion of commercial bias and perceived lack of academic credibility, as presented in the European Science Foundation European Medical Research Councils (EMRC) paper "Forward Look on Investigator-Driven Clinical Trials". The most important recommendation of this report to reverse this trend was: **To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.**

The principal clinical investigator has a crucial role in the clinical trial performance at the site. Clinical investigators are physicians who, in most cases, primarily perform diagnosis and treatment of diseases of patients under their care. Medicines under clinical investigation and the organisation of clinical trials are only a small part of their daily hectic and usually overloaded clinical activities. However, having the skills and infrastructure to enrol more patients makes the performance of a trial more worthwhile in every aspect. Yet, there is still broad lack of understanding amongst investigators about the benefits of training in efficient and reliable clinical trial performance.

All parties involved in organising and supervising clinical research agree that investigators need adequate training to carry out their duties. In particular this is stated in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and in the European Clinical Trials Directive 2001/20/EC. Large biopharmaceutical companies have developed their own GCP courses as a minimal requirement and demand that every investigator attends these courses as a prerequisite to become an investigator in their clinical trials. The current qualification standards for investigators are generally vague and vary widely between European Union (EU) countries. Only in Sweden, UK, Switzerland, Hungary and Lithuania a GCP certificate is a minimum regulatory requirement to participate in clinical trials. In some EU countries, like Germany or Italy, ethics committees expect to see a GCP certificate as a demonstration of investigator suitability. However, training over one or two days in GCP does not enable physicians to thoroughly comprehend their role in protecting trial participants and to generate quality data in an efficient way in all types of studies. Moreover most ethics committees in Europe are satisfied with a curriculum vitae documenting clinical credentials in the respective therapeutic area.

Clinical research is only very marginally subject to undergraduate medical training in Europe, and there is no post-graduate education obligation for physicians performing and taking responsibility for clinical trials in most EU countries. Clinical trial units in hospitals, private training providers and some universities (e.g. Basel, Copenhagen, Leuven…) across Europe have started to offer comprehensive investigator training to improve the competence of their investigators and the number of clinical trials successfully performed in their hospitals. However, these are local, spontaneous and often reactive activities. There is a need to develop a strategy for investigator training in Europe that

- is demonstrably able to enhance efficiency and reliability of investigator activities
- can be applied in all EU countries, fulfilling regulatory and ethics committee requirements
- fulfils pharmaceutical industry's quality expectations
- follows a syllabus that covers the full spectrum of investigator activities, not just the GCP basics
- is adapted to investigators' respective roles and responsibilities in a clinical trial
- can be integrated into the investigators' work schedule

- is provided by demonstrably qualified training organisations
- ensures demonstration of achieved learning outcomes
- is financially affordable
- can be performed without undue investment of investigators' time.

The here proposed strategy for investigator training will further improve the credibility of clinical research and increase patient throughput in clinical studies, a key objective of the Innovative Medicines Initiative (IMI).

2. PharmaTrain and ECRIN

PharmaTrain is one of the IMI Education and Training projects and focusses on the development of a comprehensive training infrastructure in the area of pharmaceutical development which includes the areas of pharmaceutical medicine, regulatory affairs and clinical trial performance. The project is based on the creation of a network of Diploma and Master Courses in pharmaceutical development and in regulatory affairs, located in many different countries. The PharmaTrain consortium partners, consisting of universities, not-for-profit organisations and pharmaceutical companies, have developed and implemented an advanced standard for content and teaching methodology based on an agreed syllabus and curriculum and including e-learning opportunities. PharmaTrain has established a European quality management infrastructure to assess quality, content and performance of the associated courses, an infrastructure to manage the examination process in all associated courses and an IT platform within EMTRAIN's "on-course" database to enable easy identification of the most suitable training opportunities.

ECRIN, the FP7-funded European Clinical Research Infrastructures Network, is a sustainable, not-for-profit infrastructure supporting multinational clinical research projects in Europe. ECRIN provides information, consulting and services to academic investigators and sponsors in the preparation and in the conduct of multi-national clinical studies, for any category of clinical research and in any disease area. This is particularly relevant for investigator-initiated (academic, non-industry sponsored) or small and medium enterprise-sponsored clinical trials and for clinical research on rare diseases where international cooperation is a key success factor. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research. Relevant tools for clinical researchers involved in multinational clinical trials are available on the ECRIN website.

Based on global and other regions' activities to increase investigator competence like e.g., the OECD (Organisation for Economic Co-operation and Development), APPI (Academy of Pharmaceutical Physicians and Investigators) or ACRES (Alliance for Clinical Research Excellence and Safety) initiatives, there is an increasing wish to harmonise investigator training requirements in the EU. However, at the same time it will be vital to build an infrastructure that gives investigators easy and affordable access to training and examination.

PharmaTrain and ECRIN have joined forces to utilize their European reach and impact on clinical research to promote and establish such a European investigator training infrastructure leading to a clinical investigator certificate (CLIC). They invited other organisations involved

in investigator training to join an Advisory Group in order to work out a suitable strategy (see composition in Section 11).

