Transvac Training Guide

Clinical Research

From Translational to Clinical Research in Europe: Requirements, Rules and Conduct of Clinical Trials

W. Kuchinke and C. Kubiak, Version 1.1, Aug. 2007

The guide is based on a **Transvac course** held at ECRIN head quarters Paris 11.-12. July 2007 and conducted by W. Kuchinke, C. Kubiak, J. Demotes, C. Sebastiani

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ECRIN: the European Clinical Research Infrastructure Network (www.ecrin.org) is an EU-wide infrastructure of national networks of clinical research centres and clinical trials units covering nearly 300 clinical trial centres having available resources for the support of clinical research in any medical field, and for any type of clinical trials, but especially for multinational studies in Europe. ECRIN aims at providing public or private (mainly biotechnology SME) sponsors with a support for translational research and multicentre clinical studies in Europe. A major objective of ECRIN consists of stimulating and facilitating the creation of Centres and National Networks, especially in the new member states, for their subsequent connection to the European network. ECRIN data centres are being developed to harbour study software to support electronic data capture and electronic study management in clinical trials for ECRIN member institutions.

Dando & Colucci specialises in facilitating the development, financing and implementation of life science based innovation 'clusters' (international consortia and/or science parks) by providing tailored insight and management, offering tactical and strategic management to permit correct financial management, leveraging of resources, positioning on the life science value chain. This stretches from fundamental research through to partnering at the time of real value creation. Their expertise includes: Consortium development and partner recruitment; Fund raising and identification of potential financial backers; Elaboration and negotiation of detailed scientific and development plan; Executive and project management; Consortium operational development and organisation; Resource and technical evaluation; Business development and market analysis; Financial co-ordination and reporting, pre-clinical to clinical planning and implementation, and Intellectual property management co-ordination. At present Dando and Colucci consults to 4 companies and 3 European research centres in fund raising and international development, and the European Clinical Research Infrastructure Network. It is actively researching how to optimise international project management and portfolio development to generate new European models which will permit a better integration and innovation.

Transvac:
Trans-vac is a Marie Curie Industrial-Academic Partnership supported by the European Commission (MKTI-CT-2006-039948) aimed to find an effective way to manage biomedical research alliances across the European continent, to achieve effective knowledge management within an organisational context with respect to and to enhance the level of creativity occurring between and within industrial and academic biomedical organisations and generate an active portfolio of projects with high potential for creating knowledge and value.

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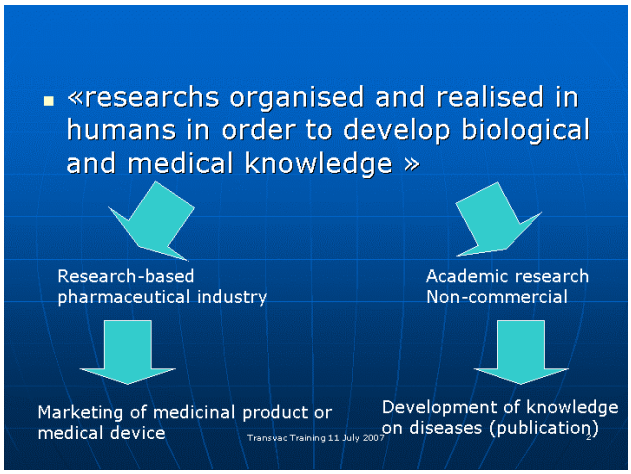
1. Clinical research overview

Research is organised and realised in humans in order to develop biological and medical knowledge.

Research performed by the pharmaceutical industry and academic research have different aims and are complementary.



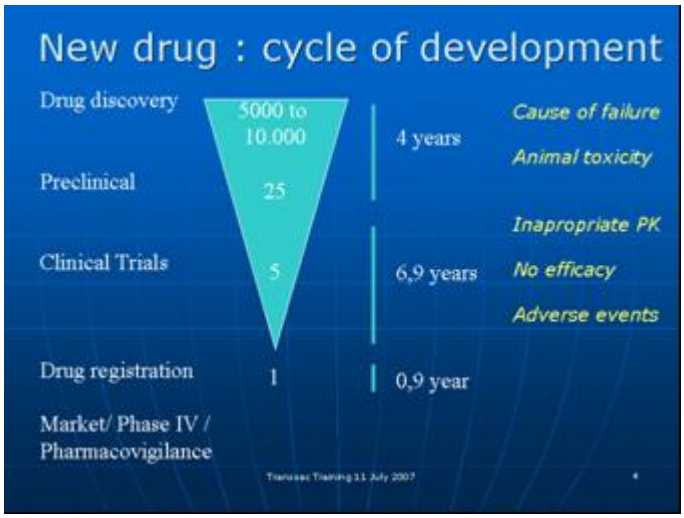
1.1 Clinical research on medicinal product

Pharmaceutical research & development is a rigorous process with an assessment of the safety and benefit in each step. To make a new medicine, the first step is to identify a specific target that is a promising focal point for a medicine.
Hundred of potential drugs can be selected following a screening phase, but only a few will undergo the complete process and will be available for patients.

1.1.1 overview

The whole process includes:

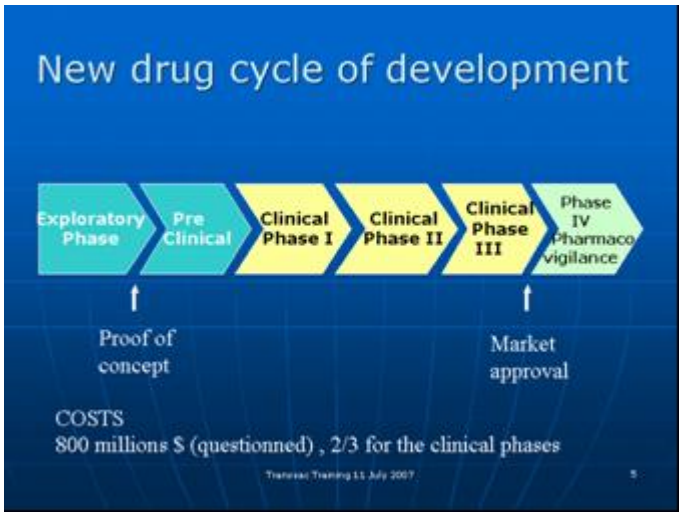
- Pre clinical development
- Laboratory and animal studies
- Evaluation of the safety
- Demonstration of the biological activity against disease target
- Pharmacokinetic
- Chemistry tests (purity, stability, shelf live)
- Pharmaceutical development studies (formulation, dosing, packaging)
- Preclinical development could take from 3 to 6 years and is not finished when clinical studies start
- Clinical development



Failure can occur at any step of the development and the main causes are animal toxicity, inappropriate pharmacokinetic, lack of efficacy, adverse events.

1.1.2 Clinical Development

The clinical development process consists of several steps.



The clinical development is made through a very rigorous methodology i.e. the clinical trials.

A clinical trial is an investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.

This development is composed of 4 phases (phase I – IV).

1.2 Phase I: Human pharmacology

Phase I is the first administration of the new drug to humans. These studies are designed to verify the safety and tolerability profile of the candidate new medicine.
Phase I clinical studies involve small group (20-100) of healthy volunteers (except for certain type of drugs where patients are included) receiving the investigational product for short periods of time and who are closely monitored.
The objective of the phase I studies is to:

- determine safety profile
- determine the dose ranging
- determine the pharmacokinetic (absorption, distribution, metabolisation, elimination and half life.

Depending on the type of disease and type of medicinal product to be developed, phases I can last from 6 months to 1 year.

1.3 Phase II: Therapeutic exploration

The phase II studies are performed on small number of patients (100 to 500) suffering from the condition the investigational drug is designed to treat. The patients are selected and very strict inclusion and non-inclusion criteria are respected. Usually those trials are placebo-controlled trials, double blind and their objectives are to:

- evaluate the efficacy
- proof the concept
- evaluate the optimal dose strength and schedule

1.4 Phase III: Therapeutic confirmatory

Phase III studies are conducted on large number of patients (from 1000 to 5000), they include also different populations to reflect the future utilisation of the new product. These studies are randomised, placebo controlled and the objectives are to evaluate the efficacy and the safety. Depending on the disease and design of studies, this phase can last from 1 to 4 years.

Following the phase III, **a marketing authorisation** can be requested to the competent authorities either through a centralised procedure, a mutual recognition or a national procedure.
The marketing authorisation application is composed of:

- part 1: “summary of the dossier” with administrative information, the summary of product characteristics, labelling and experts reports
- part 2: “pharmaceutical quality”
- part 3: “safety”
- part 4: “efficacy”. This part includes preclinical studies and clinical studies

1.5 Phase IV: Post marketing studies

After the medicine has been approved phase IV studies are performed in order to assess the use of the medicines in “real” conditions and to detect, and assess side effects after short-term and long-term use of medicines. Phases IV include larger number of patients.

1.6 Academic / Non-commercial trials

«Non-Commercial trials» are defined by the EU directive 2001/20/EC as clinical trials without the participation of the pharmaceutical /biological industry. They follow the different phases previously described.

They can consist of interventions with medicinal products used in:

- the promotion of health by comparative effectiveness as optimal-use trials
- the prevention and/or treatment of disease
- in rehabilitation and long term care

Those trials can also be early-phase clinical trials usually focusing on areas of healthcare where prospects of commercial return are limited or not immediately apparent.

2. The different categories of research

2.1 overview

Different type of research can be performed to find cures for humans. There are two major groups of research:

- **‘Interventional’ studies:**
  - Medicinal trials (incl. phase I, post-marketing...)
  - Medical device trials
  - Surgery trials
  - Radiotherapy trials
  - Biotherapy (gene, cell, tissue)
  - Mechanism of disease, genotype / phenotype
  - Imaging, diagnostic, biomarker
  - Other
- **‘Observational’ studies**

2.2 Rules and principles for the conduct of studies in humans

Clinical trials are conducted within a strict regulatory framework. The objective is to guaranty the protection of the participants, the relevance and the quality of the research.

The main **reference texts** to observe are:

- Helsinki Declaration
- Good Clinical Practices (ICH)
- Directive 2001/20/EC (4th April 2001)
- National laws

2.2.1 GCP-Directives

The EU Directive on clinical trials and the new regulatory framework (Directive 2001/20/EC/ Directive 2005/28/EC, guidance documents).

The objective of the EU 2001/20/EC directive is to give a European framework for clinical trials and harmonise practices (the Good Clinical Practices are included in the law). It also gives to EU members tools to control and follow clinical studies (EudraCT=data base that list studies in EU and **Eudravigilance** = European data base to collect adverse events). The Directive reinforce the protection of persons and data and in particular vulnerable populations.

The **changes** brought by the Directive are:

- the transposition of the ICH guidelines in national laws
- Responsibility of the member states (Competent Authorities)
- Responsibility of the sponsor
- EU-wide safety reporting
- Harmonisation
- Single ethical opinion

But the transposition into national laws is divergent as some countries implemented a product centred approach although other countries implemented a patient-centred approach (any intervention even without a medicinal product is covered by the regulation). The ethical review is not harmonised nor the definition of the Investigational medicinal product (IMP).

The Directive 2001/20/EC resulted in partial harmonisation within the European countries for clinical trials on medicinal products, but for other categories of research the regulatory requirements are different from one country to another and especially regarding:

- the sponsor
- the insurance
- the submission to ethic Committee
- the submission to Competent authorities
- the definition of the Investigational Medicinal Product
- the adverse event reporting
- the data protection
- the storage of tissues
- the radiation protection

2.3 The different actors in clinical research

The different **actors** in clinical research are:

- sponsors
- investigators
- participants
- funders
- competent authorities
- ethic committees

2.3.1 Sponsor

The sponsor is an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial (Directive 2001/20/EC). Sponsors can be public institutions (universities, hospitals), scientific agencies, foundations, charities, non for profit institutions, scientific associations, private companies.

The sponsor is **responsible** for:

- trial design
- trial management, data handling, report keeping
- quality assurance and quality control
- allocation of responsibilities
- compensation to subjects and investigators
- financing
- EudraCT number
- submission to the competent authorities, the Ethic committee and communication during the study
- management of the Investigational Medicinal Product
- Safety information
- Adverse Event reporting
- Audit
- Clinical study report

The sponsor may **delegate** any or all of its trial-related tasks to an institution/ company/ organisation (specified in writing) and for example:

- -interaction with EC
- -interaction with CA
- -adverse event reporting
- -monitoring

A number of parties may agree to form an organisation (identified by its name and the EudraCT number) and to distribute the sponsor's tasks. There must be still an overall sponsor for the trial who remains ultimately responsible for ensuring that the conduct of the trials and final data comply with the regulation.

Public sponsors or investigator-sponsor (investigator- initiated trial where the investigator has both responsibilities) have difficulties to face the increased complexity of the sponsor tasks. The sponsor has to ensure the financing of the clinical research but the funder can be different from the sponsor. The financing can be private, public or public- private partnership.

2.3.2 The investigator

The investigator is a physician or a person following a profession agreed in the Member state for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a trial at a trial site. If a trial is conducted by a team of individuals, at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator (Directive 2001/20/EC).

The investigator is **responsible** to:

- Ensure the study is conducted according to the investigator statement/agreement, protocol and regulatory requirements
- Inform the participant (fair and understandable information including risks and benefits and the right to withdraw consent at any time) and obtain his informed consent (the process must be free of any coercion or undue influence)
- Ensure the protection of the participant's rights, safety and welfare
- Ensure the control of investigational drug

The investigator **must**:

- have the resources and facilities to conduct the study (competencies, adequate staff, time, adequate recruitment, adequate facilities)
- be trained on the protocol, product, Good clinical Practice
- communicate with the sponsor (and especially any information that can impact the study)
- report the adverse events (immediately for the serious adverse events)

2.3.3 The participant to a clinical research

Directive 2001/20/EC defines the "subject" as an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control. The subject can be a patient or a healthy volunteer. Specific rules exist for vulnerable populations.

2.3.4 Competent Authorities

The competent authorities (CA) can be at the national or regional level depending on the countries. The CA:

- authorises clinical trial prior to commencement (Clinical Trial Authorisation CTA)
- authorises any substantial amendment during the clinical trial
- needs to receive from the sponsor information on the beginning/closure of the clinical trial
- need to receive information on AE (expedited reports, annual safety reports)

They can request additional information, ask for modifications, suspend or stop a study. The competent authority gives a decision on the pharmaceutical quality and safety of the medicine and security of the participants to the research.

2.3.4 Ethics committees

The Ethic committee is concerned of the safety of participating patients and gives an approval after the evaluation of:

- relevance of the trial and design
- suitability of investigator and staff and facilities (suitability of means and objectives)
- adequacy and completeness of the written information to the patient and procedure to obtain consent
- waiver of consent in emergency care
- recruitment modalities
- insurance or indemnity to cover the liability of the investigator and sponsor
- compensation fees, volunteer's file

The sponsor can submit the application at the same time to the CA and EC or processes in two steps.

3. GCP (Good Clinical Practice)

3.1 Introduction and overview into the rules

The best way of an introduction is to look at the GCP glossary, because GCP consists mainly of a number of buildings block: definitions, roles, rules. To understand GCP it is necessary to learn these building blocks.

3.2 Glossary

3.2.1 Adverse Drug Reaction (ADR)

all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a **reasonable** possibility, i.e. the relationship cannot be ruled out. Importance especially in the pre-approval clinical phase, when experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established.

3.2.2 Approval (in relation to Institutional Review Boards IRB)

means the affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

3.2.3 Audit

A systematic and independent examination of the trial and its trial related activities and documents to determine whether the trial was conducted, and the data were recorded, analyzed and accurately reported according to the protocol, the sponsor's standard operating procedures (SOPs), the Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

3.2.4 Audit Trail

Documentation that allows a reconstruction of the course of events

3.2.5 Blinding / Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double- blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

3.2.6: Clinical Trial / Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and / or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and / or to study absorption, distribution,

metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

3.2.7 Clinical Trial (Study) Report

It is a written description of a trial of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the "*ICH Guideline for Structure and Content of Clinical Study Reports*")

3.2.8 Compliance

means the adherence to all the trial-related requirements, to Good Clinical Practice (GCP) requirements, and to the applicable regulatory requirements.

3.2.9 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

3.2.10 Essential Documents

Trial documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

3.2.11 Data-Monitoring Committee (DMC) (Data and Safety Monitoring Committee)

such an independent committee may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

3.2.12 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human participants (subjects) involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

3.2.13 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

3.2.14 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

3.2.15 Investigator

A person who is responsible for the conduct of the clinical trial at a trial site (center). If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

3.2.16 Investigator's Brochure

A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

3.2.17 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

3.2.18 Protocol

The Clinical Trial Protocol describes the trial completely. It is a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

3.2.19 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

3.2.20 Regulatory Authorities

This term stands for bodies having the power to regulate. In the ICH GCP guideline the expression “Regulatory Authorities” includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

3.2.21 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity.

3.2.22 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

3.2.23 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays,

subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

3.3 Rules to protect human wellbeing during research

History showed that there is a dire need to establish regulations to protect humans in any kind of research. Several basic rules were established.

3.3.1 Nuremburg Code

The Nuremburg Code was one of the first attempts to regulate the ethics of medical research. It was written shortly after the Second World War, following revelations at the Nuremberg Trials that unethical research was carried out by certain members of the medical profession during the Nazi period in Germany. The Code has 10 requirements and begins with the, now widely recognised, principle that voluntary consent of human participants in research is paramount. The Code has since been superseded by documents such as the Declaration of Helsinki and Good Clinical Practice.

3.3.2 Belmont Principles

the Belmont Report is a report created by the former United States Department of Health, Education, and Welfare entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (April 18, 1979). The Belmont Report identifies three fundamental ethical principles for all human subject research:

- respect for persons,
- beneficence,
- justice.

In 1991, 14 Federal departments and agencies joined HHS in adopting a uniform set of rules for the protection of human subjects, identical to subpart A of 45 CFR part 46 of the HHS regulations. This uniform set of regulations is the Federal Policy for the Protection of Human Subjects, informally known as the “**Common Rule**”. Today, the Belmont Report continues as an essential reference for institutional review boards (IRBs) that review HHS-conducted or -supported human subjects research proposals involving human subjects, in order to ensure that the research meets the ethical foundations of the regulations.