3. Different levels of competence

Not all professionals involved in clinical research need to acquire the same level of competence in clinical trial performance. In fact, some are only involved in the study site team. Others assume responsibility as principal investigators. Still others may consider clinical research as a major component of their professional life and even initiate new studies on sponsor level. A somewhat different combination of knowledge and skills is required for investigators performing Phase I trials in a dedicated unit. A training approach adapted to the training needs in human pharmacology studies might be initiated in near future by experts in that field.

To date a concept of 3 levels of competence has emerged. It is found in the Swissmedic (Swiss Agency for Therapeutic Products) guidelines (1), which distinguish sub-investigator, investigator and sponsor-investigator, as well as in the USA-based Academy of Pharmaceutical Physicians and Investigators (APPI) Statement of Clinical Investigator Competence (2), which relates them to the depth of commitment to clinical research.

It is therefore recommended that courses offer the option of different levels of training related to distinct responsibilities in the performance of clinical trials:

- Level 1: site staff
- Level 2: (principal) investigator (responsibility for a clinical trial at a site)
- Level 3: sponsor-investigator (overall responsibility for a clinical trial)

These 3 levels represent increasing competence and individuals may move from one level to an upper level over time.

Level 1 encompasses a basic core of knowledge that is common to the various professionals in a study team involved in the preparation and conduct of studies at investigational sites. The target audience is therefore constituted by medical (sub-investigator) and non-medical (study nurse, study coordinator, study manager…) staff.

Level 2 represents the knowledge in regulatory and managerial aspects of a clinical trial requested from a principal investigator according to ICH-GCP definition, EU and national legislation.

Level 3 corresponds to investigators for whom clinical research is a major element of their professional life and who assume responsibility for investigator-initiated trials. The term “sponsor-investigator” is not optimal since in general the sponsor is an institution (e.g. an hospital or university) and not an individual, but in contrast to “trial-initiating investigator”, “sponsor-investigator” expresses the type of knowledge such type of investigator needs to have.

These 3 levels also differ by their national versus international dimension. The content of the courses will include national regulations at level 1, an overview of the international

regulatory environment at level 2 and a detailed knowledge of EU and international regulations at level 3.

To demonstrate the acquired level of knowledge required to receive the respective Investigator Training Certificate, the Advisory Group recommended to require a mandatory examination.

4. Content and learning outcomes of clinical investigator courses

This question has been addressed in several documents:

- A European syllabus for Training Clinical Investigators (European Science Foundation, 2003) (3)
- Swissmedic guidelines defining the training content requested for a sub-investigator, investigator and sponsor-investigator respectively (1)
- The APPI Consensus Statement (2)
- The Innovative Medicines Initiative (IMI) PharmaTrain Manual (4) defining the contents and learning outcomes of courses in pharmaceutical medicine/medicines development sciences, of which clinical research is an essential component.

Based on these previous documents, the Advisory Group has redefined a syllabus and learning outcomes for each of the 3 levels defined in section 2. They are included in the Appendix. The course content is presented incrementally, i.e., the level 3 syllabus and learning outcomes only contain the elements to be taught in addition to those of levels 1 and 2. This syllabus is currently focused on medicinal products and should later be expanded to other areas of research such as medical devices.

5. Format and duration of the courses for clinical investigators

It will be left to the student to decide on the number of hours he/she will invest into learning and the modus of learning. Courses for clinical investigators can be entirely face-to-face or involve mostly e-learning complemented by a short face-to-face session. The PharmaTrain e-library includes a course for clinical investigators in which the content has been stratified according to the 3 levels of competence, mentioned earlier (5). There is a broad offering of investigator training options by many different organisations in different countries. These existing resources should be used, provided they are in line with the above mentioned syllabus and learning outcomes.

At level 1 and 2, the courses could be given in the local language or in English, whereas English is mandatory for level 3.

The optimal duration of a clinical investigator course will depend on the targeted level of competence. The ESF syllabus suggested a 3-5 days training duration (3). Although these

figures are approximate (especially for e-learning) and not mandatory, the following durations are recommended :

- 2 days (16 hours) for level 1
- 5 days (40 hours) for level 2, that is a 3 days increment as compared to level 1
- 8 days (64 hours) for level 3, that is a 3 days increment as compared to level 2.

Beside these basic courses, there is also room for more extensive courses such as full master programmes in clinical research, or diploma courses in clinical trial practices and management that are organised in some European countries.

The Advisory Group proposed a grandfathering clause for duration of 3 years after implementation, allowing that the established investigators will be eligible to receive the certificate without passing the examination, provided that they sit the examination in form of self-control and submit a detailed CV, including the list of clinical trials in which they have been involved.

A Continuous Professional Development (CPD) programme requiring the attendance to short refresher/update courses, at least every 3 years, should also be established.

6. Course accreditation

As part of PharmaTrain's network of course providers in pharmaceutical medicine/medicines development sciences, a European network of CLIC course providers will be established. The course providers will be accredited by the PharmaTrain Central Office according to the agreed and implemented PharmaTrain quality standards.

PharmaTrain will establish a "CLIC Course Recognition" award for those courses fulfilling the PharmaTrain quality criteria and syllabus/learning outcome requirements.

It is proposed to develop a database in the PharmaTrain Central Office containing the accredited courses as well as the contact details of those certified course participants who gave permission to keep their personal data in order to remind them of their CPD needs.

7. Examination and certification

The Advisory Group proposed that one obligatory face-to-face day encompassing the examination will be required as pre-requisite for the certificate. Examinations will be organized at a local level by course providers. Candidates who have not attended courses will be allowed to sit these examinations. These will consist of a multiple choice questionnaire (MCQ) involving the physical presence of candidates in order to be sure of their identity; this could change with time in relation with technological evolution. Distinct questions will be proposed for the different levels of competence required. The MCQs should include at least 50 questions (level 1), 60 questions (level 2) or 80 questions (level 3).

The Advisory Group proposed to establish a pool of ca. 500 questions for the 3 levels, subject to a continuous improvement process and sensitivity analyses. The questions will be made publicly available ("drivers-licence approach").

The course/examination providers will request 80% of the questions from the PharmaTrain Central Office, whereas 20% of the questions can be related to national legislation/regulations and be prepared by the local examination/course providers.

At levels 1 and 2, the examination might be in national language rather than English; national course providers will be encouraged to provide the translation of the questions to the central question pool.

Management and scoring of the examinations will be performed by a central unit, according to the Good Examination Guidelines established by PharmaTrain. Answers will be entered on a computerised sheet and automatically evaluated by the central unit selected by the PharmaTrain Central Office, to ensure objectivity and to maintain standards and comparability of scoring.

Certificates will be issued preferably by national universities. If this is not achievable in a country then issuing by national physician associations or nation-wide academic institutions should be sought.

The certificates will be delivered by the course provider containing the university stamp, the PharmaTrain and ECRIN labels and the course provider's label. The certificates will mention the level of competence and all nationally required information.

8. Conditions of success and impact

The development of a European programme of clinical investigator training and certification aims at further increasing the quality of clinical trials in Europe, in order to support the faster discovery and development of better medicines for patients and to enhance Europe's competitiveness, which are the goals of the Innovative Medicines Initiative. At the end of the day the impact of investigator training on the quality of clinical research will need to be evaluated using qualitative and quantitative indicators, such as a decrease in the number of observations during audits and inspections.

Success depends on the full cooperation and involvement of investigators, sponsors, ethics committees, medical associations and regulatory authorities. In particular the pharmaceutical sponsors should view clinical investigator training as a new opportunity to enhance quality and efficiency, with the ultimate aim of accruing more patients data in European countries and facilitating EU regulatory filings. These training courses should reduce/obviate the need for sponsor-organised GCP training sessions that cover only part of the training needs and lead to a needless redundancy. They should recommend and motivate their investigators to attend formal training courses to obtain formal certification. Ethics committees and regulatory authorities should aim at harmonizing regulations and creating a minimal and mutually recognised certification requirement for investigators throughout Europe.

9. Recommendations

The Advisory Group recommended the following steps to improve and harmonize clinical investigator training and certification in Europe.

- EU and national regulatory authorities should harmonize regulations and create a minimal and mutually recognized certification requirement for investigators throughout the EU.

- Pharmaceutical sponsors should reduce the need for redundant GCP training sessions that cover only part of the needs and motivate instead investigators to attend training courses and obtain formal certification.

- A European platform should be created to provide a suitable course and examination infrastructure, assess courses and harmonise examinations throughout the EU in order to improve quality and comparability. That platform should be based on current and past European projects in the field such as IMI PharmaTrain and ECRIN.

10. References

1. Requirements for the training of co-investigators, principal investigators and sponsor-investigators involved in clinical trials on therapeutic products, http://www.swissmedic.ch/bewilligungen/00089/01100/index.html?lang=en

2. Statement of clinical investigator competence, APPI Consensus Statement, Monitor, August 2011: 79-82

3. A European Syllabus for Training Clinical Investigators, European Science Foundation, July 2003, http://www.esf.org/publications/medical-sciences.html?tx_ccdamdl_pi1%5Bpointer%5D=1&cHash=5facba551e13516e3a4b9154f8680f35

4. PharmaTrain Manual, 2011

5. eCLIC, http://www.pharmatrain.eu/ or http://clic.bio-med.ch/cms/Default.aspx

6. PharmaTrain, Good Examination Practices, 2011

11. Advisory Group

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Appendix

Table 1 Clinical Investigator Training – Level 1

Topics	Content	Learning Outcomes	Duration (h)
Introduction to the ethics of clinical research and Good Clinical Practice	➢ History and justification of the regulations for subject protection ➢ Origin and principles of ICH-GCP ➢ Responsibilities of the various players	• Recognise the impact of historical events that have contributed to the current regulations and guidelines • State the documents that have contributed to current regulations and guidelines • Describe the objectives and role of the International Conference on Harmonisation • Explain the impact of the principles of ICH-GCP • Describe the roles of Sponsor, Monitor, Investigator, Ethics Committee, Regulatory authorities • Summarise the rights of subjects in clinical trials and the role of the investigator in protecting them • Define fraud and misconduct in clinical research	1
Overview of the medicine development process	➢ The various steps of the medicines development process: sequence and duration	• Understand the various phases of medicines development, their timelines and attrition	1
Introduction to clinical research methodology	➢ Definition of the phases of clinical development (I-IV) and related research objectives ➢ Structure of a clinical trial ➢ Key elements of trial design ➢ Definitions of parallel groups versus crossover, control, placebo, randomisation, blinding, bias, intention-to-treat	• Define the research questions to answer and types of endpoints in each clinical trial phase • Define the subject population, size and duration of trials in each phase • Explain the design aspects of a Randomised Controlled Trial • Describe the different periods a clinical trial may contain from identification of the subject until his/her last visit • Describe the different types of study populations in the statistical evaluation	1
Legislative framework and	➢ International regulatory	• Explain the link between ICH-GCP, EU Directives/Regulations and	1