3.3.3 Declaration of Helsinki

The Declaration of Helsinki is a statement of ethical principles developed by the World Medical Association to: "provide guidance to physicians and other participants in medical research involving human subjects". This includes research on people, identifiable human material or identifiable data. The Declaration was first adopted in 1964 and has since undergone several revisions (1975, 1983, 1989, 1996, and in 2000). The declaration established such important new achievement like the “informed consent”. The Declaration includes principles on:

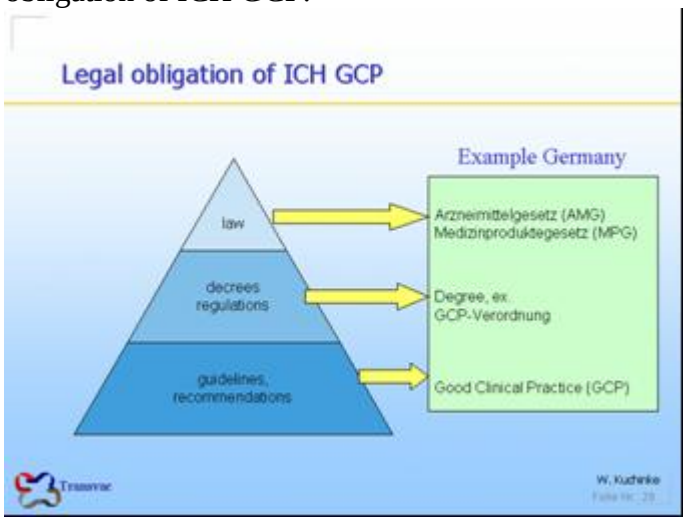
- Safeguarding research subjects
- Informed consent
- Minimising risk
- Adhering to an approved research plan/protocol

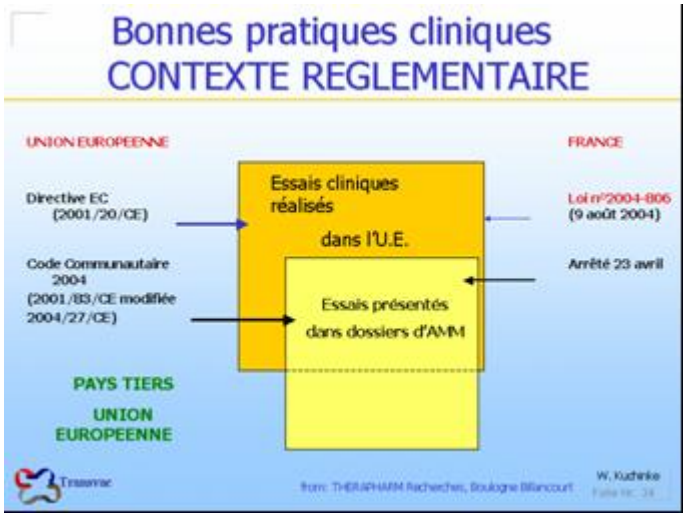
The Declaration is considered the fundamental document in the ethics of healthcare research. The ideas of the declaration were further developed in GCP (Good Clinical Practice).

3.4 Legal obligation and implementation of GCP Directive

There exists a pyramid of number of regulatory documents and their legal obligation. Only a small number of laws have the full power of laws, but a large number of guidelines have only little obligatory power. Nonetheless the rules established in the guidelines have to be fixed on laws to guide actions. Approximation of laws: in contrast to EC-decrees and the decisions that are binding in all their parts, guidelines impose merely the goal to be reached on their recipients and leave the procedure to the recipient. This procedure has the advantage of regulatory flexibility. In this way GCP had to be fixed in the legal framework.

The authoritative regulation for the EU is the Clinical Trials Directive (2001/20/EC) = EUCTD. The EUCTD is a legal document, published in 2001, which sets out how clinical trials investigating the safety or efficacy of a medicinal product in humans must be conducted. It includes medicinal trials with healthy volunteers and small scale or pilot studies. Member States must transpose the EUCTD into national law. As examples the situations in Germany and France are given. Legal obligation of ICH GCP:





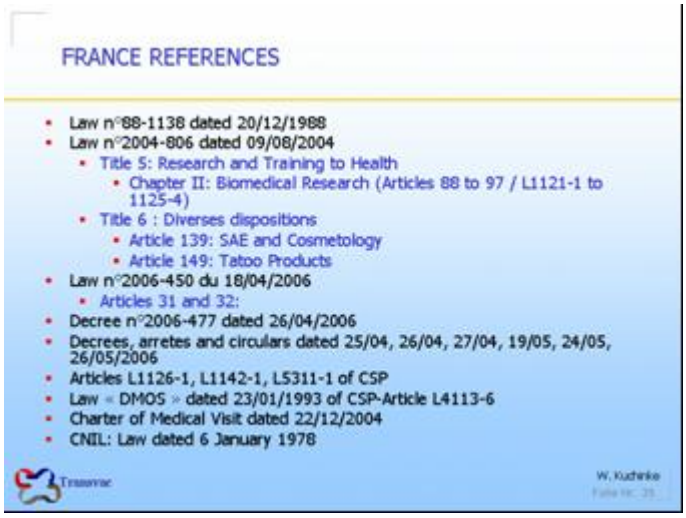
3.5 France: Les Bonnes pratiques cliniques (BPC)

3.5.1 Realisation of BPC

Ensemble d'exigences de qualité dans les domaines éthique et scientifique, reconnues au plan international, devant être respectées lors de la conception, la mise en place, le recueil des données et l'expression de leurs résultats afin de garantir (Dir 2001/20/CE art.1., GCP-E6),

- que les droits et la sécurité des personnes se prêtant à l'essai ainsi que la confidentialité des informations qui les concernent sont protégés
- que les données sont intègres, authentiques et vérifiables
- Bonnes pratiques cliniques

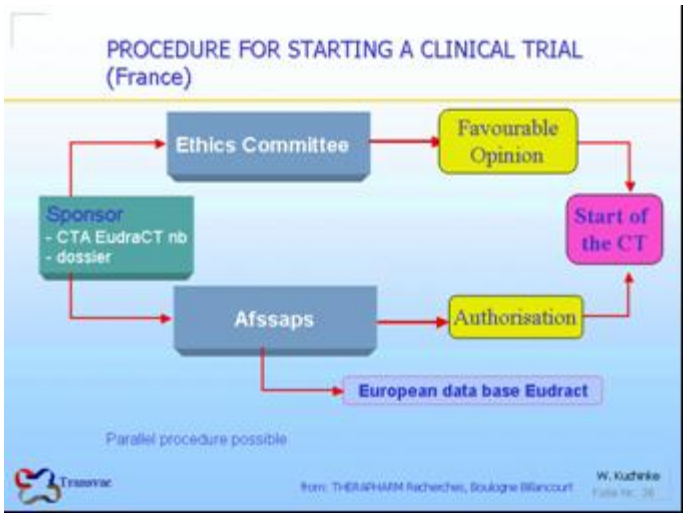
There are a number of **laws** which establish BPC in France:



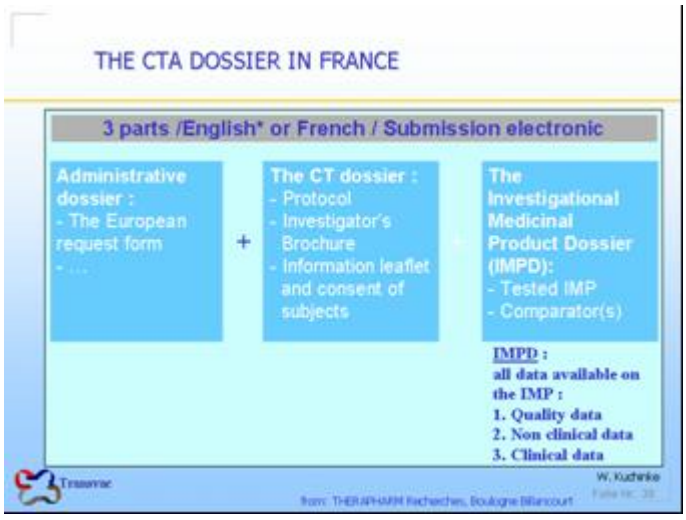
Contexte reglementaire:

UNION EUROPEENNE	FRANCE
Directive EC	Loi n°2004-806 (2001/20/CE) (9 août 2004) Arrêté 23 avril 2004
Code Communautaire (2001/83/CE modifiée 2004/27/CE)	Law n°88-1138 dated 20/12/1988 Law n°2004-806 dated 09/08/2004 Law n°2006-450 du 18/04/2006 Law « DMOS » dated 23/01/1993 of CSP-Article L4113-6

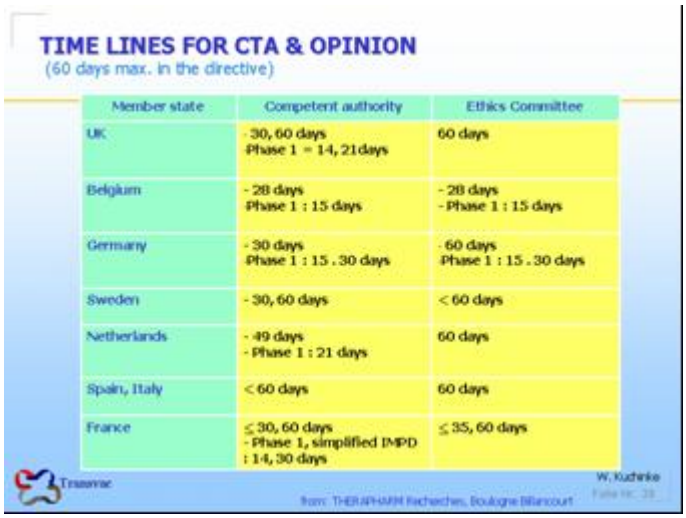
These rules define following procedure for starting a clinical trial in France: according to BCP there are two authorities involved: the ethics committee and the AFSSAPS.



For clinical trial authorisation (CTA) a dossier must be submitted to competent authority. It must consist of 3 parts.



For the evaluation of the CTA dossier in different EU countries different time frames are in place. The GCP directive dictated a max of 60 days.

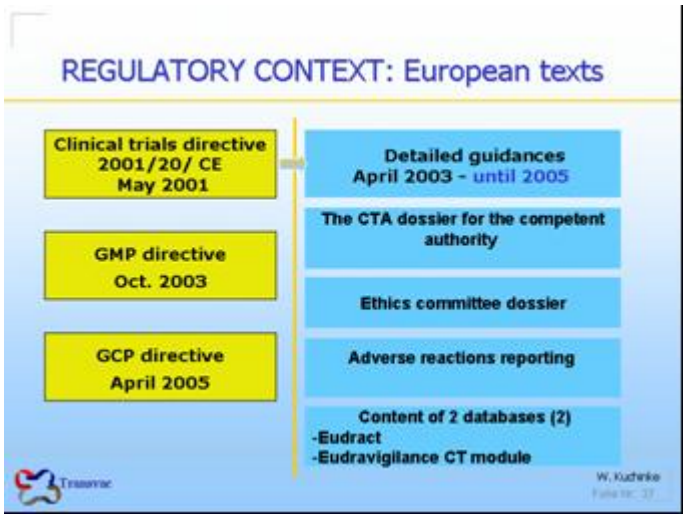


3.6 Implementation of GCP regulation in UK

3.6.1 EU Directives

It was implemented into UK law in May 2004, as the Medicines for Human Use (Clinical Trials) Regulations 2004. The Medicines for Human Use (Clinical Trials) Regulations 2004 control how research is undertaken to ascertain the safety or efficacy of a medicinal product in human participants should be conducted. The Regulations were a legal requirement, transposing the EU Clinical Trials Directive into UK law.

The implementation of GCP has to be seen in context with other regulations:



Most of the legal requirements were already part of current UK clinical trials practice. However, new controls include:

- Each clinical trial must have an identified sponsor who takes responsibility for its initiation and management
- Pharmacology studies in healthy human volunteers (Phase 1) must be authorised by MHRA

- Ethics Committee system established on a statutory basis
- Specific timescales for ethics review
- Investigational medicinal products (IMPs) must be manufactured only at licensed manufacturing sites to good manufacturing practice (GMP) standards
- Additional protection for incapacitated adults and minors in clinical trials
- MHRA inspections of clinical trials must be facilitated

It is also now a legal obligation in UK to conduct clinical trials of medicinal products in accordance with the ICH principles on good clinical practice (GCP).

3.6.2 The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

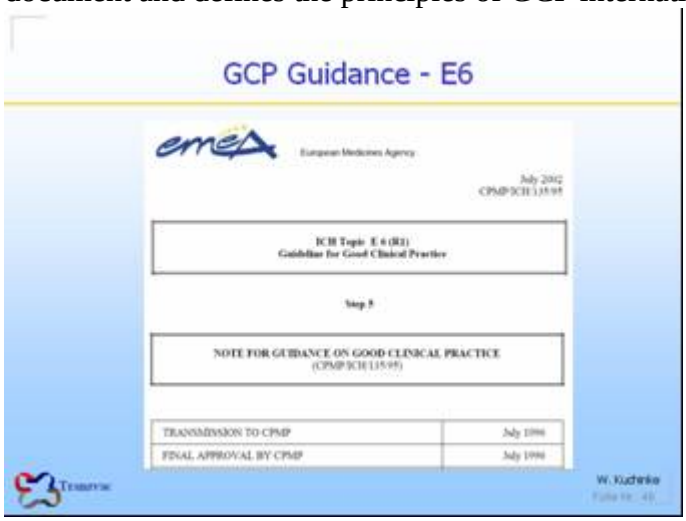
This amendment served the implementation of Directive 2005/28EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice (GCP) as regards investigational medical products for human use, as well as the requirements for authorising of manufacturing or importing of such products and other miscellaneous amendments. It was modified Feb. 2007, and includes now a regulatory impact assessment section.

4 The GCP regulations in detail

4.1 The ICH GCP Guidance - E6

4.1.1 Introduction

The ICH GCP guidance is known as CPMP/ICH/135/95. It represents the most basic and general document and defines the principles of GCP internationally.



The ICH GCP **E6** consists of different parts:

- GLOSSARY
- THE PRINCIPLES OF ICH GCP
- INSTITUTIONAL REVIEW BOARD (IRB)/UNABHÄNGIGE ETHIK-KOMMISSION
- INVESTIGATOR
- SPONSOR
- CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)
- INVESTIGATORI‘S BROCHURE
- ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

4.1.2 The principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). Before a trial is initiated, **foreseeable risks and inconveniences** should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks. The **rights, safety, and well-being** of the trial subjects are the most important considerations and should prevail over interests of science and society. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

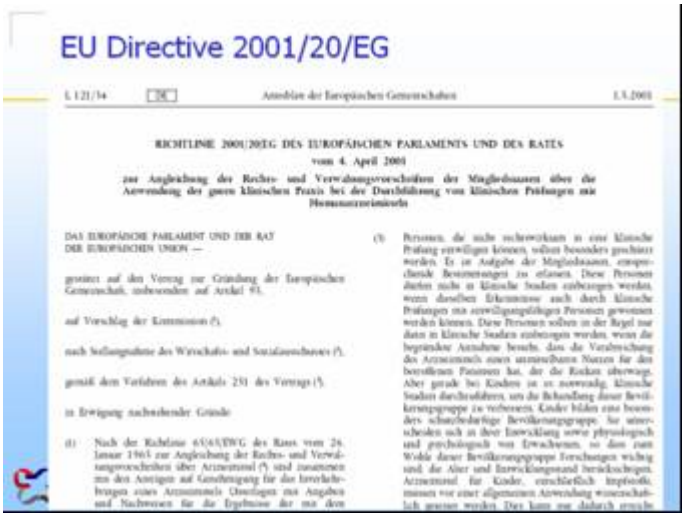
A trial should be conducted in compliance with the protocol that has received prior **institutional reviewboard (IRB) / independent ethics committee (IEC)** approval/favourable opinion. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s). Freely given **informed consent** should be obtained from every subject prior to clinical trial participation. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

4.2 EU Directive 2001/20/EG

4.2.1 Introduction

Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 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. This document defines GCP for the EU.



It demands that **foreseeable risks and inconveniences** have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the **Ethics Committee** and/or the **competent authority** comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored. The verification of compliance with the standards of good clinical practice and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and

reported are essential in order to justify the involvement of human subjects in clinical trials. It furthermore defines some important terms, one of the “vulnerable population”.

4.2.2 Vulnerable Population

Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit.

4.2.3 Article 1, chapter 2

Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

4.2.4 Article 1, chapter 4

All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice. This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one member state ‘multi-centre clinical trial’: a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries.

'Non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data; 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorised form.

4.2.5 Qualification

The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an **appropriately qualified doctor** or, where appropriate, of a qualified dentist.

4.2.6 Establishment of ethics committees

For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested. In preparing its opinion, the Ethics Committee shall consider, in particular:

- the relevance of the clinical trial and the trial design;
- whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified
- Documentation and Archiving
- Documentation is one of the most important parts of clinical trials
- GCP is based on the statement 'What has never been documented, never happened'

Once the study is finished, the investigational site is required to archive all the documentation related to the study and to ensure that these documents, as well as source documents (e.g. subject files, medical charts) are not lost or prematurely destroyed. If an inspection is required and the study documentation or parts of it are not complete or have been lost or destroyed, the study could be rejected. It is therefore important that the documentation and archiving of study documents is taken seriously.