guidance for clinical research	environment ➢ Applicable national regulations	national regulations • Describe how EU Directives impact on national regulations • Explain the key national legal requirements for clinical trials in your country	
Planning and preparation of a trial	➢ Review of protocol and related material ➢ Interactions between investigator and sponsor (pre-study visit, investigator selection, budget and contract, initiation visit) ➢ Submission to the ethics committee ➢ Submission to national regulatory authorities ➢ Preparation of study-related processes and documentation	• Explain how to explore the suitability of the indication and protocol implications for your site • Understand the need of an effective communication between the various stakeholders (sponsor, investigative team members, ethics committee, regulatory authorities, hospital administration, patients, treating physicians) • Order key events in the conduct of a clinical trial • Define the key dossier elements and timelines for national ethical review • Define the key dossier elements and timelines required for study approval by the national competent authorities • Understand the protocol-required site processes • Explain how to prepare the required study documentation together with the sponsor	2
Site organisation and management	➢ Evaluation of resources needed for the clinical trial ➢ Organisation of the investigative site team ➢ Organisation of a patient visit	• Describe the process of defining the staff level, staff time and facilities required for a clinical trial • Explain the activities required to prepare the investigative site team for the study initiation visit • Explain the activities required to organise a patient visit	2
Subject recruitment, enrolment and retention	➢ Challenge and strategy of recruitment ➢ Different phases of recruitment and enrolment ➢ Patient information and informed consent process in adults and children ➢ Randomisation in practice ➢ Compliance check	• Understand the challenge of enrolling the required number of subjects in the given timelines • Describe options for finding study subjects including advertisement requirements • Define screening, recruitment and enrolment • Define the informed consent process for adults and for children/parents and how it is documented • Recognize the importance of understandable, complete and honest information for the patient's autonomous decision on participation	2

	➢ Subject retention ➢ Personal data confidentiality, patient privacy	in the study before any trial-related procedure • Identify the people that may be involved in the informed consent process and recognize what can be delegated by the principal investigator • Explain the differences between consent withdrawal, patient withdrawal and early study termination • Describe the randomisation process in open and blinded studies • Describe the options to identify and supervise patients' compliance • Describe ways to improve subject retention • Recognize the patients' rights on privacy and data protection and describe best practices to achieve this	
Overview of in-trial procedures	➢ Source documents and essential documents ➢ Subject visits, measurements and assessments ➢ Completion, correction and control of the Case Report Form ➢ Management of the investigational product ➢ Monitoring visits ➢ Trial close-out	• Understand the difference between essential and source documents • List the main documents that must be in place prior to randomization of the first subject • Recognize the responsibility of the investigative team in collecting complete, accurate and traceable data • Describe the aspects required to ensure quality measurements and assessments • Define the different types of data and data sources in a clinical trial • Describe the technical options for case report forms, the process and staff involved in case report form completion and correction • Understand the consequences of missing data • Understand the role of the investigative team in the management of the investigational medicinal products and the differences with routine medicines prescription • Describe the activities required for correct study medication handling • Describe the process of drug accountability • Understand the basic aspects of biological samples management • Define the types of monitoring visits • Describe the site's activities required for preparation, execution and follow-up or a monitor's visit • Understand the requirements for	4

		storage and archival of essential documents at the investigational site • Describe the site's activities required to study close-out	
Introduction to safety	➢ Basic definitions and classification of adverse events (AE, SAE, ADR, SUSAR…) ➢ Reporting and management of adverse events, including un-blinding ➢ Emergency situation handling	• Recognize that the on-going collection of safety data is a regulatory requirement and allows adequate evaluation of the risk/benefit ratio • Match key safety terms and abbreviations to the appropriate definition • Understand the difference between adverse event and adverse reaction • List the criteria defining a serious adverse event • Understand the difference between serious and severe events • Describe the process of identification, adequate reporting and management of serious adverse events • Understand the implications of breaking the blind and list circumstances where un-blinding is justified • Understand the need for continuous emergency situation training of the site staff and the control of the emergency equipment	1
Quality assurance, monitoring, audits and inspections	➢ Basic concepts in quality management (Quality assurance incl. SOPs, quality control… ➢ Monitoring versus audits versus inspections ➢ Audit and inspection findings	• Recognize the importance of quality management in clinical trials • Describe the elements of a quality management system like quality assurance, quality control, training , CV and job description(s), and define the difference between quality control and quality assurance • Define the difference between monitoring, audits and inspections • Describe potential outcomes/consequences of audits and inspections	1

Table 2 Clinical Investigator Training – Level 2

Contents and learning outcomes of Level 1 (Table 1) +

Topic	Contents	Learning outcomes	Duration (hrs)
Basic concepts for designing and evaluating clinical trials	➢ Basic statistical concepts and definitions (confidence interval, statistical significance, odds ratio…) ➢ Types of study (observational versus experimental) and level of proof ➢ Types of design (inter-patients, intra-patients, sequential) ➢ Types of comparison (superiority, non-inferiority…) ➢ Various types of bias and measures to avoid them ➢ Sample size calculation ➢ Types of analysis (intention-to-treat versus per protocol) ➢ Meta-analysis and evidence-based medicine ➢ Subgroups and post-hoc analyses ➢ Statistical significance and clinical interpretation	• Match basic statistical terms with their definition • Describe basic statistical principles and methods for clinical data analysis and reporting • List the major types of bias in clinical trials • Identify the benefits of randomization as a means to reduce bias and confounding • Justify the use of blinding to minimise bias • Describe the information required to calculate the sample size • Understand the difference between intention-to treat and per protocol analysis • Explain the principles and limitations of meta-analyses • Evaluate the strength of evidence of clinical trials • Describe the limitations of clinical trials in predicting effectiveness • Define the rules for subgroups and post-hoc analyses • Explain the meaning of "statistical significance" and its relevance for clinical interpretation	3
Study protocol	➢ Structure and contents ➢ Objectives and endpoints ➢ Inclusion/exclusion criteria ➢ Study diagram and flowchart ➢ Measurements and assessments	• List the major sections of a protocol • Understand the relevance of primary and secondary objectives and endpoints for the performance of the study at site • Understand the practical implications of adherence to in- and exclusion criteria for subject recruitment	2

	➢ Protocol amendments	• Understand the usefulness of study flowcharts for the management of the study • Describe how to ensure optimal execution of the study activities described in the flowchart during a subject's study visits at the site • Describe how measurements and assessments for clinical trial subjects according to a protocol differ from routine measurements and assessments • Describe the practical implications of a protocol amendment	
Ethics of clinical research	➢ Investigator responsibilities ➢ Criteria for the ethical evaluation of studies (scientific validity, equipoise…) ➢ Risk-benefit assessment ➢ Ethical review procedures ➢ Use of placebo ➢ Follow-on treatment ➢ Conflicts of interest ➢ Misconduct and fraud ➢ Publication bias and clinical trial registries	• Describe the investigator's responsibility for the study subjects' safety, integrity and well-being • Acknowledge the investigator's responsibility for fully knowing the scientific background of the study and clinically relevant aspects of the study medication • Understand the investigator's responsibility for the selection of studies with acceptable benefit/risk ratio and suitability for his/her site • Explain the ethical problems in placebo-controlled studies • Understand the need for transparency in study organisation and fair access to study medication • Describe the investigator's role in ensuring adequate follow-on treatment for study participants • Identify the areas of investigators' potential conflicts of interest • Summarize the role an ethics committee assumes to protect the rights and safety of subjects • Define the criteria used by an ethics committee for approving a study • Describe the documentation that must be received from the ethics committee before starting a study • List the minimum on-going communication required by ethics committees	2

		• List indicators that could lead to suspect fraud or misconduct • Recognize the implications of confirmed fraud or misconduct in a clinical trial • Understand the need to register a study in a publicly accessible registry • Recognize the need and difficulties in publishing every study, independent of its outcome	
Informed consent process	➢ Right of subjects ➢ Information transmission and understanding of the subject ➢ Re-consent	• Acknowledge the investigator's responsibility for ensuring an adequate informed consent process and documentation • Explain the requirements for appropriate language when writing a patient information sheet and informed consent form • List instances in which a subject cannot provide informed consent • List the characteristics required from a witness • Explain the difference between and conditions for "consent" and "assent" • Define the need and process for including a legal representative in the informed consent process • Explain your national requirements for informed consent in emergency situations • Appreciate that informed consent is an on-going process	1
Introduction to clinical studies in special and vulnerable populations	➢ Children ➢ Elderly subjects ➢ Incapacitated adults ➢ Pregnancy and breast-feeding ➢ Orphan diseases	• Identify vulnerable patient groups and the methods used to protect them • Understand why these populations are considered vulnerable • Understand the purpose and content of the Paediatric Investigation Plan • Acknowledge the additional complexities in managing studies with children, elderly, mentally handicapped or unconscious patients • Recognize the special protection	1

		needs for pregnant or breast-feeding women in clinical trials	
Document management	➢ List of the essential documents generated before, during and after the trial ➢ Investigator site file ➢ Rules for archival (investigator versus sponsor file, duration)	• List all essential documents that must be in place prior to randomization of the first subject • Identify all documents required to be in the Investigator Site File at study end • Define the site documents that are not supposed to go into the Trial Master File • Understand appropriate document management, including corrections and version control • Recognize that investigators are responsible for the archival of essential documents for the time period defined by local regulations or longer if required by the sponsor	2
Safety data	➢ AE collection and assessment ➢ SAE assessment and reporting	• Describe the process for reliable adverse event collection, qualified assessment, complete documentation and adequate reporting • Describe the elements of a CIOMS form • Explain the rules for causality and expectedness assessment	2
Insurance issues	➢ Various types of insurance contracts and coverage ➢ Variability of insurance regulations between countries	• Understand the concept of no-fault liability • Acknowledge the need for the investigator's medical mal practice insurance and a study-related subject liability insurance • Describe the national subject insurance requirements	1
Management of the investiga-tional medicinal product	➢ Types of medication in a study ➢ Packaging and labelling ➢ Storage and handling ➢ Return and accountability ➢ Compliance monitoring	• Define the different types of medication administered to study subjects and the respective financial coverage conditions • Understand the process and timelines for study medication preparation including stability timelines, blinding, labelling and packaging • Identify the investigator's responsibilities for appropriate study medication handling and	1