4.2.7 Essential documents

According to ICH GCP 4.1.3 and 4.9.5, the investigator/institution should be aware of and comply with GCP and any applicable regulatory requirements and should retain essential documents. This includes the following duties:

- providing each subject with a card identifying them as study participants
- if laboratory data are collected, commenting on the clinical significance of abnormal values and filing your comments;
- ensuring that subject's medical records are marked to indicate that they are taking part in a study;
- documenting your activities during the study carefully and filing your documentation properly;
- ensuring that the subject identification register is archived for the time period required;
- keeping subject data and other source documents

4.3 Effect of GCP directive on clinical trials

With guideline 2001/20/EG a consequential reorganisation of clinical trials in the EU has been established. This means, the physician as the initiator of a IIT appear as investigator as well as sponsor (Investigator-Sponsor) and in accordance with GCP is responsible for the Initiation, conduct and conclusion of a clinical study. It has burden academic clinical trials with additional administrative burden. References:

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The Lancet Oncology, 2003; 4:717-19: EORTC

"…increase in the amount of administration…without any notable improvement in patient safety"

R. Gray, University of Birmingham/UK DIA Multi-Track Meeting 29-30 Nov 2004, Paris

"*Universities and hospitals do not all have the experience or expertise to judge what constitutes good scientific and ethical conduct of clinical trials*". Academic clinical research is hampered by a number of problems. Evaluation has identified several areas of problems:

- vote of EC is missing
- CRFs are completes after long delay
- informed consent is missing
- AEs and SAEs are reported often after long intervals
- delay between treatment and documentation
- systematic and current assessment of AE is missing

4.4 Directive 2005/28/EC

4.4.1 Introduction

the directive is of 8 April 2005, laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

4.4.2 Content of Directive 2005/28/EC

Whereas Directive 2001/20/EC requires the adoption of principles of good clinical practice and detailed guidelines in line with those principles, minimum requirements for authorisation of the manufacture or importation of investigational medicinal products, and detailed guidelines on the documentation relating to clinical trials to verify their compliance with Directive 2001/20/EC. The principles and guidelines for good clinical practice should be such as to ensure that the conduct of clinical trials on investigational medicinal products, as defined in Article 2(d) of Directive 2001/20/EC, is founded in the protection of human rights and the dignity of the human being. Manufacturing requirements to be applied to investigational medicinal products are provided for by Commission Directive 2003/94/EC of 8 October 2003 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. With regard to the protection of trial subjects and to ensure that unnecessary clinical trials will not be conducted, it is important to define principles and detailed guidelines of good clinical practice whilst allowing the results of the trials to be documented for use in a later phase. To ensure that all experts and individuals involved in the design, initiation, conduct and recording of clinical trials apply the same standards of good clinical practice, principles and detailed guidelines of good clinical practice have to be defined.

Provisions for the functioning of the Ethics Committees should be established in each Member State on the basis of common detailed guidelines, in order to ensure the protection of the trial subject while at the same time allowing a harmonized application in the different Member States of the procedures to be used by Ethics Committees. To secure the compliance of clinical trials with the provisions on good clinical practice, it is necessary that inspectors ensure the practical effectiveness of such provisions. It is essential therefore to provide detailed guidelines on the minimum standards for the qualification of inspectors, in particular as regards their education and training. In conducting clinical trials on investigational medicinal products for human use, the safety and the protection of the rights of trial subjects should be ensured. The detailed rules adopted by Member States pursuant to Article 3 (1) of Directive 2001/20/EC, to protect from abuse

individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as in emergency situations

4.4.2 2005/28/EC on Ethics Committees

Each Ethics Committee established under Article 6(1) of Directive 2001/20/EC shall adopt the relevant rules of procedure necessary to implement the requirements set out in that Directive and, in particular, in Articles 6 and 7 thereof. The Ethics Committees shall, in every case, retain the **essential documents** relating to a clinical trial, as referred to in Article 15(5) of Directive 2001/20/EC, for at least three years after completion of that trial. They shall retain the documents for a longer period, where so required under other applicable requirements. Communication of information between the Ethics Committees and the **competent authorities** of the Member States shall be ensured through appropriate and efficient systems.

4.4.3 2005/28/EC on Investigator's Brochure

information in the investigator's brochure, referred to in Article 2(g) of Directive 2001/20/EC, shall be presented in a concise, simple, objective, balanced and **non-promotional form** that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. If the investigational medicinal product has a marketing authorisation, the Summary of Product Characteristics may be used instead of the investigator's brochure.3. The investigator's brochure shall be validated and up dated by the sponsor at least once a year

4.4.4 2005/28/EC on competent authority

The competent authority shall issue the authorisation only after verifying the accuracy of the particulars provided by the applicant pursuant to Article 10 by the means of an inquiry carried out by its agents. Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation is completed within 90 days of the day on which the competent authority receives a valid application. The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 10(1), including in particular information concerning the qualified person at the disposal of the applicant in accordance with point (e) of Article 10(1).

4.4.5 2005/28/EC on Trial Master File and Archiving

The documentation referred to Article 15(5) of Directive2001/20/EC as the **trial master file** shall consist of **essential documents**, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have **complied with the principles and guidelines of good clinical practice** and with the applicable requirements. the trial master file shall provide the basis for the audit by the sponsor's independent auditor and for the inspection by the competent authority. The content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial. Sponsor and the investigator shall retain the **essential documents** relating to a clinical trial for at least **five years** after its completion They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator. Essential documents shall be **archived in a way that ensures that they are readily available**, upon request, to the competent authorities. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice (Article 17).

The sponsor shall appoint individuals within its organisation who are responsible for archives. Access to archives shall be restricted to the named individuals responsible for the archives. The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request. Any alteration to records shall be traceable (Article 19 + 20).

5. Clinical study design

5.1 Types of study design

There exist many different types of clinical study:

- Experimental
- Randomized controlled trial
- Double-blind
- Single-blind
- Non-blind
- Nonrandomized controlled trial
- Non-experimental
- Cohort study
- Prospective cohort
- Retrospective cohort
- Nested cohort
- Case-cohort study
- Case-control study (case series)
- Nested case-control study
- Cross-sectional study
- Descriptive
- Community survey

When choosing a study design, many factors must be taken into account. Different types of studies are subject to different types of bias. For example, recall bias is likely to occur in cross-sectional or case-control studies where subjects are asked to recall exposure to risk factors. Subjects with the relevant condition (e.g. breast cancer) may be more likely to recall the relevant exposures that they had undergone (e.g. hormone replacement therapy) than subjects who don't have the condition.

5.2 Description of study design related terms

5.2.1 General

A "retrospective study" looks at past behaviour, while a "prospective study" looks at future behaviour. "Superiority trials" are designed to demonstrate that one treatment is more effective than another. "Non-inferiority trials" are designed to demonstrate that a treatment is at least not appreciably worse than another. "Equivalence trials" are designed to demonstrate that one treatment is as effective as another. When using "parallel groups", each patient receives one treatment; in a "cross-over study", each patient receives several treatments. A longitudinal study studies a few subjects for a long period of time, while a cross-sectional study involves many subjects measured at once.

5.2.2 Cross-sectional study

Cross-sectional studies can be thought of as providing a "snapshot" of the frequency and characteristics of a disease in a population at a particular point in time. This type of data can be used to assess the prevalence of acute or chronic conditions in a population. However, since

exposure and disease status are measured at the same point in time, it may not always be possible to distinguish whether the exposure preceded or followed the disease.

5.2.3 Randomized controlled trial

The study design that provides the most compelling evidence of a causal relationship between the treatment and the effect, is the randomized controlled trial. Observational studies in epidemiology such as the cohort study and the case-control study are clinical studies in that they involve human participants, but provide less compelling evidence than the randomized controlled trial. The major difference between clinical trials and observational studies is that, in clinical trials, the investigators manipulate the administration of a new intervention and measure the effect of that manipulation, whereas observational studies only observe associations (correlations) between the treatments experienced by participants and their health status or diseases. Currently some Phase II and most Phase III drug trials are designed to be randomized, double-blind, and placebo-controlled. This means that each study subject is randomly assigned to receive one of the treatments, which might be the placebo. Neither the subjects nor scientists involved in the study know which study treatment is being administered to any given subject; and, in particular, none of those involved in the study know which subjects are being administered a placebo.

5.2.4 Phase I

Phase I trials are the first-stage of testing in human subjects
Normally a small (20-80) group of healthy volunteers will be selected
Phase I trials normally include dose-ranging studies so that doses for clinical use can be refined
The tested range of doses will usually be a small fraction of the dose that causes harm in animal testing

5.2.5 SAD and MAD

Single Ascending Dose (SAD) studies are those in which small groups of patients are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of patients is then given a higher dose. MAD: Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, whilst samples (of blood, and other fluids) are collected at various time points

5.2.6 Phase III

Phase III studies are randomized controlled trials on large patient groups (300–3,000 or more depending upon the condition) and are aimed at being the definitive assessment of the efficacy of the new therapy, in comparison with current 'Gold Standard' treatment. Phase III trials are the most expensive, time-consuming and difficult trials to design and run; especially in therapies for chronic conditions.

5.2.7 Open trial

In an open trial, the researcher knows the full details of the treatment, and so does the patient. These trials are open to challenge for bias, and they do nothing to reduce the placebo effect. However, sometimes they are unavoidable, particularly in relation to surgical techniques, where it may not be possible or ethical to hide from the patient which treatment he or she received. Usually this kind of study design is used in bioequivalence studies.

5.2.8 Single-blind trial

In a single-blind trial, the researcher knows the details of the treatment but the patient does not. Because the patient does not know which treatment is being administered (the new treatment or another treatment) there should be no placebo effect. In practice, since the researcher knows, it is possible for them to treat the patient differently or to subconsciously hint to the patient important treatment-related details, thus influencing the outcome of the study.

5.2.9 Double-blind trial

In a double-blind trial, one researcher allocates a series of numbers to 'new treatment' or 'old treatment‘. The second researcher is told the numbers, but not what they have been allocated to. Since the second researcher does not know, they cannot possibly tell the patient, directly or otherwise, and cannot give in to patient pressure to give them the new treatment. In this system, there is also often a more realistic distribution of sexes and ages of patients. Therefore double-blind (or randomized) trials are preferred, as they tend to give the most accurate results.

5.2.10 Triple-blind trial

Some randomized controlled trials are considered triple-blinded, although the meaning of this may vary according to the exact study design. The most common meaning is that the subject, researcher and person administering the treatment (often a pharmacist) are blinded to what is being given. Alternately, it may mean that the patient, researcher and statistician are blinded. These additional precautions are often in place with the more commonly accepted term "double blind trials", and thus the term "triple-blinded" is infrequently used.

5.3 Randomization in clinical trials

5.3.1 General

There are two processes involved in randomizing patients to different interventions. First is choosing a randomization procedure to generate a random and unpredictable sequence of allocations. This may be a simple random assignment of patients to any of the groups at equal probabilities, or may be complex and adaptive. A second and more practical issue is allocation concealment, which refers to the stringent precautions taken to ensure that the group assignment of patients are not revealed to the study investigators prior to definitively allocating them to their respective groups.

5.3.2 Randomization procedures

Importance of balance in randomization: since most statistical tests are most powerful when the groups being compared have equal sizes, it is desirable for the randomization procedure to generate similarly-sized groups. Selection bias: depending on the amount of structure in the randomization procedure, investigators may be able to infer the next group assignment by guessing which of the groups has been assigned the least up to that point. This breaks allocation concealment and can lead to bias in the selection of patients for enrolment in the study. Accidental bias: if important covariates that are related to the outcome are ignored in the statistical analysis, estimates arising from that analysis may be biased.

5.3.3 Complete randomization

In this commonly used and intuitive procedure, each patient is effectively randomly assigned to any one of the groups. It is simple and optimal in the sense of robustness against both selection and accidental biases. However, its main drawback is the possibility of imbalances between the groups. In practice, imbalance is only a concern for small sample sizes ($n < 200$).

5.3.4 Permuted block randomization

In this form of restricted randomization, blocks of k patients are created such that balance is enforced within each block. For instance, let E stand for experimental group and C for control group, then a block of $k = 4$ patients may be assigned to one of EECC, ECEC, ECCE, CEEC, CECE, and CCEE, with equal probabilities of 1/6 each. Note that there are equal numbers of patients assigned to the experiment and the control group in each block. Permuted block randomization has several advantages. In addition to promoting group balance at the end of the trial, it also promotes periodic balance in the sense that sequential patients are distributed equally between groups. This is particularly important because clinical trials enrol patients sequentially, such that there may be systematic differences between patients entering at different times during the study. Unfortunately, by enforcing within-block balance, permuted block randomization is particularly susceptible to selection bias. That is, since toward the end of each block the investigators know the group with the least assignment up to that point must be assigned proportionally more of the remainder, predicting future group assignment becomes progressively easier. The remedy for this bias is to blind investigator from group assignments and from the randomization procedure itself.

There exist several standard methods of ensuring allocation concealment:

- Sequentially-Numbered, Opaque, Sealed Envelopes (SNOSE)
- Sequentially-numbered containers
- Pharmacy controlled
- Central randomization

5.4 Cohort study

A cohort study is a form of longitudinal study used in medicine and social science. It is one type of study design. A cohort is a group of people who share a common characteristic or experience within a defined time period (e.g., are exposed to a drug or a vaccine). The comparison group may be the general population from which the cohort is drawn, or it may be another cohort of persons thought to have had little or no exposure to the substance under investigation, but otherwise similar.

5.5 Case-control

Case-control studies are one type of epidemiological study design. It is used to identify factors that may contribute to a medical condition by comparing a group of patients who have that condition with a group of patients that do not. Case-control studies are a less-expensive and often-used type of epidemiological study that can be carried out by small teams or individual researchers in single facilities, in a way which more structured trials often cannot.

5.6 Open-label trial

An open-label trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. This contrasts with single blind and double blind experimental designs, where participants are not aware of what treatment they are receiving (researchers are also unaware in a double blind trial). An open-label trial may still be randomized. Community-based clinical trial. Community-based clinical trials are clinical trials conducted directly through doctors and clinics rather than academic research facilities. They are designed to be administered through primary care physicians, community health centers and local outpatient facilities.

5.7 Observational study design

5.7.1 Different sort of studies

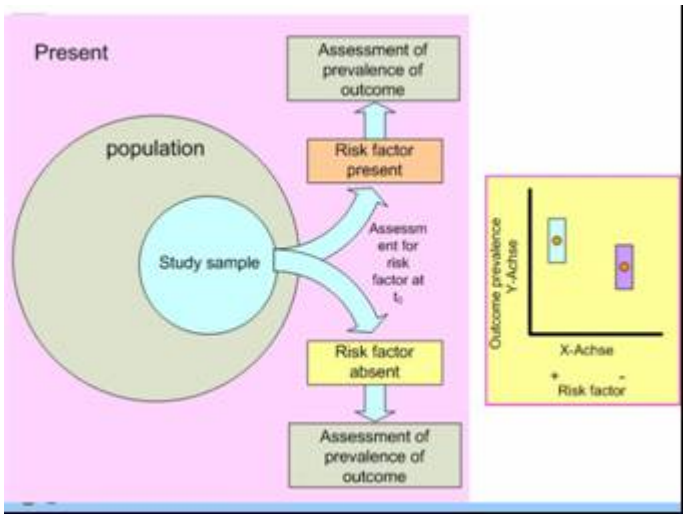
Experiments: INV controls the process by which some research participants are exposed to an intervention while others are not. Observational studies: exposure is not under the INV's control so randomization is impossible. By using appropriate study design and analysis the investigator can minimize the effects of confounding variables and other biases and maximize valid inference. Observational studies are considered as versatile (outcome can be the development of a cure, surrogate outcome (e.g. Blood pressure), the risk factor can be genotype or a gene expression pattern, medical therapy, medical image,…). They can elucidate putative mechanisms of diseases (e.g. cigarette smoking and lung cancer) and avoid ethical barriers inherent to human experiments involving environmental toxins and genes. The can be completed more quickly and less expensively than experimental studies.

5.7.2 Cross-sectional studies

For example, the investigator studies a group of individuals at a given time. Individuals represent a sample of people taken from a population of interest. The time is usually the date on which the key measurements have been made. Cross-sectional studies can therefore be useful for determining prevalence of a risk factor or disease in a sample population. In translational research the risk factor may be a particular genotype, micro array data,… Important aspects are:

- Cannot establish temporal relationships
- INV collects all key measurements at one time
- Most difficult aspect = choice of control

Example.: study about quiescent CD4+ T lymphocytes. Prevalence of CD4+ T lymphocytes harbouring latent HIV was not lower in patients who had taken antiviral therapy



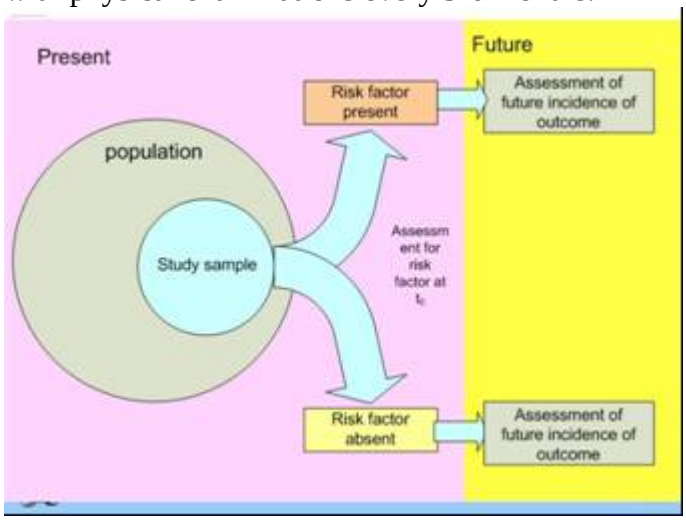
The weaknesses of cross-sectional studies:

- Diseases of short duration are underrepresented
- Studies that rely on input from patients cannot be used to study fatal diseases
- Confounding variables can cause apparent associations
- Inefficient when study outcomes and risk factors are rare
- Study of high-risk population
- choice of control

5.7.3 Prospective cohort study

Investigator follows participants with or without a risk factor forward in time and notes the development (incidence) of outcomes. It is done prospectively, because the investigator can decide on quality and quantity of data and biological specimens that are collected at enrolment time. It is common to use multiple cohorts

Example: thromboembolism study: 599 patients with recent venous thromboembolism were analysed. They were treated with a standard course of anticoagulant therapy and plasma D-dimer level (= fibrin degradation product, fibrinolysis) was determined. Investigator followed patients with physical examinations every 3-6 months.