		accountability • Acknowledge the need for respecting and controlling IMP storage conditions • Appreciate the importance of seamless documentation of accountability for IMP from receipt to return or destruction • Explain the investigator's potential interaction with the pharmacy • Recognize the investigator's responsibility for subjects' reliable medication compliance	
Biological samples management	➢ Use of biological markers for patient selection and evaluation of efficacy and safety ➢ Shipment requirements ➢ Archival in biobanks	• Identify the specific role of biological outcomes • Recognize the potential need for additional informed consent when samples are taken for genetic analysis • Respect that stored biological samples can only be used for the purposes described in the protocol and the informed consent • List the reference documents for the management of biological samples • Acknowledge the investigator's responsibility for sampling, work-up, storage and shipment of biological samples • Understand the principles of biobanking including the rules for anonymisation of samples	1
Data collection and management, final reporting	➢ Structure of the CRF ➢ Data collection and documentation process ➢ Central monitoring and quality control, data queries ➢ Advantages and disadvantages of electronic data capture ➢ Confidentiality and data protection ➢ Final reporting	• List the key elements of a CRF • Explain the standard data collection, documentation, control and investigator review process • Understand that the reliability of study results is based on the completeness, consistency and correctness of the data provided by the investigator in the CRF • Explain the importance of maintaining an audit trail • List the advantages and disadvantages of electronic data capture over paper CRF • Understand the difference between the source documents and the CRF	2

		• Explain the key confidentiality rules between investigator and sponsor as well as investigator and subject • Describe the process of subject data pseudonomisation and anonymisation • Explain the investigator's role and support to final reporting of the study	
Clinical project management	➢ Adequate resources and facilities ➢ Project planning ➢ Screening, recruitment and retention ➢ Management of deviations and mistakes ➢ Interaction with monitors, auditors and inspectors ➢ Communication ➢ Quality management ➢ Training ➢ Supervisory committees	• Explain the process to ensure suitable staffing, medical competence and facilities in all departments involved in the study at this site • Describe the study planning process for this site • Recognize the options for delegation of responsibilities for screening, enrolment and medical care of subjects • Explain how to ensure adequate emergency coverage during a study • Describe how to identify and handle mistakes, deviations and omissions in a study • Describe investigator tasks, responsibilities and delegation options in interaction with monitors, auditors and inspectors • Explain how to initiate and manage the communication process inside and to the outside of the study site team • Acknowledge the need for quality assurance, quality control, and adequate staff competence documentation • Explain the training requirements and documentation in a clinical study • Understand the roles and responsibilities of Scientific Advisory Boards, Data and Safety Monitoring Boards, Data Review committees, etc.	4
Financial and contractual	➢ Investigator contract	• Explain the key elements of an investigator contract and	2

study management	➢ Calculation of investigative site budget ➢ Patient compensation and travel expenses ➢ Invoicing	negotiation options • Understand the need to define the publication rules in investigator contracts for mono- and multi-centre studies • Describe the elements, calculation process and payment condition options for a site budget • Explain how to calculate and handle subject compensation and travel expenses • Acknowledge the investigator's role in the site's invoicing process	

Table 3 Clinical Investigator Training – Level 3

Contents and learning outcomes of Level 1 (Table 1) and Level 2 (Table 2) +

Topic	Contents	Learning outcomes	Duration (hrs)
Medicines discovery, develop-ment, optimisa-tion and observation	➢ Medicines discovery ➢ Pre-clinical development ➢ Exploratory and confirmatory development ➢ Marketing authorisation for medicinal products in the EU ➢ Pharmacovigilance in medicines development ➢ Off-label use of medicines ➢ Treatment optimisation ➢ New indications and patient populations ➢ New galenic formulations ➢ Health economics ➢ Pharmaco-epidemiology	• List current challenges and opportunities for medicines development • Outline the discovery process • Understand the importance and principles of toxicology studies • Describe concept and elements of exploratory and confirmatory medicines development • Explain the principle regulatory options for marketing authorisation in the EU • Describe the principles of pharmacovigilance in medicines development • Understand when and why to develop a risk management plan • Explain the problems of off-label use • Define the principles of treatment optimisation studies • Describe the regulatory process and types of studies required to achieve marketing authorisation for a new indication or patient population • Explain the need and general content of a Paediatric Investigation Plan (PIP) • Understand the key technical and regulatory requirements for the development of a new galenic formulation of chemical and biological products • Outline the types of studies required to answer health economic questions • Explain the types of studies performed in pharmaco-epidemiology and their regulatory environment	3
Sponsor responsibili ties	➢ Overall study responsibility ➢ Scientific and ethical responsibilities ➢ Regulatory responsibilities	• Recognise that the sponsor is ultimately responsible for all aspects of the study and for ensuring compliance with the protocol and all applicable regulations • Explain the options and challenges of co-sponsoring in multi-national trials	4