Advantages of prospective cohort study:

- Strategy is efficient way to study outcomes associated with risk factors that are rare ore infrequently documented
- Multiple outcomes can be evaluated during a single study
- Risk factor is identifies prior to the outcome (temporal relationship)

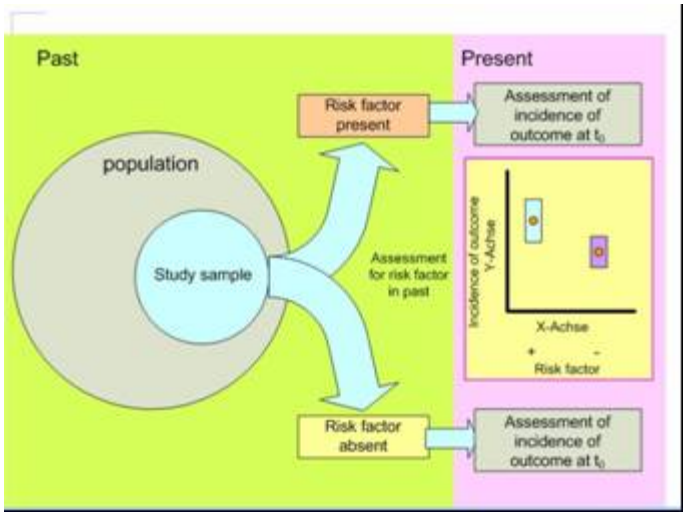
But:

- Often expensive (prolonged periods of time), patient lost to follow-ups
- Can be impractible (esp. If incidence rate of outcome is low)
- Observed associations may be due to baseline differences between cohorts, silent preclinical disease, or unmeasured confounding variables

5.7.4 Retrospective cohort study

he main characteristic of a retrospective cohort study is, that existing data are available und used. Therefore it is fast and cheap. The investigator studies existing medical records of non-diseased patients, some of whom were exposed to risk factor of interest. Then the investigator continues to assess patients by examining later records moving towards the present time. Obviously, the investigator lacks control over information that is available.

Example: study about EGF association.
Quantification of association between activating mutations in EGFR and responsiveness of non-small cell lung cancer to anti-tumour drug (Gefitinib, inhibits tyrosine kinase of EGFR). The investigator began with patients who had non-small cell lung cancer and had received Gefitinib. Then he sequenced exon of EGFR gene and correlated mutations with prior clinical response. The investigator found mutations in 8 of 9 responders and 0 in 7 non-responders.



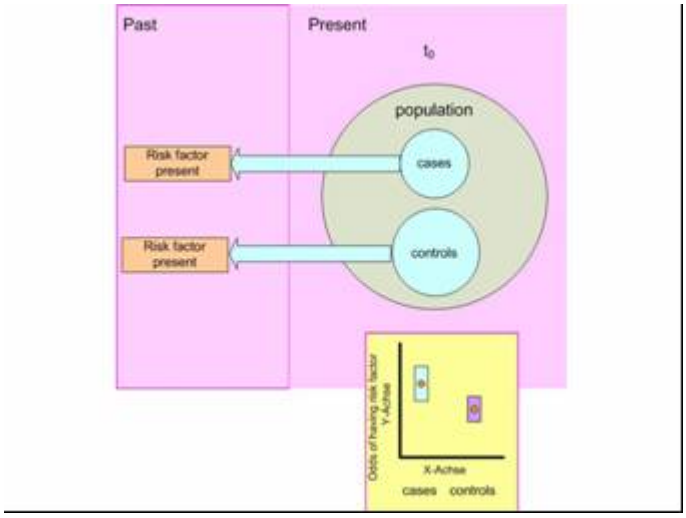
The advantages of retrospective cohort study are:

- Provide incidence rates
- Quantify how risk factor correlates with the outcome
- Easy interpretation
- No waiting for outcome

5.7.5 Case-control study

A Case-control study begins with patients who already developed the outcome of interest (cases). The investigator begins with identifying cases and matches these cases to one or more controls from the same population sample. The investigator determines history of prior exposure to the risk factor in the case and control patients. Therefore the investigator has no control over the fact that the information is available or not. This design is used commonly for rare outcomes or diseases with long latency periods.

Example: study about COX-2 gene mutation, that analyses mutations in COX-2 gene and risk of myocardial infarction and ischemic stroke. The investigator matched 864 patients with their first myocardial infarction and ischemic stroke with 864 hospitalized controls. The groups were matched for age, sex, BMI, smoking, hypertension, hypercholesterolemia and diabetes.

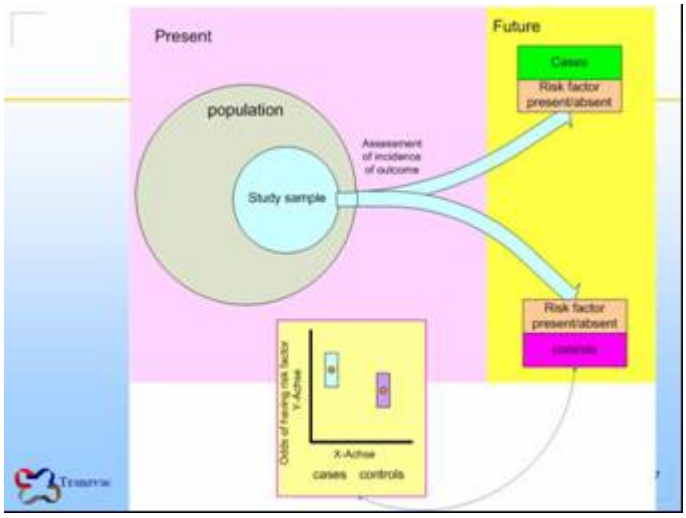


The advantages of Case-control study:

- investigator has not to wait for the outcome event
- Includes many cases (great statistical power)
- Allows the matching on potential confounding variables to be employed in the selection of control participants
- Is effective for studying rare diseases and when risk factor is difficult to ascertain
- Risk factor has to be measured in all participants

5.7.6 Nested case-control study

The Nested case-control study can be seen as a prospective incident case-referent study. Participants have been followed in a prospective cohort. At the studies completion, the investigator studies only cases and a number of controls. This design is ideal when the outcome is rare and in case the predictor variable is too difficult or expansive to obtain on all participants.



5.8 Experimental study design

5.8.1 General

The main advantage of the experimental study design is, that the investigator has control over the experimental intervention (e.g. doses of drug, device, change in diet). Consequently, the investigator is free to manipulate key aspects of study design (timing, dose, duration of treatment,…). The other advantages are:

- Treatment allocation can be randomized and blinded
- Eliminates bias

Many options are available to eliminate bias in experimental setting:

- Genetically identical animals
- All animals studied at the same time
- Known confounders (e.g blood pressure, heart rate, blood sugar) may be controlled

In clinical studies randomisation and blinding is used to that end. But it is a fact that individual responses to the same intervention vary. The observed outcome may only occur if the very limited conditions of the experiment can be reproduced. It may also have little external validity (results may not extend to the target population).

5.8.2 Important term: confounder

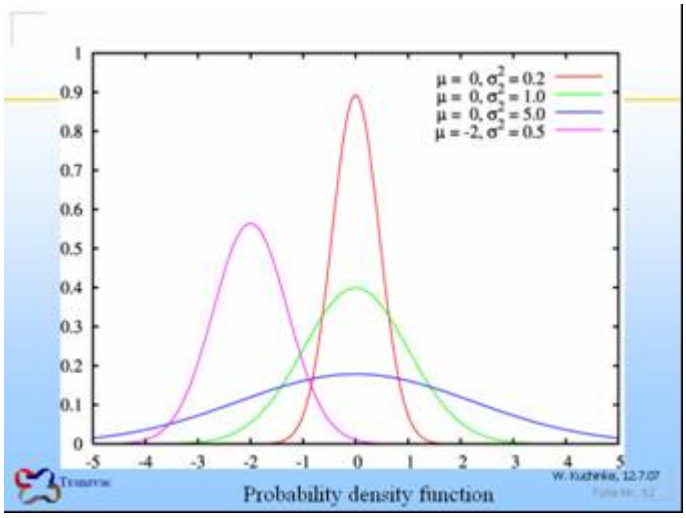
the confounder is a lurking variable (confounding factor or variable). It is an extraneous variable in a statistical or research model that affects the dependent variables in question but either has not been considered or has not been controlled for. The confounding variable can lead to a **false conclusion** that the dependent variables are in a **causal relationship** with the independent variable. For example, in a city ice cream consumption and murder rates are highly correlated. They are joint effects of a common cause or lurking variable, namely, hot weather.

5.8.3 “Normal” distribution of data

Part of a proper study design includes a plan for how the data will be analysed. In such a plan standard statistical models are used to compare groups (e.g. t-test or analysis of variance). It is assumed that the participants in each group represent randomly selected members of a larger target population. Data extracted from the measurements follow a **„normal“ distribution**. Study design can be divided into two simple categories:

- Between subject design
- With-in subject design

The assumption is always the existence of a normal distribution of patient data. The normal distribution (Gaussian distribution) is an important family of continuous probability distributions, applicable in many fields.



Each member of the family may be defined by two parameters, location and scale: the mean ("average") and standard deviation ("variability"), respectively.
The standard normal distribution is the normal distribution with a mean of zero and a variance of one (green graph in figure above).

5.8.4 Variance

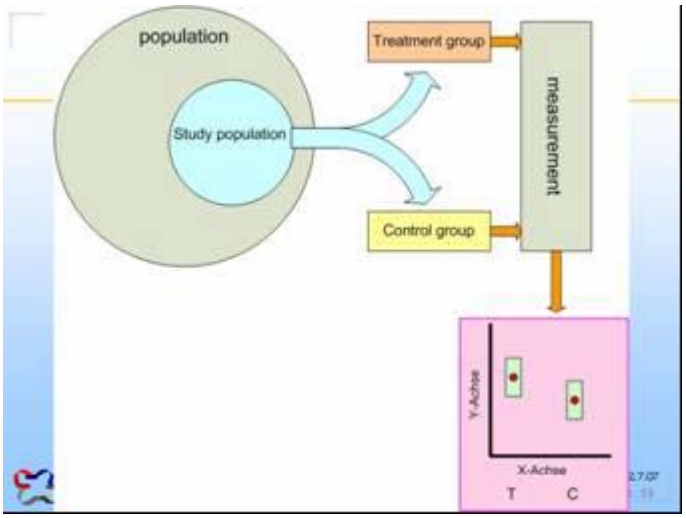
the variance of a random variable is a measure of its statistical dispersion, indicating how its possible values are spread around the expected value. While the expected value shows the location of the distribution, the variance indicates the variability of the values. An important other measure is the square root of the variance, called the **standard deviation.** As its name implies it gives in a standard form an indication of the usual deviations from the mean.

5.8.5 Cohort

a cohort is a group of subjects from a given population defined by experiencing an event (typically birth) in a particular time span. For example, Irish women born in the year 1945 would form a single cohort, when their health or mortality, or education, or marriages were studied. A **cohort study** often tracks a cohort over extended periods of time and returns to the same sample groups decades later. It represents a basic experimental design.

5.8.6 Between subject study

In this case a cohort of research participants is enrolled (identified, recruited and consented). One half of the participants will be exposed to the intervention, while the other half will not. The data from the two groups will be compared.



5.8.6 Within subject study

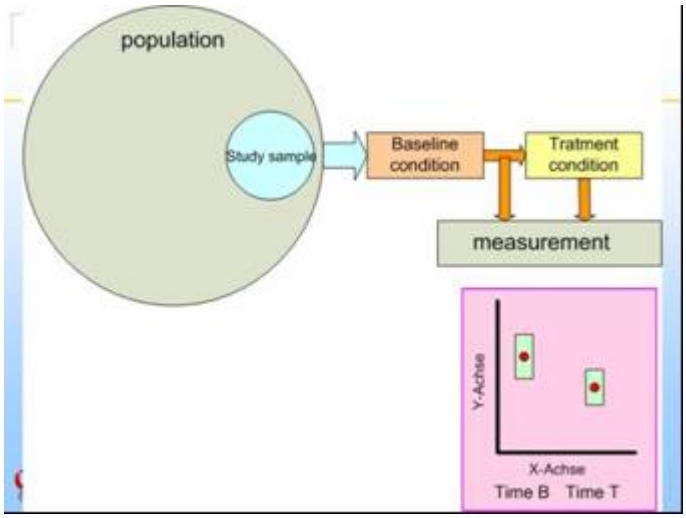
In this case after a cohort of research participants is identified, recruited and consented, a baseline measurement is made before exposure to the intervention. After all participants received the treatment a measurement is made after the exposure.

5.8.7 Simple forms of between-subject and within-subject designs

The simplest form of a between-subject study is when after a cohort of research participants is identified, recruited and consented, one-half of the participants will be exposed to the experimental intervention, while the other half will not. A measurement will be performed on each participant. The simplest form of a within-subject study is when after a cohort of research participants is identified, recruited and consented, a baseline measurement is made before exposure to the intervention and all participants receive the treatment. A measurement will be performed on each participant.

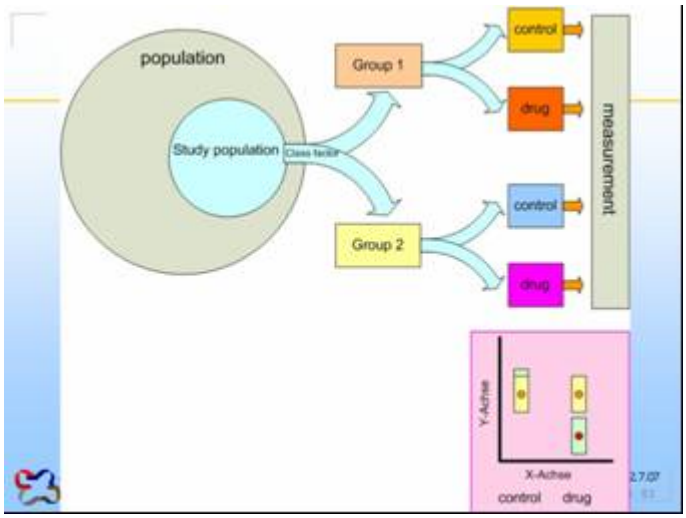
5.8.8 Between-subject factorial study design

Attributes are used to characterize and differentiate one group from another. They are referred to as factors. Factors can have different levels (e.g. different doses of a drug). A study with a between-subject factorial study design is an investigation of a drug with different effects in men and women (in this case gender is a factor, whether an active drug was received is another factor).



5.8.9 Mixed factorial study design

This form of study combines elements of between-subject with within-subject factorial study designs. For example: the participants are randomized to either receive a test drug or not (= factor) and measurements are made before and after (= factor) the intervention (drug and placebo). This results in four experimental groups. This design represents one of the most common and important designs in clinical trials.

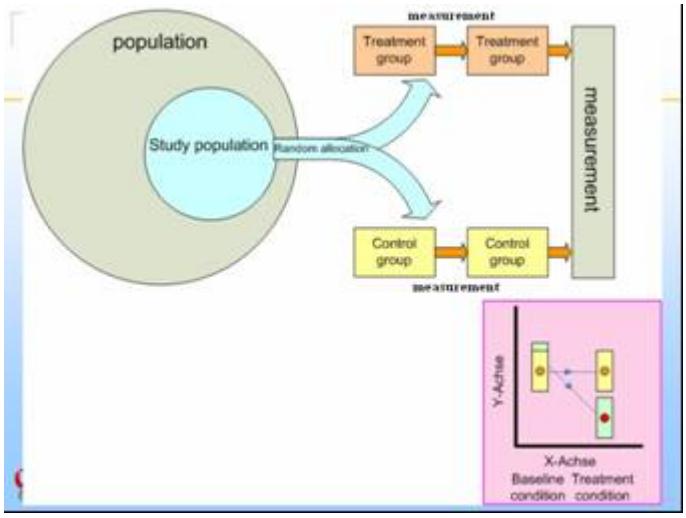


5.8.10 Within-subject design

Following aspects have to be considered:

- Defining characteristic: when measurement was made
- Eliminating the influence of biological variation
- Within-subject studies are more powerful an BSS

Because no random assignment of treatment is made, every participant receives the treatment. The main disadvantage is in the fact that the group of participants is not the same after treatment as it is before the intervention.

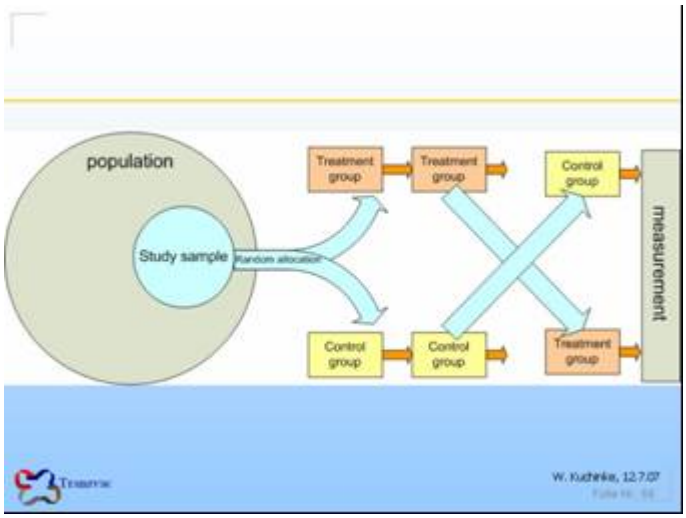


Investigators try via experimental design to control known confounders that may change over time (e.g. blood sugar,) or they measure other variables (covariates) to demonstrate that the individual in the two states is similar (except for only one variable).

5.8.12 Crossover design

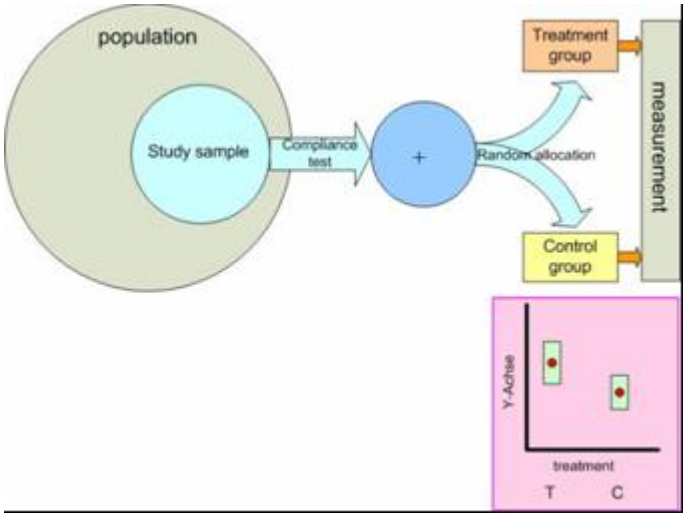
Crossover studies represent a variation of the within-subject design with the same intend (study the effects of more than one factor) while retaining the advantages of within-subject format. The characteristics of a crossover study are:

- Participants are exposed to more than one factor in sequence
- No interaction will occur
- Wash-out period



5.8.13 Run-in design

The adherence to the research protocol is critical for the success of a trial. But often patients drop out of a trial soon after the treatment began. Therefore a run-in period can be useful. Run-in period is a period in which it is determined whether a particular volunteer is likely to adhere to protocol (e.g. studies that depends on diet). Both placebo and active interventions can be used during run-in.



6. Informed consent

6.1 Introduction

The aim of the Informed consent is the informed patient. The patient must be informed about the trial by the **investigator**, who may be a physician or a dentist (see for example § 40 (2) AMG). Trial subjects may withdraw their consent to participate in a clinical trial at **any time** verbally or in writing and without giving reasons to the investigator, without jeopardising their further treatment. If potential trial subjects are not in a position to understand the nature, significance and possible consequences of a trial ('person unable to give informed consent'), they may only participate in a trial under very strict conditions. In such cases, consent is given by a **legal representative**, after this person has received full information.

6.2 What is an „informed consent"?

4.2.1 Legal condition

Informed consent is a legal condition whereby a person can be said to have given consent based upon an appreciation and understanding of the facts and implications of an action. The individual needs to be in possession of relevant facts and also of his reasoning faculties, such as not being mentally retarded or mentally ill and without an impairment of judgment at the time of consenting. In cases where an individual is considered unable to give informed consent, another person is generally authorized to give consent on their behalf. Examples of this include the parents or legal guardians of a child and caregivers for the mentally ill. Informed consent can be complex to evaluate, because neither expressions of consent, nor expressions of understanding of implications, necessarily mean that full adult consent was in fact given, nor that full comprehension of relevant issues is internally digested. Many times consent is implied within the usual subtleties of human communication, rather than explicitly negotiated verbally or in writing. In medical or formal circumstances explicit agreement by means of signature which may normally be relied upon legally, regardless of actual consent, is the norm.

6.2.2 Problem areas

There exist several problem areas for assessing informed consent. A person may verbally agree to something from fear, perceived social pressure, … and the person requesting the action may honestly be unaware of this and believe it is genuine, and rely upon it. A person may state they understand the implications of some action, as part of their consent, but in fact not have appreciated the possible consequences fully and later deny the validity of their consent for this reason. All these concerns flow into the preparation of two documents, the Patient Information and Informed Consent Form for clinical trial participation.

6.3 Regulations

6.3.1 Regulation according to GCP-V and DH

§ 3 (2b) of the German GCP Regulation (GCP-V) gives the following definition of informed consent: *giving informed consent is the voluntary decision of a person capable of doing so, to take*

part in a clinical trial, documented appropriately and given in writing, dated and signed after being properly informed of the nature, significance and (…). The Declaration of Helsinki issued by the World Medical Association decrees that persons involved in medical research must do this **voluntarily** and must be **fully informed** about the research project.. possible consequences and risks of the trial

6.3.2 ICH E6-GCP

Informed Consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a **written, signed and dated informed consent form.**

2.9 Freely given informed consent should be obtained from **every subject** prior to clinical trial participation.

ICH E6-GCP: 4.8 Informed Consent of Trial Subjects: 4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. **Prior to the beginning of the trial**, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects **should be revised** whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available (…).

4.8.3 Neither the investigator, nor the trial staff, should coerce or **unduly influence** a subject to participate or to continue to participate in a trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a **copy of the signed and dated written informed consent form** and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

6.4 the Informed Consent process

6.4.1 Information of investigator

The investigators must be informed by the sponsor of the clinical trial that:

- information on the trial may be given to the patient only by the investigator

- trial subjects (or their legal representatives) must sign the Informed Consent Declarations (including the Data Protection Declaration) themselves with the date and, if required, the place
- every trial subject (or legal representative) must be given a copy of the Patient Information and the original or a copy of the Informed Consent Declaration (including the Data Protection Declaration)
- an original of the signed Informed Consent Declaration is archived in the ISF.

6.4.2 Written Patient Information

To conform with the requirements for informed consent the information the patient receives must satisfy many requirements: It **must**:

- be well-arranged and easily readable (manageable sections with subheadings, information grouped in appropriate subsections, use of bold typeface, appropriate font size).
- be kept as short as possible without missing out important information.
- be written in language understandable to non-health-professionals.
- be in the mother-tongue of the trial subject (Note: interpreters can be used; if so, they must also sign the Informed Consent Declaration)
- not contain words not in the subject's mother tongue or medical terminology if these are not explained.
- match the intellectual level of the persons addressed (level of education, mental and physical condition).
- be addressed to a legal representative if this person will be giving informed consent.

The Patient Information **must** contain the following information:

- trial-specific contact point: fields for the name and telephone number of the investigator and the address of the investigational site (hospital or practice)
- In clinical trials covered by the AMG: details of a central contact point at the competent higher federal authority
- Sponsor/contractor, director of the clinical trial, financers
- A reference to the fact that this is a Patient Information and the full title of the clinical trial
- trial subjects must be addressed personally
- the following should be included with detailed information:
    - Brief introduction
    - Scientific background
    - Reasons for conducting the clinical trial
    - Design of the clinical trial
    - Information on the trial treatment
    - Trial conduct
    - Details of alternative treatment (advantages/risks), possible benefit for the patient
    - Risks and undesirable effects
    - Pregnancy
    - Subject insurance
    - Voluntary nature of participation
    - Information on premature withdrawal of trial subjects
    - Confirmation of confidential handling of data/data protection

6.4.3 Written Informed Consent Declaration

The following information must be covered in the declaration:

- A reference to the fact that this is an Informed Consent Declaration and the full title of the clinical trial, Patient name, patient number, date of birth (and screening number, if required)
- Every form must have a signature field for the investigator and trial subject (and, if applicable, legal representative) with details of date and place, if required.

The following points are to be confirmed by the trial subject:

- Provision of verbal and written information by the physician
- That he or she has understood the content
- That the decision to take part was voluntary
- That he or she has given consent to participate
- That he or she was given enough time to decide
- That he or she was informed that they can revoke their decision at any time
- Information on insurance cover and the related obligations (if required, receipt of a copy of the General Conditions of Insurance Cover)
- Information on the further processing, evaluation and storage of trial findings, usually in anonymised form
- Consent to submission of data to third parties yet to be named in non-pseudo-anonymised form and to inspection of medical records (emphasise)
- Receipt of Patient Information and Informed Consent Form
- Agreement that attending physicians (e.g. general practitioner) may be informed that the patient is participating in a clinical trial

6.4.4 Procedure for revoking consent

The trial subject can freely revoke the consent. If a trial subject revokes his or her consent to participation in a clinical trial with a medicinal product, the data already stored may be further used if necessary to establish the following:

- The efficacy of the medicinal product under study
- The interests of the trial subjects were not harmed
- Submission of required documentation to the competent authorities has been fulfilled.

It must be established how far the data collected needs to be passed on to third parties. Data not required must be immediately deleted (§ 40 (2a) AMG) or anonymised, according to the procedures agreed in the written Patient Information. Required and non-required information should be defined before the trial starts.

6.4.5 Written Data Protection Declaration

The Data Protection Declaration must either be a visibly separate part of the Informed Consent Declaration or be signed by the trial subject or legal representative as a separate document.

Fig. Checklist for the Preparation of Documentation for Subject Informed Consent

	Patient Information and Informed Consent Declaration	n.r.	n. k.
01	Title of the document 'Patient information and informed consent declaration'	☐	☐
02	Page numbering and version number	☐	☐
03	Content and organisation of the document	☐	☐
04	Comprehensibility of the document	☐	☐
05	Manner of obtaining informed consent and suitability of documentation for subject population	☐	☐

	Patient information and informed consent declaration: **Patient Information**	n.r.	n. k.
06	Title of this part of the document 'Patient information'	☐	☐
07	Title, brief, trial ID, number of the research project	☐	☐
08	Patient is personally addressed, requested to participate	☐	☐
09	Sponsor (contractor), director of the research project responsible and the sponsor	☐	☐
10	Contact persons for the subject	☐	☐
11	Aim and purpose of research project, aim of collection of data	☐	☐
12	Reference to research	☐	☐
13	Conduct of clinical trial, treatments, invasive procedures	☐	☐
14	Duration of participation	☐	☐
15	Blinding, unblinding	☐	☐
16	Randomisation	☐	☐
17	Trial medication (method of administration, side effects etc.)	☐	☐
18	Requirements of subject/patients (duties of participants)	☐	☐
19	Description of the experimental aspects of research project	☐	☐
20	Description of risks and benefits	☐	☐
21	Possible alternative treatments	☐	☐
22	Reference to pregnancy	☐	☐
23	Insurance cover and resulting obligations	☐	☐
24	Financial outlay for trial subjects, compensation, commercial use of results of the research project	☐	☐
25	Timely information on relevant new information	☐	☐
26	Number of participating subjects/patients	☐	☐
27	Ethics committee approval	☐	☐
28	Voluntary participation, withdrawal	☐	☐
29	Premature withdrawal of subjects from research project	☐	☐
30	Reference to data protection	☐	☐
31	Reference to person responsible for data processing	☐	☐
32	Agreement to the use of body fluids and tissues for investigational purposes	☐	☐
33	Purpose of data collection	☐	☐
34	Type of data collected, data categories, collection of additional data	☐	☐
35	Method of data processing and anonymisation or pseudo-anonymisation	☐	☐
36	Users of data collected	☐	☐
37	Authorisation of third parties to have access to data	☐	☐

7. Ethic committee

7.1 Introduction in Ethics Committee

The Ethics Committee, according to Directive 2001/20/EC, is an independent body in a Member State of the European Union, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. With the Clinical Trials Directive, the European Union (EU) envisioned a harmonization of research ethics committees (RECs) across Europe, including the time taken to assess a trial proposal and the kinds of issues a committee should take into account.

7.2 Regulations

7.2.1 Directive 2001/20/EC on Ethics committee

For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested. In preparing its opinion, the Ethics Committee shall consider, in particular:

- the relevance of the clinical trial and the trial design
- whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified

for this purpose the ethics committee has to **consider**:

- the protocol;
- the suitability of the investigator and supporting staff;
- the investigator's brochure;
- the quality of the facilities;
- the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent
- provision for indemnity or compensation in the event of injury or death attributable to a clinical trial
- any insurance or indemnity to cover the liability of the investigator and sponsor
- the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site
- the arrangements for the recruitment of subjects
- Application for approval
- Application form
- The forms required for:
- application for ethics committee approval before the start of a clinical trial

- application for ethics committee approval of subsequent amendments
- notification of the end of a clinical trial
- Application for approval before the start of a clinical trial

The local requirements of the chief ethics committee, and, in case of exceptions, those of the participating ethics committee(s) must be observed. The documents required by the ethics committee regarding the staffing and technical qualification of the investigators and investigational sites should be completed and returned by the investigators in good time so that they are available to submit with the application.

7.2.2 EudraCT number

this number can be found in the European Clinical Trials Database (EudraCT) of the European Agency for the Evaluation of Medicinal Products (EMEA), (https://eudract.emea.eu.int). The Clinical Trial (CT) Application Form "*Request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the company*" must also be submitted with the application. This form is the same as "Module 1" (Annex 1) of the ENTR/CT 1 Detailed Guidance. After receipt of the EudraCT number The CT Application Form can be downloaded from the EudraCT Database and completed (https://eudract.emea.eu.int). The form "Module 2" of the ENTR/CT 2 (7.3) Detailed Guidance must also be completed and submitted for multicentre trials. The complete application and required documentation also have to be supplied on an electronic data carrier and submitted with an accompanying letter to the competent/chief ethics committee. For multicentre trials, a copy of the application and required documentation on paper and an electronic storage medium must also be supplied to all other competent/participating ethics committees. Each application to competent/participating ethics committees must also be accompanied by a letter. Copies of the application and all correspondence with ethics committees must be archived in the trial master file.

7.2.3 Evaluation of an application for approval

In multicenter trials in Germany for example there are one competent/chief ethics committee and several ethics committees. The competent/chief ethics committee confirms receipt of the reviewable application within 10 days. This confirmation may require that formal errors be corrected within 14 days and that the application be resubmitted. After receipt of a reviewable application, the competent/chief ethics committee announces its decision within defined periods. These periods are determined by the type of clinical trial. The competent/chief ethics committee may request additional information only once during the approval of an application. The original approval document issued by the ethics committee must be archived in the trial master file and copies in the site-specific ISFs.

7.2.4 Approval of amendments

Amendments to a trial protocol approved by the competent/chief ethics committee must be approved by the competent/chief ethics committee before they can be implemented. This applies insofar as the changes:

- have implications for the safety of the persons concerned,
- have implications for the interpretation of the documentation that forms the scientific basis for the trial, or for the scientific power of the results,
- make significant modifications to way the trial is supervised or its conduct,
- have an impact on the quality or safety of the medicinal product,

- have implications for the health of non-involved persons or the environment, in clinical trials with medicinal products composed of or which contain genetically modified organisms

The clinical trial Amendment Form “Request for authorisation of a substantial amendment to a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the company” must be used for application for approval of amendments during a clinical trial.

7.2.5 Approval of new investigational sites

Details of the trial site must be supplied with the application for approval of a new trial site. The application documents are to be sent to the competent/chief ethics committee. The competent/participating ethics committee for the new investigational site receive:

- A copy of the application for approval of a new trial site with all necessary documentation.
- Evaluation of new investigational sites

The competent/chief ethics committee contacts the other ethics committees involved. If, after receipt of a properly completed application, the competent/chief ethics committee does not object within 30 days, this means that the application for the new trial site has been approved. The chief ethics committee informs the BOB (Bundesoberbehörde = competent authority in Germany) of its decision. Further items that have to be notified to ethics committees:

- Notification as part of pharmacovigilance
- Duties with regard to pharmacovigilance activities such as reporting
- undesirable effects
- any information that implies that the benefit-risk ratio of the medicinal product should be re-evaluated
- measures to afford persons concerned protection from any direct dangers
- Notification of closure, abandonment or interruption of a clinical trial

The competent/chief ethics committee must be informed within 90 days of closure of a clinical trial. If the clinical trial is interrupted or abandoned, notification is required within 15 days. The CT End of Trial Form “Declaration of the end of a clinical trial” must be used for reporting within the prescribed periods (https://eudract.emea.eu.int). This form and all correspondence with ethics committees must be archived in the trial master file.

7.2.6 Report after ending a clinical trial

Within one year of ending a clinical trial, a summary of the report on the clinical trial with all important results must be sent to the competent/chief ethics committee. The report and all correspondence with ethics committees must be archived in the trial master file.

8. Data management in clinical studies

8.1 What is data management?

Data management in clinical trials consists of several aspects:

- Paper based studies and electronic CRF design
- Database design & programming
- Data acquisition and entry into the database
- Data review (monitoring)
- Data validation (cleaning)
- Coding and database finalization

Data management is often undervalued. Bt it plays a central part in clinical research. “It’s the **black box** between interviewing the participant and handing over a file for statistical analysis.” One should not forget the quality of the data management is directly related to the credibility of the study results!

There are many data management topics:

- Study Design and Planning.
- Data Definition, Forms, and Database Design.
- Computers in Clinical Trials: Hardware, Operating Systems, and Database Management Systems.
- Data Entry and Distributed Computing.
- Patient Registration.
- Local Data Management Systems.
- Central Quality Control of Data.
- Data Management and Good Clinical Practice.
- Software Tools for Trials Management.
- Follow-Up and Closeout Phase.
- Training and Education

8.2 Data recording and Case Report Forms

the need for accurate recording and processing of patient data is fundamental to any clinical trial. If data stored are incorrect, conclusions of the analyses will also inevitably be incorrect. One should keep in mind that only accuracy, correctness and completeness of the data collected, as well as timely form return, will lead to the reporting of valid results. The main purpose of having well designed forms is so that patient evaluations can be made suitable for statistical analysis. With multi-centre trials the whole process of data collection and resolution of queries becomes easier if each centre has an on-site data manager. There is a need for close collaboration between Chief Investigator and Data Centre personnel in form design, and with on-site data managers in training in form completion. All forms should be returned in a timely manner according to the Schedule of Form Return in the Protocol This is particularly so with Serious Adverse Event Forms, where

Centres must report SAEs within 24 hours of knowledge of the event. This is essential for 'real time' safety monitoring of the trial.

8.3 Web-based Data Management

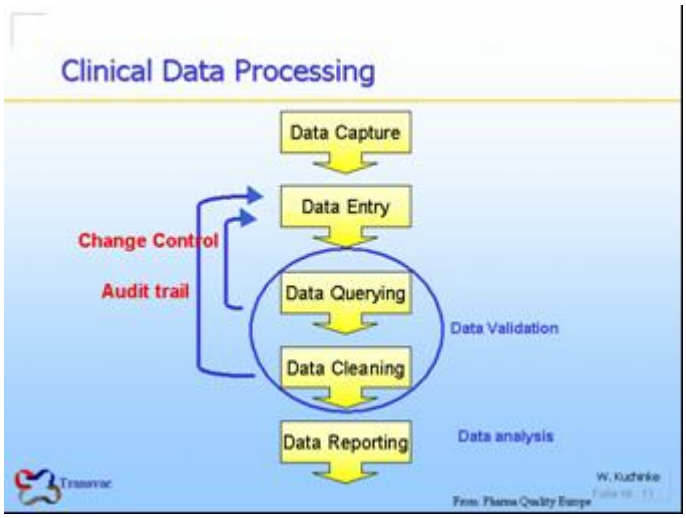
8.3.1 Computerized systems in clinical trials

Based on the FDA guideline "COMPUTERIZED SYSTEMS USED IN CLINICAL TRIALS" (dated 4/99) the Society for Clinical Data Management has developed a guidance document "SCDM Good Clinical Data Management Practices" (dated 9/03) which states:
"*…the need for good clinical data management practices has become even more important as…regulatory bodies rely more and more on the evaluation of electronically transmitted clinical trials data for critical data-based decision making*."