	➢ Organisational responsibilities ➢ Quality responsibilities ➢ IMP responsibilities ➢ Contractual responsibilities ➢ Insurance responsibilities ➢ Financial responsibilities ➢ Obligations to the public	• Explain the sponsor's responsibility for selection of scientifically and ethically relevant study objectives and suitable study design to answer the scientific question • Define the approvals/licences/authorizations required in the EU and the investigator's country when conducting interventional and non-interventional studies • Define the criteria that must be met for a trial to be described as non-interventional • Identify the time points when communication with regulatory authorities and ethics committees is required • Explain the process of CTA approval and substantial amendments • List the content of a CTA submission dossier in the investigator's country • Explain the process and requirements for achieving a favourable ethics committee opinion in the investigator's country for the study and substantial amendments • Describe the sponsor's safety reporting obligations • Describe the sponsor's reporting obligations to competent authorities and ethics committees during and at the end of the study • Explain the sponsor's obligations for site selection including its capacity and qualification • Recognize the sponsor's obligation to ensure patient and data protection, unbiased data evaluation, final reporting and publication • Describe the principles of quality management and its applicability to an investigative site • List the types of contracts a sponsor needs to have in place before starting the study • Acknowledge the sponsor's obligation to have suitable product liability and patient liability insurance in place	

		• Recognize the sponsor's obligation to have sufficient financial means to perform the study	
Human pharma-cology	➢ Non-clinical requirements for First-in-Human studies ➢ Calculation of the first dose in man ➢ Principles of First-in-human studies ➢ Mechanisms of **A**bsorption, **D**istribution, **M**etabolism and **E**limination ➢ Bioanalytics ➢ Pharmacokinetics and pharmacodynamics ➢ Bioavailability and bioequivalence ➢ Interaction studies ➢ Genetic testing	• Understand the specificity and risk factors of a First-in-human study • Understand the main pre-clinical requirements for studies in humans as described in the ICH-M3 guideline • Define the basic concepts for calculation of the first human doses (NOAEL, MABEL…) • Describe choice of subjects, possible dose escalation schemes, stopping rules, set-up and and precautions to be applied in human pharmacology studies • Understand the conditions for reliable sample collection, work-up, storage, shipment, analysis, and reporting of biological data • Understand the main pharmacokinetic parameters • Explain the principles of bioavailability and bioequivalence • Describe concept and need for interaction studies • Understand the concepts of genetic characterisation of study participants	1
Concepts for Phase II and III studies	➢ Research questions ➢ Primary and secondary objectives ➢ Primary and secondary parameters ➢ Design of the study ➢ Treatment duration ➢ Assessments and procedures ➢ Statistical concepts ➢ Study population	• Describe the process required to define a suitable research question including the concept of equipoise • Acknowledge the relevance and suitability of drug-related guidelines • Identify appropriate primary and secondary objectives and parameters to answer the research questions • Explain various study designs and their strength and weaknesses in terms of internal and external validity for the different phases in medicines development • Define the criteria for deciding on the treatment duration in a study • Acknowledge the conflict between statistically required sample size, study conduct practicalities and available budget • Recognize the need for limiting the number of visits and assessments /	3

		procedures per subject to enable efficient and timely study performance • Recognize main types of analysis (continuous outcomes, binary outcomes, survival analysis, multivariate analyses) and which applies to a given outcome • Understand the concept and implications of interim analyses • Explain the concept and practical challenges of adaptive designs • Describe the principle and benefits of stratification • Define the different types of analysis populations and the need for a blind data review process • Understand the need for clearly defined inclusion criteria and the detrimental effect of too many and too narrow exclusion criteria	
Outcomes and comparator in a clinical study	➢ Types of outcomes ➢ Outcomes evaluation ➢ Tools for reduction of variability ➢ Types of comparison ➢ Placebo ➢ Active comparator ➢ Blinding options	• Define "outcome study" and "surrogate endpoint" • Recognize the need to identify outcomes that are relevant to patients • Understand the importance and complexity of collection of quality of life data and patient reported outcomes • Define biomarker and the criteria for using a biomarker as surrogate endpoint • Acknowledge the need for extensive training and supervision in outcomes with potentially large inter-reader variability • Describe the advantages and disadvantages of centralised collection and reading of data (e.g., central ECG or image reading, central lab, central event review, DSMB, etc.) • Define the concept of "comparison" in interventional and non-interventional studies • Identify situations where placebo is scientifically required and ethically acceptable • List criteria for a comparator to be acceptable • Describe the options, logistic complexities and regulatory	1