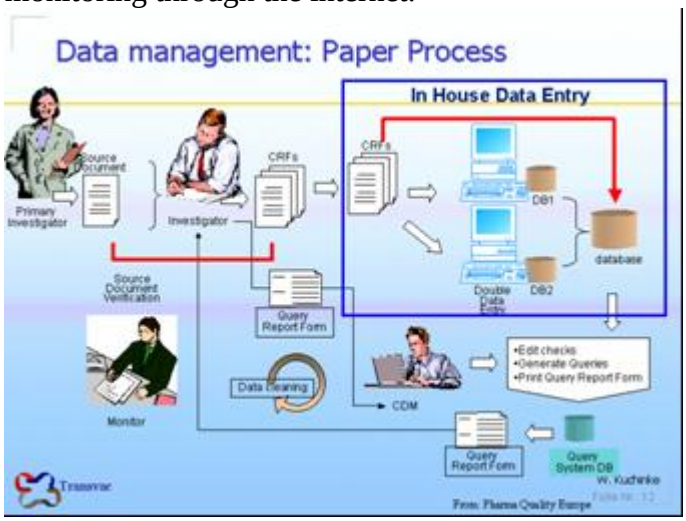
Computerized systems in clinical trials are not anymore confined to data capture alone, but support clinical trials in many ways. Therefore data management standards & guidelines focus on several topics:

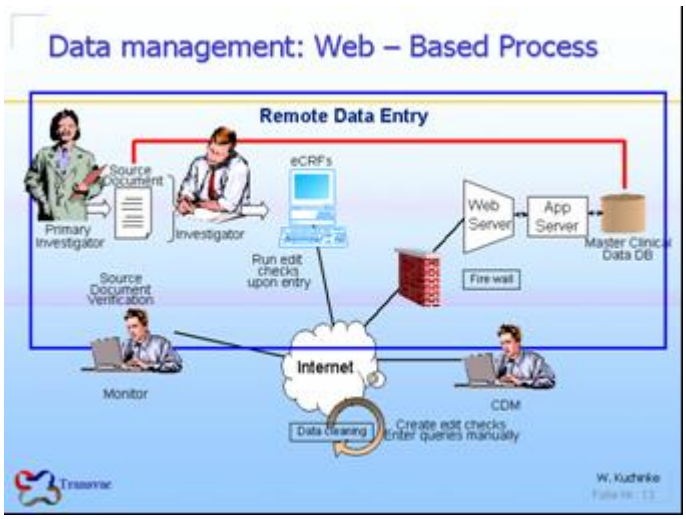
- Data Acquisition
- Data Entry
- Data Audits
- Data Storage
- Database Closure (locking)
- Data Archiving
- Data Privacy
- Documented Procedures (SOPs)
- Infrastructure for data acquisition
- Case Report Form (CRF) development
- CRF Administration Instructions development
- Data Dictionary (DD) development
- Participant management assistance
- What forms are/were administered when
- standard data management reports
- Computer System used for data management in Clinical Studies
- Randomisation system
- Recruitment systems
- Data Capture System
- automatic measuring device
- manual data input (In house data entry, Remote Data Entry)
- automatic data input
- Clinical Database Management System
- Drug Supplies Accountability System
- Statistical System
- Pharmacovigilance System
- Clinical Data Processing

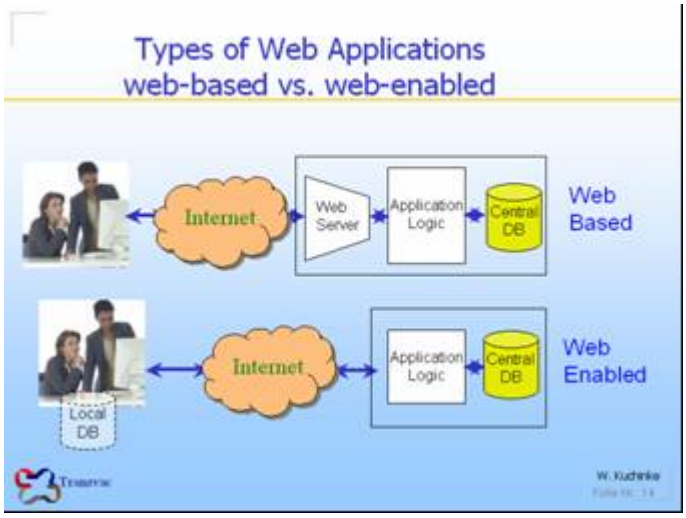
The processing of clinical data is a multi-step process. The aim of this process is to obtain clean, validated data which can be used for analysis.



Increasingly data are being captured not with paper but with electronic forms. But web based data management differs from the paper based process not only in the data capture form, but the entire process is different (see fig.). See for example the new role of the monitor, who can perform the monitoring through the internet.

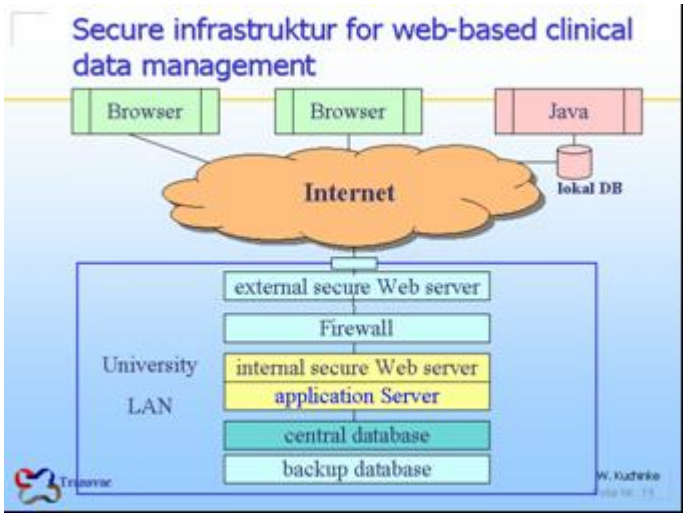




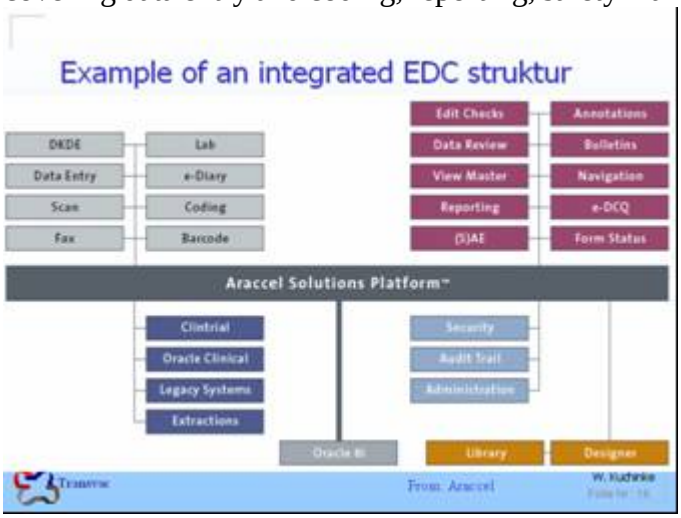


There are two ways to use the internet in clinical trial data management: electronic data management systems can be either web-based and web enabled.

Important is the existence of a secure infrastructure for web-based clinical data management. The figure gives an example of a secure integrated EDC structure. The special aspect of this infrastructure is that there are two web servers, this is not always necessary. The corresponding clinical study software resides on the application server. Data collection can be done by internet browser (small client) or by a Java application. Because the Java application has its own data base, clinical data can be collected even in case the internet connection is not available or disconnected.



Example for an **integrated** EDC-System (Araccel). Many functions are available in such a system, covering data entry and coding, reporting, safety management, patient diary (e-Diary), Fax, etc. the



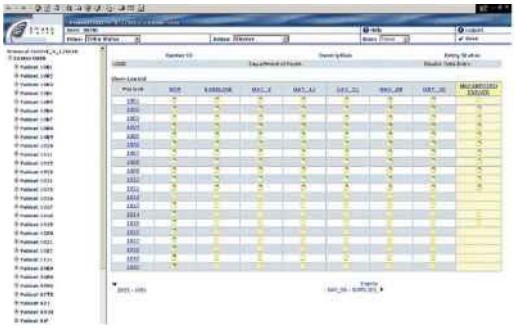
system can import data from other clinical trial software (Clintrial, Oracle Clinical).

8.3.2 Example screens of web based clinical trials applications.

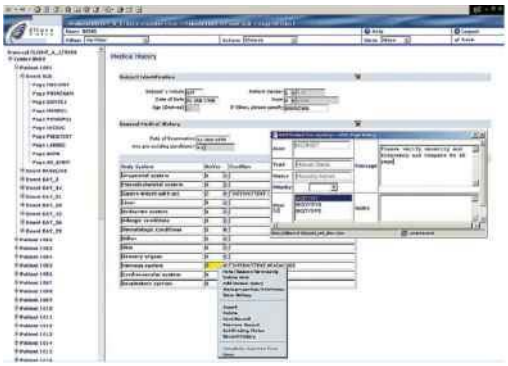
Profiler-Research (CRF with lab data table)

secuTrial showing overview over patients

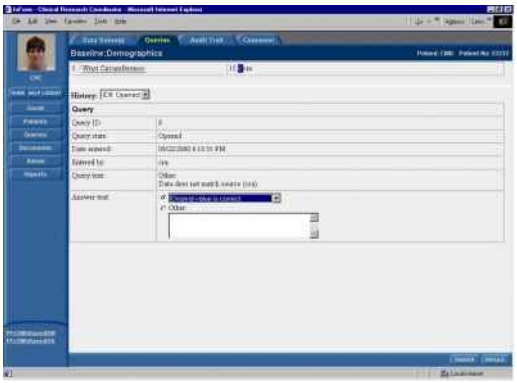
eResearch showing overview over patients and treatments



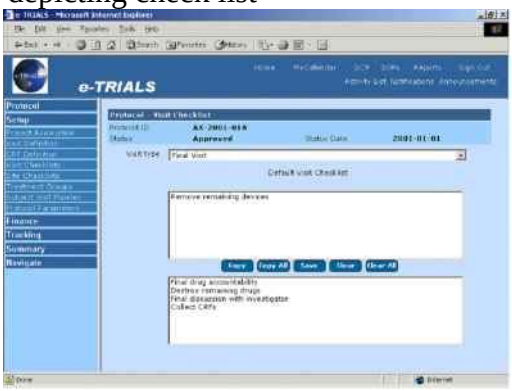
eResearch with data monitoring page



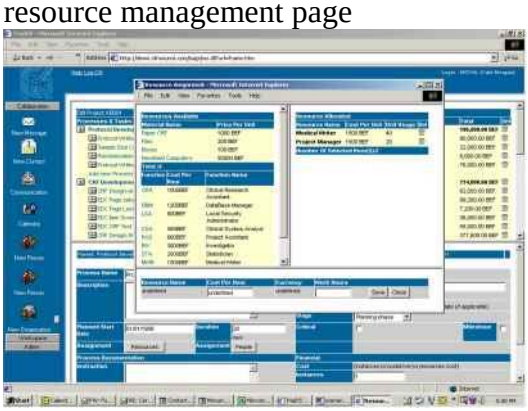
InForm showing query resolution



eTrials study management page depicting check list

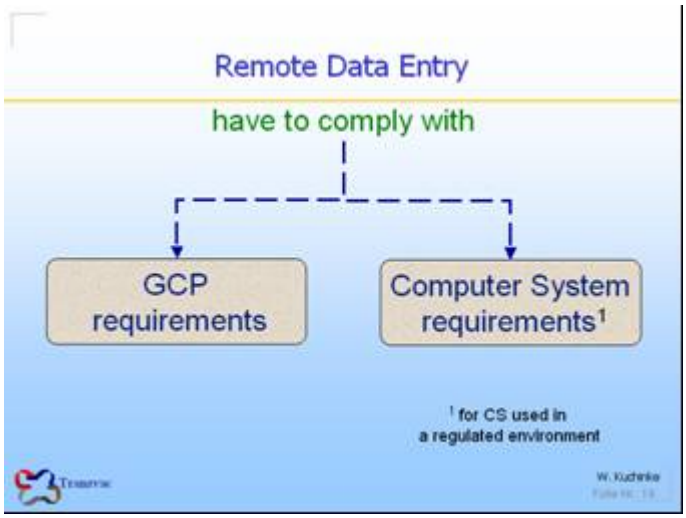


eTrials study management depicting resource management page



8.4 Data management and compliance

Data management too must conform to GCP regulations. A computer system used in clinical trials is used in a “regulated environment”. Its proper use must be confirmed, it has to be validated. Requirements for computer systems used in clinical trials are called Computer System Requirements”. An important point in this context is the definition of roles in data management.



8.4.1 Principal investigator

The principal investigator (or study chair):

- develops scientific concepts to be tested
- is responsible for ongoing conduct of the trial

8.4.2 Statistician

The statistician:

- is involved in the design of the study
- is responsible for calculating sample size
- is crucial for the definition of statistical methology used in trial and analysis
- analyses of trial data, and monitors progress of study

8.4.3 Clinical research associate (CRA)

The CRA is the person on the participating site, the center. The CRA isresponsible for completing the CRFs and submitting them to the coordination center (or sponsor).This activity can involve patient entry, scheduling visits, preparation of regulatory documents. Therefore, CRA should be involved to some degree in study design and pilot testing.

8.4.4 Data coordinator (DC)

The DC is on the participating site or the coordination center and his activities involve: quality control of data, generation of queries and data requests, preparation of data sets for analysis. In single center trials the CRA can operate as a data manager.

8.4.5 Database administrator

The activities of the database administrator involve designe and implementation of the database, its maintenance. He ensures database integrity and security.

8.4.6 System analyst, programmer

His activities involve the design of trial software, overseeing development and testing of study software.

8.4.7 Data collection system designer

His activities involve the design of trial software, overseeing development and testing. He has a role at the coordinating centre/Trials Unit.

8.4.8 Trial Coordinator

In multi-centre trials, the coordinating centre (or Trials Unit) has a vital role in registration and randomisation of patients, collecting and processing patient records, dealing with enquiries, monitoring toxicity, and providing feedback. In addition the Trials Unit will work with Chief Investigators to ensure compliance with the increasing number of regulatory needs. It is the trial coordinator in the Trials Unit who is responsible for a trial in terms of data collection and conduct of administrative matters relating to that trial. The trial coordinator should also design/review any new forms to ensure that they are clear, easy to complete, contain all the relevant information, and do not contain unnecessary information.. Once the trial is up and running the Trial Coordinator will be the focal point for all aspects of trial conduct (form return, resolution of queries, data checking, data entry, generation of reports, follow up etc).

8.5 Data management and GCP

8.5.1 Data compliance

Data management goes beyond the issues of adequate backups, archiving or disaster preparedness. It must guaranty the security of all data. No data should be altered or deleted uncontrollably from the system. Government regulations and other legislation now mandate the integrity, accessibility and long-term retention of data. Data integrity assures that information has not been changed or lost through corruption or media failure. This usually involves read-only media like CD or DVD discs, along with write-once disk platforms like content addressed storage (CAS).

Data retention defines how long clinical study data must be kept by an organization. This is usually the main focus of any compliance regulation, but "keeping" the data just isn't enough; data must be retrieved quickly to meet the demands of compliance auditors or legal discovery requests. Data security ensures that only authorized individuals can access data and that policies and procedures are implemented to protect data against loss or theft.

8.5.2 ICH-GCP (E6) demands on data management

The ICH-GCP regulation has several requirements for GCP compliant data management. It requires the evaluation of the study software system (validation) by the sponsor. An further important GCP requirement is that quality control should be applied to each stage of data handling.

5.5.3 When using electronic trial data handling and / or remote electronic trial data systems, the sponsor should:
a) ensure and document that the electronic data processing system(s) **conforms to the sponsor's established requirements** for completeness, accuracy, reliability, and consistent intended performance (i.e. **validation**).
4.9.1 The investigator should ensure the accuracy, **completeness, legibility, and timeliness** of the data reported to the sponsor in the CRFs and in all required reports.
4.9.2 Data reported on the CRF, that are derived from **source documents**, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. The investigator should retain records of the changes and corrections.
4.9.4 The investigator/institution should maintain the trial documents as specified in **Essential Documents** for the Conduct of a Clinical Trial and as required by he applicable regulatory requirement(s).
5.1.1 The sponsor is responsible for implementing and maintaining **quality assurance and quality control systems** with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
5.1.3 **Quality control should be applied to each stage of data handling** to ensure that all data are reliable and have been processed correctly.
5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.
5.5.2 The sponsor may consider establishing an independent **data-monitoring committee** (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals …
5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.
5.5.5 The sponsor should use an **unambiguous subject identification** code that allows identification of all the data reported for each subject.

8.5.3 Guidelines and regulations to be considered by data management

ICH Topic E6 Guideline for Good Clinical Practice, "Note for Guidance on Good Clinical Practice" (CPMP/ICH135/95)
ICH Topic E2A Notice for Guidance on Clinical Safety Data Management: definition and standard for expedited reporting (CPMP/ICH/377/95)
ICH Topic E2B Notice for Guidance on Clinical Safety Data Management: data elements for transmission of individual case safety reports (CPMP/ICH/287/95)
ICH Topic E2C Notice for Guidance on Clinical Safety Data Management: periodic safety update reports for marketed drugs (CPMP/ICH/288/95)
US FDA - Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs, January 1999
US FDA - Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations, January 1999 US FDA - Guidance for Industry: Preparing Data for Electronic Submissions in ANDAs, September 1999
US FDA - Guidance for Industry: Electronic Submissions of Case Report Forms (CFRs), Case report Tabulations (CRTs) and Data to the Center for Biologics Evaluation and Research - Draft, May 1998

8.5.3 Instructions for the use of Computer Systems for clinical data management

USA:
FDA - 21 CFR Part 11: Electronic Records; Electronic Signatures. August 1997

EU:
Directive 91/356/EEC, Annex 11: Computerised Systems
Directive 1999/93/EC: Community framework for electronic signature
Directive 95/46/EC: Data Protection

Italy:
Recepimento Annesso 11 della Direttiva Europea 91/356/EEC, 1992
Legge 675, Tutela della Privacy, 31 dicembre 1996
DPR n. 318, Regolamento recante norme per l'individuazione delle misure minime di sicurezza per il trattamento dei dati personali, a norma dell'articolo 15, comma2 della legge 31 dicembre 1996, 28 luglio 1999

8.6 Annex 11: Computerized Systems

For EU the Annex 11 gives the most detailed instructions and is applicable. It consists of following requirements.

8.6.1 Annex 11 - Personnel

It is essential that there is the closest co-operation between key personnel and those involved with computer systems.
Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers.
This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerised system.

8.6.2 Annex 11: Computerized Systems

Validation
The **extent of validation** necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system.
This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying.

System
A written detailed description of the system should be produced ….
The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.
The system should include, where appropriate, built-in checks of the correct entry and processing of data.
Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results.

Data should only be entered or amended by persons authorised to do so.
The system should record the identity of operators entering or confirming critical data
Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change.
For quality auditing purposes, it should be possible to obtain clear printed copies of electronically stored data.
Data should be secured by physical or electronic means against wilful or accidental damage
Data should be protected by backing-up at regular intervals.
A procedure should be established to record and analyse errors and to enable corrective action to be taken.

8.7 Computer System – other guidelines to consider

ACDM/PSI: Computer Systems Validation in Clinical Research - A practical guide" ACDM/PSI, 1998
GAMP Forum, Good Automated Manufacturing Practice - Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture, v. 4.0 December 2001.
PIC/S Good Practices for computerised systems in regulated "GXP" environment, Pharmaceutical Inspection Co-operation Scheme draft guidance, January 2002

8.8 21 CFR Part 11 - Electronic Records

With Part 11 the FDA gives requirements for the use of electronic records and electronic signatures in clinical trials. It defines following requirements:
Persons who used closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records,….

8.8.3 Procedures and controls:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance
(b) ability to generate accurate and complete copies of records in both human readable and electronic form
(c) protection of records to enable their accurate and ready retrieval throughout the records retention period
(d) Limiting system access to authorized individuals.
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and action that create, modify, or delete electronic records.
(f) Use of operational system checks
(g) Use of authority checks to ensure that only authorized individuals can use the system
(i) education, training, and experience
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions …
(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
(2) Revision and change control procedures to maintain an audit trail that document time-sequenced development and modification of systems documentation.

8.8.4 Electronic signature - composition

Signed electronic records shall contain information associated with signing that clearly indicates all of the following:

- The printed name of the signer.
- The data and time when the signature was executed; and
- The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

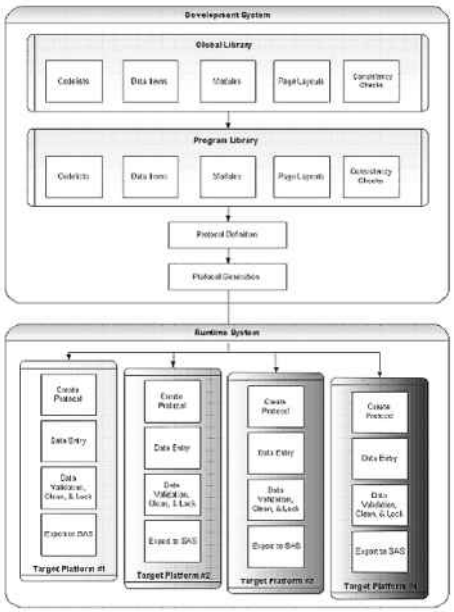
8.9 Examples for EDC data collection and data management software

secuTrial – Visits
secuTrial – integrated Pseudonymisation
secuTrial - discrepancy
Profile|RES: Investigator: status of patient
Profiler|RES: Monitoring
eResNet – Visits and eCRFs
eResNet (Data collection with drop-down lists)
eResNet – Datenvalidierung
InForm – Query

8.10 Data model of clinical trials

Using eResNet (eData Management) as example the data model of a clinical trials software is explained in detail. Important is the fact, that the model is strictly hierarchic. On can see that the data model is orientated towards the demands of pharma industry and less on the requirements of academic studies.

Structure of clinical trials data model of eResearch:



8.10.1 Program

A program in eData Management represents a group of drug or device related clinical trials in one therapeutic area that are all contributing to a single IRF/NDA. This is a useful requirement for pharma industry. The IRF/NDA will then be used as the basis to prepare product license applications.

8.10.2 Protocol

A protocol in eData Management represents the data requirements for a single clinical trial. This is usually equivalent to a single region or study. However, if a number of regions have common data requirements, a protocol can be developed using eDM that relates to the clinical trial as a whole.

8.10.3 Centers

A center is the location at which patients are recruited by an investigator for participation in a clinical trial. Centers are also known as a site.

8.10.4 Patients

A patient is the individual involved in a clinical trial to whom products, in the form drugs or devices (or placebos or comparators), are administered. Until the end of the screening phase, these individuals are often referred to as subjects. In eData Management (eDM), these individuals can be assigned a Screening ID in order to capture screening data in eDM and track them through the process. Once the individuals are participating in a trial by moving beyond the screening process by meeting the required protocol criteria, they are referred to as patients and are assigned a unique patient identifier (patient ID) that is defined by the sponsor.

8.10.5 Events

A CRF book consists of a number of events. An event is a discrete point in time at which data is collected during a clinical trial. There are two types of events:

- Predefined events that occur at fixed times, such as a baseline visit, when a standard set of data is collected per the study protocol.
- Unexpected (ad hoc) events that occur, for example, if a patient makes an unplanned visit to the investigator and provides them with information that may be relevant to the clinical trial but which does not fit in to information regarding a scheduled event.

8.10.6 Data Entry Pages

A data entry page in eData Management (eDM) is an electronic representation of a hardcopy Case Report Form. It is used to collect data on a patient at a specific event during the course of a protocol. One or more data entry pages can be associated with an event at a given time. Further, as the same set of data can be collected at several events, the same data entry page can be used for more than one event. For example, each event could include a data entry page on which the patient's vital signs (blood pressure, weight, respiration rate) are recorded.

Data entry pages are made up of a number of elements and use various methods for collecting data. Elements such as zones and modules make up the actual data entry page. Further data entry pages may employee codelists and dictionaries as methods of collecting data. Elements that Make Up a Data Entry Page:

8.10.7 Data Items

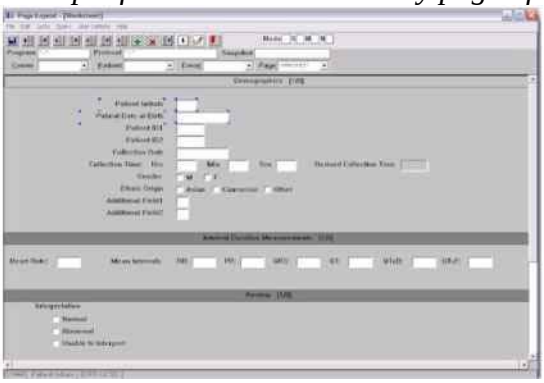
A data item is a record (field) or a variable of eData Management (eDM) data entry. Data items appear as data entry fields/records on a data entry page. The following criteria can be supplied when defining a data item:

- Type and size
- Data entry prompt
- Data entry Help
- Possible data ranges for number type data items
- A default value for the data item
- Possible selection from a codelist or dictionary column

There exist a number of different data fields. Available Field Types:
CHAR
A character field can contain any character found in your computer's standard
NUMBER
number field can contain a number, with or without a decimal point. For example, 9, 74.8, 10963, 0.01.
DATE
date field must contain a date in the format selected for the protocol.
TIME
time field contains a time value in format HH24:MI.
Field Characteristics
Mandatory
You must enter data in a mandatory field. In some instances, you will not have access to the next field until valid data has been entered in the current field.
Non-Updateable
Once a value has been entered and stored in a non-updateable field, the information cannot be modified.
Optional All fields

are optional entry fields unless otherwise specified as a mandatory field. It is not necessary to enter data in these fields.
UPPER CASE
An upper case field will display only upper case characters. Any characters entered in lower case will be converted automatically to upper case.

Example for electronic data entry page of eResearch (eData management):



8.10.8 Codelists

The primary purpose of an eData Management (eDM) codelist is to enable you to select predetermined values from a list (in the form of either a dropdown list or popup menu). A codelist contains alphanumeric abbreviations (or codes) and a corresponding description. A code acts as the value that populates a data item. For example, a data item can be called Severity. The values that you may wish to use for this data item could be: Mild, Moderate, or Severe. Each description can be coded as 1, 2, and 3, respectively

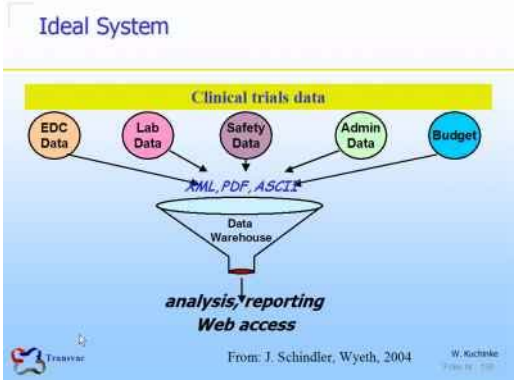
8.10.9 Data Entry Access Statuses

Different states are accompanied with data entry. Making data changes encompasses:
Changing the data value in individual fields
Deleting records
Adding records
Adding pages
Adding events
Adding patients
Data entry statuses
Users can be assigned access to any of the following data entry statuses:
0 = No Data
1 = First Data Entry
2 = Second Data Entry
D = Both Entries
V = Verified
S = Secured
R = Released
Q = QA Controlled
L = Locked

8.11 Data exchange standards in clinical data management

The import, export and exchange of clinical trials data plays an increasingly important role in clinical research. Until now clinical data exchange was hampered by the number of different proprietary data standards. Recently, with CDISC data exchange between different study software solutions became possible.

Schema of data integration in an ideal system:



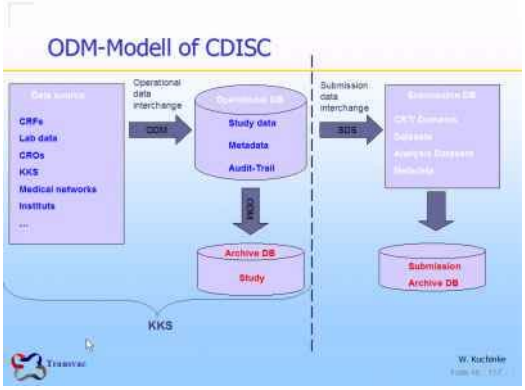
8.11.1 What is CDISC?

CDISC is an open, multidisciplinary, nonprofit organization committed to the development of industry standards to support the electronic acquisition, exchange, submission and archiving of clinical trials data and metadata for medical and biopharmaceutical product development.

8.11.2 The four main CDISC standards:

Operational Data Modeling (ODM)
vendor neutral, platform independent format for interchange and archive of data collected from various sources in clinical trials. The ODM model represents study metadata, clinical data and administrative data
Submission Data Standards (SDS)
set of standards that are intended to guide the organization, structure, and format of standard clinical trial tabulation datasets submitted to a regulatory authority (FDA,...)
Laboratory Data (LAB)
model for acquisition and interchange of clinical trial laboratory data
Analysis Data Set Modeling (ADaM)
set of guidelines for analysis datasets used to generate the statistical results for submission to a regulatory authority.

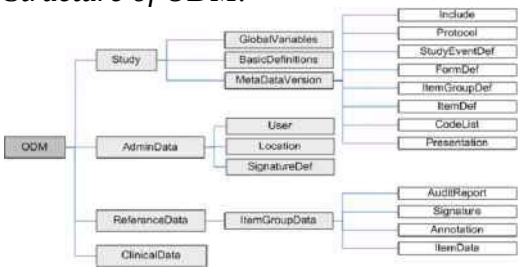
Position of ODM in standard based clinical trials:



8.11.3 ODM

The Operational Data Model (ODM) is a vendor neutral, platform independent format for interchange and archive of data collected in clinical trials. The model represents study metadata, data and administrative data associated with a clinical trial. Only the information that needs to be shared among different software systems during a trial, or archived after a trial is included in the model. Version 1.2 contains a number of new features that improve the functionality, security and convenience of the model. Beginning with version 1.2, both an XML Schema and a DTD are provided with the ODM model.

Structure of ODM:



The ODM model consists of four principal sections. GlobalVariables contains descriptive information about the study as a whole. StudyName, StudyDescription, and ProtocolName are some examples of Global Variables. BasicDefinitions contain definitions of information that is not likely to vary between studies. Example, *TimeZone* is defined here, so that every place that a time zone needs to be referenced within the study can refer to this same set of definitions. One or more *TimeZones* may be defined in BasicDefinitions, as indicated by the "*" preceding *TimeZone*.

MetaDataVersion

This is the section that contains the metadata definition for the study.

AdminData

includes information about the users of the system, the clinical sites involved in the study, and associated security information

8.11.4 Metadata and data exchange

If two systems are to exchange data during a clinical trial, then the metadata information may be exchanged once at the beginning of the trial, and then exchanged again each time the protocol is updated. There is no need to send the metadata each time the clinical data for a given visit is sent, for example. The overall structure of the data is the same for every patient, even though the actual data values are different for each patient, and each visit. Of course, that means that the structure must take into account the presence of repeating pages, repeating visits, and repeating groups of items. The metadata includes six major components:

- Items – clinical data items, analogous to fields or variables
- ItemGroups – groups of Items, analogous to datasets, panels or tables
- Forms – clinical data collected and signed together, analogous to pages
- StudyEvents – significant planned or unplanned timepoints, analogous to visits
- Protocol – overall data collection framework for the study
- Presentation – details of how data is presented and collected in forms

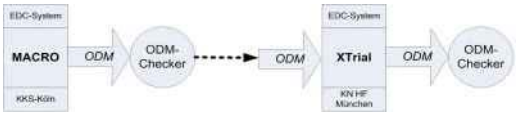
8.11.5 Proof-of-concept for a complete study data exchange

With the CDISC (Clinical data Interchange standards Consortium) a standard is available for clinical studies, which is however hardly used in academic clinical research. From this the following question arose for us: is it possible in context of a Proof-of-Concept to transfer Metadata of an entire clinical study in a software independent way under everyday conditions, therefore without great programming efforts and between different study software systems (EDC systems) used routinely by TMF registered associations?

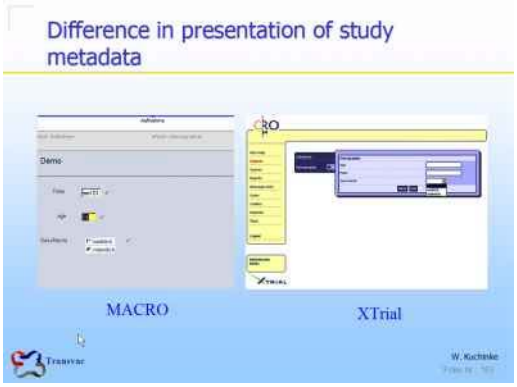
Metadata transfer

The metadata transfer between different EDC systems was realized with the ODM standard a mini-test study was created with MACRO and exported in ODM-XML through the MACRO web interface. For viewing, modification and validation of the ODM export file XML-Spy (Altova) and CDISC ODM Checker version 0.5 (XML4Pharma) were used. Metadata exchange was based on ODM-DTD version 1.2.0. ODM-Checker was used to validate the conformity of the ODM file across two levels against ODM (DTD or XML schema): level 1: validity of ODM against DTD/XML schema; level 2: consistency of the contents of the file with ODM.

Schema of metadata exchange:



Result of „Proof-of-concept“: Difference in presentation of study metadata. Shown are the data input screens of MACRO and XTrial. Same metadata but different visual representation!

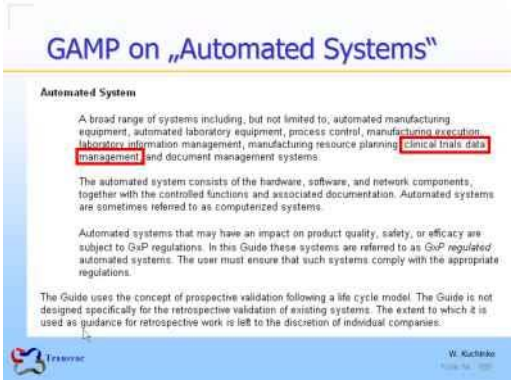


8.12 Systemvalidation

8.12.1 What is validation?

According to FDA validation means “*to establish **documentary evidence** that provides a high degree of assurance that the computer systems will consistently produce a product or result meeting predetermined specifications, requirements and quality attributes. This evidence is presented to concerned parties to provide assurance that systems and processes as well as test methods are under control and are repeatable*.”

The GAMP Guide is the fundamental document for validation of study software. Important is its definition of automated systems. Highlighted in red is the reference to clinical trial management.



8.12.2 Glossar of validation terms

Acceptance Criteria
Standards or requirements specified in a protocol, which must be met in order to demonstrate acceptability of a given qualification or system.

Approval
A Protocol, Addendum or Final Report has been approved once it has been reviewed and signed by representatives. Approval of a protocol constitutes authorization to proceed with execution within the policy guidelines defined in this plan.

Change Control
Change control is a formal monitoring system by which qualified representatives review proposed or actual changes that might affect a validated system or process. The program provides a corrective action that will ensure that the system or process retains, or the clinical trial is placed back into a validated state of control. Change control should be based with risk assessment.