		requirements for blinding study medication	
Writing a protocol	➢ Structure of the protocol ➢ Elements of the protocol ➢ Development and review process ➢ Protocol authorisation process ➢ Protocol modification	• Acknowledge the need for a protocol for all types of studies in humans • Describe the structure of the protocol including the relevance of a summary, the background description, and the instructions for study physicians • List the key contributors and stakeholders when developing and reviewing a protocol • Describe tools and procedures to increase the quality of a protocol including patients' role in this process • Describe the protocol authorisation process and list the required signatures on a protocol • Provide examples of changes to a study that would require a substantial or non-substantial amendment • Describe the format and development process for a substantial amendment	2
Budget of a clinical study	➢ Budget elements ➢ Cost calculation process ➢ Funding options ➢ Budget supervision process ➢ Changes to the budget ➢ Final study costs	• Define the complete list of budget elements in a clinical study • Describe the process of cost calculation in a clinical study • Differentiate the routine care costs and the study costs • Understand the financial rules in public hospitals • Describe funding options for sponsor-investigators and related application processes • Explain the options and conditions in public-private partnerships • Describe the principles and tools of budget supervision including the concept of "cost versus budget comparison" • Explain conditions and processes involved in calculating and approving budget changes • Understand the process of final cost consolidation and reporting	2
Clinical study manage-ment	• Feasibility • Selection of participating countries and sites • Clinical study team	• Explain the process for obtaining reliable feasibility information • Describe the criteria and process for selection of participating countries and sites	3

	• Assignment of responsibilities • Project management • Study initiation • Monitoring • Reporting • Risk management	• Explain the management structure in a clinical study • Acknowledge the need for project management resources, skills and tools as well as the benefit of preparing a project management plan that includes a detailed risk analysis • Acknowledge the benefits of preparing manuals in multi-centre studies for crucial processes like monitoring manual, IMP manual, CRF manual, safety data manual, etc. • Explain how to estimate the required human resources to perform all study activities • Describe the concept of outsourcing and tools to identify the suitability of service providers • Explain the process of clearly assigning roles and responsibilities within the project • Explain the process and tools for recruitment projection • List the requirements for study initiation • Explain how the level of monitoring is defined in a risk-based approach • Describe process, advantages and disadvantages of central monitoring • Describe how to calculate the resources required for monitoring • Define the format for monitoring reporting, the process for the monitoring reports' review and for initiation of corrective actions • Explain the process for reporting on study progress • Describe the options for early risk identification and mitigation • Describe measures to rescue a study that is delayed and/or over budget	
Study medication	➢ Definitions ➢ GMP conformity of study medication ➢ IB ➢ SPC	• Explain the criteria for defining study medication, baseline treatment, rescue medication, concomitant medication, etc. • Explain the types of study medication the sponsor is obliged to provide for free • Understand the requirements for	1

		GMP-conform manufacturing, labelling and packaging of study medication • List the situations when a sponsor needs to work with GMP-certified pharmacies at the investigators' sites • Describe the content of an Investigator Brochure for non-authorised medicines • Explain the content of an SPC • Recognize the sponsor's responsibility for drug reconciliation	
Pharmaco-vigilance in a clinical study	➢ SUSAR ➢ DSUR ➢ Early study termination ➢ External safety supervision	• Explain the assessment process from SAE to SUSAR • Describe the expedited SUSAR reporting process and timelines in national and multi-national studies • Define the process and timelines for preparation of Development Safety Update Reports (DSURs) • Explain how to calculate the resources for the pharmacovigilance process Identify the reasons why a trial can be stopped (efficacy, safety concern, futility) • Explain conditions requiring external safety supervision in a clinical study	1
Data manage-ment and Statistics	➢ CRF preparation ➢ Data management process ➢ Statistical Analysis Plan ➢ Statistical evaluation	• Define the documents that will be used to create the structure of the CRF • Explain the criteria for selecting a paper or electronic CRF approach and the respective implications for data base programming, study management and data cleaning process • Describe the data management process from CRF preparation, to validation, completion, and cleaning until data base lock • List the procedures that can be used to ensure that high quality data are reported in the CRF • List the identifiers that must be on every page of the CRF • Explain how to calculate the resources required for the data management process in a study • Describe the content of a Statistical Analysis Plan and the process of its generation • Define process and timelines for	1

		preparation of the statistical evaluation • Recognize the importance of a clearly defined database lock • Understand the difference between per-protocol analysis and post-hoc analyses • Explain the statistician's role in preparation of the Clinical study report	
Documen-tation, reporting and archiving	➢ Trial Master File ➢ Investigator Site Files ➢ Archiving ➢ Clinical study report ➢ Result communication	• Explain the need and content of a Trial Master File (TMF) • Acknowledge the archiving responsibilities of a sponsor • Describe archiving tools and processes • Identify the needs and requirements for clinical study reports • Describe the content and structure of a clinical study report • Understand the process of critical review of the report • Acknowledge the importance of results communication to participants	1
Quality manage-ment	➢ Auditing ➢ SOPs ➢ Training ➢ Qualification documentation	• Explain how to define the extent of auditing • Describe the course of a typical audit and its potential outcomes • Prioritise the need for SOPs in different clinical study aspects • Acknowledge the sponsor's responsibility for training of all resources • Define the required extent, process and documentation of training for the different stakeholders in a clinical study • Explain the need for proper documentation of qualification within a clinical study by CVs related to defined job descriptions	1