Computerized System
A group of hardware components that consists of one or more processing units and peripheral equipment, that is controlled by internally stored programs, and is designed to perform a specific functions or group of functions. The computerized system encloses the users, training and documents associated with the proper use of the system.

Final Report
An approved document that addresses the results derived from execution of a protocol. The report summarizes the test procedures and results, evaluates data, describes deviations and exceptional conditions, and includes a summary of conclusions indicating qualification success or failure. A final report should be written for every protocol executed.

Maintenance
A term used of describe the system life cycle phase after systems initial validation.

Protocol
An approved test plan, that when executed as prescribed, is intended to produce documented evidence that the system/process does what it purports to do.

Standard Operating Procedure (SOP)
A written and approved description of important operations and policies which define essential steps, their sequence, and precautionary measures, necessary to assure that these operations can be accomplished routinely and in a uniform manner. The SOP represents the detailed description of how an activity is to be performed, what is to occur, and the expected results.

Verification
Comparison of a measurement standard of known accuracy with another standard to detect, correlate, or report, but not to eliminate any variation in the accuracy of the item being compared. Implies no adjustment of the compared item is needed.

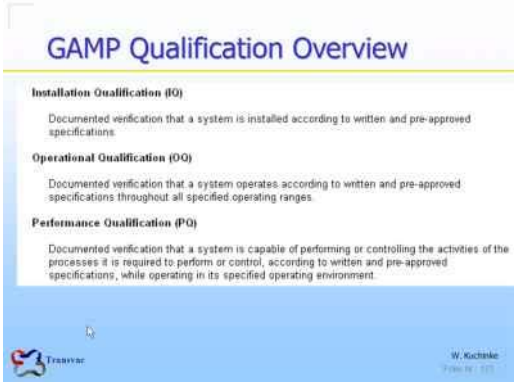
SVMP
System Validation Master Plan. Is the central document of system validation. The SVMP is a compendium of all documents, processes and descriptions necessary for system validation and gives a summary of the validation policy of KKS. It references all important validation documents that deal with details of the validation process or which are provided by the software vendor.

the validation guide GAMP on „Automated Systems“ describes the validation procedure of the single validation steps in relation to the system life cycle and to GCP. The validation Life Cycle step are:

1. System Specification
2. System Classification

3. Validation Planning
4. Establishing of the validated state
5. Maintaining the validated state
6. System Retirement

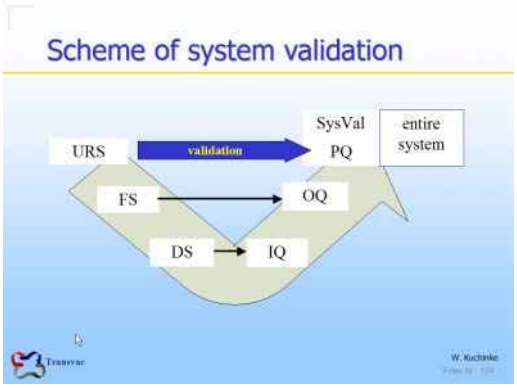
The main three steps of system qualification: IQ, OQ, PQ



8.12.3 Validation program

The validation program consists of following steps and topics the validation team has to consider:

Validation is done according to the V-Model.



1. If applicable an audit of a qualified computer systems vendor can be conducted. A vendor selection procedure has been be established. The vendor selection process also considers vendors compliance with GCP / FDA and qualification documentation.
2. Written procedures for test methods shall be established and validated where appropriate.
3. **Acceptance criteria** shall be established and specified in each protocol.
4. Any planned deviation from validation procedures outlined in protocols must be approved in writing by all persons responsible for the initial approval of the protocol. An addendum describing the deviation and the approval by responsible persons will be attached to the protocol.
5. In the course of executing a protocol, any **exceptions / deviations from validation requirements** must be explained. An evaluation of the impact on the integrity of the test data included in the Final Report.

6. **Standard Operating Procedures** for maintenance, operation and parameterisation shall be written prior to execution of the applicable Operational Qualification protocol.
7. Computers and additional equipment shall be validated prior to clinical trial processes.
8. Product **Performance Qualification** using data of a test study is the last step in the validation sequence. It shall not be performed until computers, equipment, test methods and processes have achieved a validated state.
9. A Final Report shall be written for each completed qualification/validation protocol.
10. Validation will encompass the computerized system used for clinical trails as parts of the centers security infrastructure.
11. Once the systems has been considered validated a **Change Control** Program will be implemented to ensure that both planned and unplanned changes are documented and revalidated if necessary.
12. Maintenance and Change Control is part of the life cycle approach to validation of computer systems. Maintenance of computer-related systems will be conducted according to schedule to ensure proper function.
13. During the life of the computerize systems, its operating conditions during performance of clinical trails will be **reviewed** on a continuous or regular, periodic basis and compared with predetermined criteria. Any deviations from the acceptable operating criteria will be investigated and appropriate action will be taken.
14. The life cycle approach to validation and change management ensures that the computer system is always validated for the proper conduction of GCP-clinical studies during its entire duration of use.
15. A **validation audit** will be conducted to ensure completeness of validation efforts.

8.12.4 validation plan

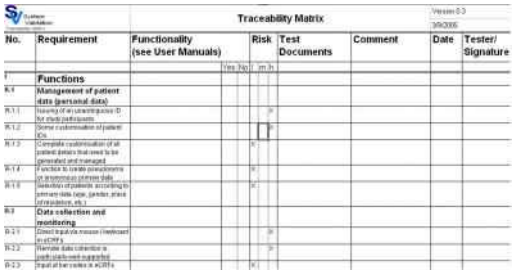
For validation a validation plan has to be created, defining each step of validation.
Content of Validation Plan:

1. Introduction and Scope
1.1. Business Process Description
1.2. System Description
1.3. GCP Criticality Assessment
1.4. Assumptions, Exclusions, and Limitations
1.5. Roles and Responsibilities
2. Establishing of the Validated State
2.1. Categories of System Components
2.2. Risk Assessment
2.3. Qualification Measures
3. Validation Documentation
4. Standard Operating Procedures
5. Maintaining the Validated State
6. Training
7. System Retirement
8. Project Management

8.12.5 Traceability matrix

The central document for system validation is the Traceability matrix. It references the list of requirements to the testing scripts of validation.

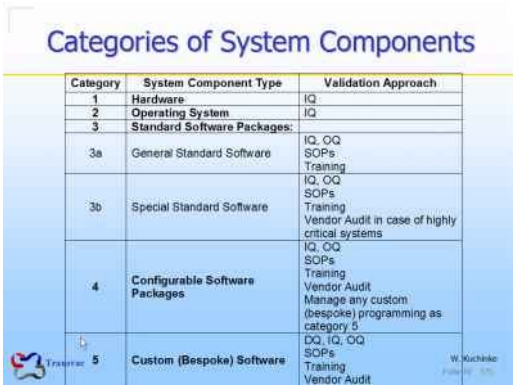
Scheme of system validation:



Traceability Matrix

No.	Requirement	Functionality (see User Manuals)	Risk	Test Documents	Comment	Date	Tester/ Signature
			Yes / No / m.h.				
1	**Functions**						
K1	**Management of patient data (personal data)**						
K1.1	Issuing of an unambiguous ID for study participants		x				
K1.2	Some customization of patient IDs						
K1.3	Complete customization of all patient details that need to be generated and managed		x				
K1.4	A function to create pseudonyms or anonymize primary data		x				
K1.5	Selection of patients according to primary data (age, gender, place of residence, etc.)		x				
K2	**Data collection and monitoring**						
K2.1	Direct input via mouse / keyboard in eCRFs			x			
K2.2	Remote data collection a path (path-net supported)			x			
K2.3	Input of text codes in eCRFs		x				

Categories of System Components. The deepness of validation is decided by the category of the system component to be validated:



Categories of System Components

Category	System Component Type	Validation Approach
1	**Hardware**	IQ
2	**Operating System**	IQ
3	**Standard Software Packages:**	
3a	General Standard Software	IQ, OQ SOPs Training
3b	Special Standard Software	IQ, OQ SOPs Training Vendor Audit in case of highly critical systems
4	**Configurable Software Packages**	IQ, OQ SOPs Training Vendor Audit Manage any custom (bespoke) programming as category 5
5	**Custom (Bespoke) Software**	DQ, IQ, OQ SOPs Training Vendor Audit

W. Kuchinke

8.12.6 Maintaining the validated State of study software

In a computerised system changes in hardware, software and network configuration are required frequently. Uncontrolled changes or incomplete documentation could have negative impact on the reliability of the system and on the quality of the clinical trial conducted. Thus it is inevitable to document changes on a system in a controlled procedure which is called Change Control.

A SOP describes the Change Control procedure of for example planned changes and should help to ensure that these changes follow documented procedures. The procedure applies whenever any component of a network is changed. This can be network devices, cables, network operating systems, computer hardware, peripherals, application software and even software documentation. The approval or rejection of a change as well as the implementation of the change takes place on the basis of a special template "Change Request". This template regulates the proceeding and the size of the change control procedure. Change Control procedures are required to document all changes on a system during its entire life cycle!

In case of extensive changes or changes with serious consequences a special testing step becomes necessary and it is to be proceeded according to the life cycle model (specification, implementation, testing, release) which has to be specified in the system validation plan. Every change request is

numbered by the project manager with a unique ID (Change ID). All requests must be archived. Every change request should be validated according to its risk for clinical trials data. They should be classified by the following classifications: low, medium, high, depending on the impact on data quality and the availability and system safety. Basic principle of impact analysis is the system specific documentation (requirements -, technical – and functional specification, risk analysis).

Change Management in general is conducted according to several SOPs. SOPs for Change Control:

4-001 Overview Change Management
4-003 Change Control Planned
4-004 Change Control Unplanned
4-005 change announcement
4-006 change protocol
4-007 Change Request Planned
4-008 Change Log Planned
4-009 Change Request Unplanned
4-010 Change Log Unplanned
4-011 System Documentation
4-12 System Inventory List

9. Pharmacovigilance

9.1 Safety

During clinical trials, safety aspects are closely monitored and all the adverse events have to be documented.

9.1.1 Definitions

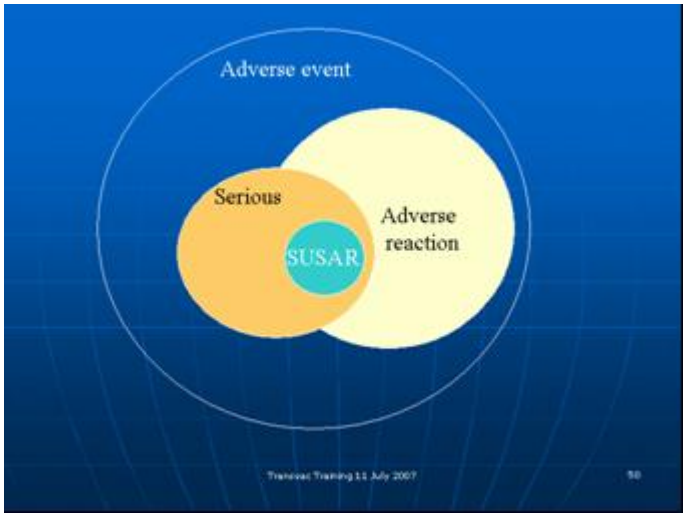
Adverse event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medical product and which does not necessarily have a causal relationship with his treatment

Adverse reaction (AR): any untoward and unintended responses to an investigational medicinal product related to any dose administered

Serious AE or AR: any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistant or significant disability or incapacity or is a congenital anomaly or birth defect

Unexpected AR: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg IB or SPC)

Suspected unexpected SAR: serious event suspected (possibly, probably or definitely) to be related to the IMP and unexpected (i.e. not previously documented in any of the product information or protocol).



9.1.2 Intensity

The AE can have different intensities.

- Mild: transient or mild discomfort, no medical intervention or therapy required
- Moderate: mild to moderate limitation in activity- some assistance may be needed. No or minimal medical intervention/therapy needed
- Severe: Marked limitation in activity, some assistance usually required, medical intervention/therapy required. Hospitalisation is possible.

9.1.3 Causality

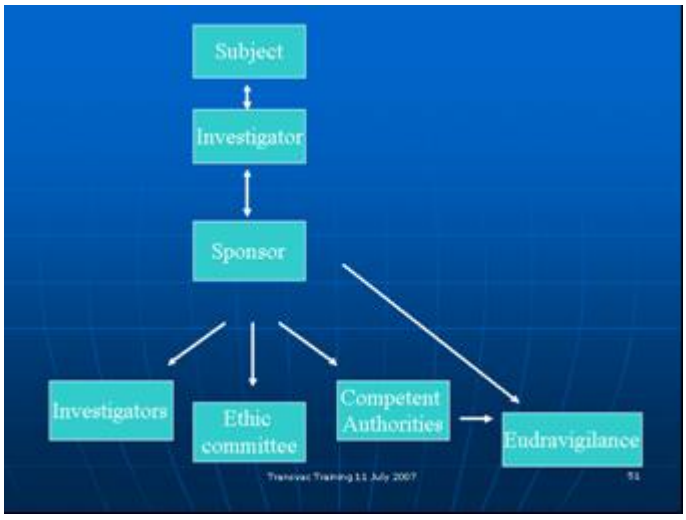
Causality determines whether an exposure or an event is causally related. There are different degrees of causality:

- Certain: occurring in a reasonable time after study drug was given and cannot be explained by concurrent disease or drug
- Probable: occurring in a reasonable time after study drug was given and is unlikely be caused by concurrent disease or drug
- Possible: occurring in a reasonable time after study drug was given and could be explained by concurrent disease or drug
- Not likely: an event which is most likely caused by some factor not related to study drug
- Unrelated: event reasonably caused by some factor not related to study drug
- Evaluation of the unexpected aspect

Certain, probable and possible are considered as related, and not likely and unrelated are considered as non-related. If sponsor disagrees with the investigator assessment both conclusions will be mentioned in the report.

9.2 Sponsor's responsibilities

Each trial is characterised by a hierarchy of responsibilities.



The sponsor must ensure that the necessary quality standards are observed in:

- case documentation
- data collection
- validation
- evaluation

- reporting of adverse events
- standard operating procedures

In addition, the sponsor's responsibilities are:

- the safety evaluation of experimental medicinal product or medical device continuously during research
- the setting of written procedures to guaranty data collection, cases documentation, validation evaluation, reporting and archiving
- evaluation of the seriousness of SAEs reported by the investigators
- evaluation of the causality of the SAEs
- evaluation of the unexpected aspect of the SAEs

Special responsibilities exist in case of SUSARS.

9.3 The investigator's responsibilities

The investigator's responsibilities too, are clearly defined

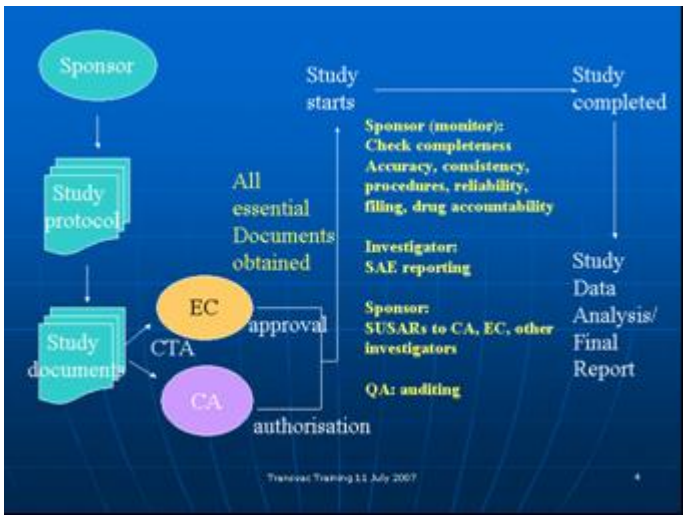
- Collect AE through observation, questioning, voluntary report
- Record all AE and report sponsor as required by protocol (timeframe defined in the protocol)
- Report all serious AE to the sponsor without delay
- Forward all additional information

10. Monitoring

10. 1 Oversight over the CT process

Monitoring is the act of overseeing the progress of a clinical trial and of ensuring that it is conducted, recorded and reported in accordance with the protocol, the standard Operating Procedures (SOPs), the Good clinical Practice(GCP) and applicable regulatory requirements and is part of the quality management process.

An important part plays the monitoring of “essential documents” according to GCP.



The objectives are to ensure that the rights and well being of the participants are protected, that the reported trial data are accurate, complete and verifiable from source documents and that the conduct of the trial is in compliance with the protocol/amendment, GCP, applicable regulatory requirements. According to the ICH GCP, the sponsor should ensure adequate monitoring and determine the extent and nature of monitoring.

The extent of the monitoring should be based on objective, purpose, design, complexity, blinding, size, endpoints. In general the monitoring is on-site monitoring but in some circumstances central monitoring in conjunction with investigators’ training, meetings, guidance can be used. A statistically-controlled sampling is acceptable for selecting data to be verified.

10.2 On Site monitoring

10.2.1 Site selection

The objective is to verify that the investigator at a selected site has the capacity to perform the study (competencies, adequate staff, time, facilities, and recruitment).

Initiation visit can be performed with the objective to:

- remind protocol and study procedures
- collect all essential documents if not done
- clarify the role of each participant, verification of the ressources (human, technical…) and the training of the staff
- remind the process of inclusion of subjects (consent, procedures..)
- review the CRF and how to complete it especially when eCRF
- discuss technical or medical procedures
- review the AE reporting
- review the IMP management

10.2.2 Study monitoring visit

The number, the frequency and the content of the visits are specified by the sponsor at the beginning of the study and are dependent of the study (phase, complexity, and hazard). The objective of those monitoring visits is:

- -Verify protocol and procedures compliance
- -Verify the consent forms
- -Document any deviation, violation
- -Resolve any issue following the first inclusions
- -Verify data of the case report form against source documents and follow corrections
- -Verify the AE reporting
- -Verify the trial master file
- -IMP management (accountability, expiry date, storage conditions, resupplying, return, destruction)
- -Biological sample management if applicable

The visit is followed by a written report.

10.2.3 Closure visit

This visit is performed at the end of the study to close the centre with the following objective:

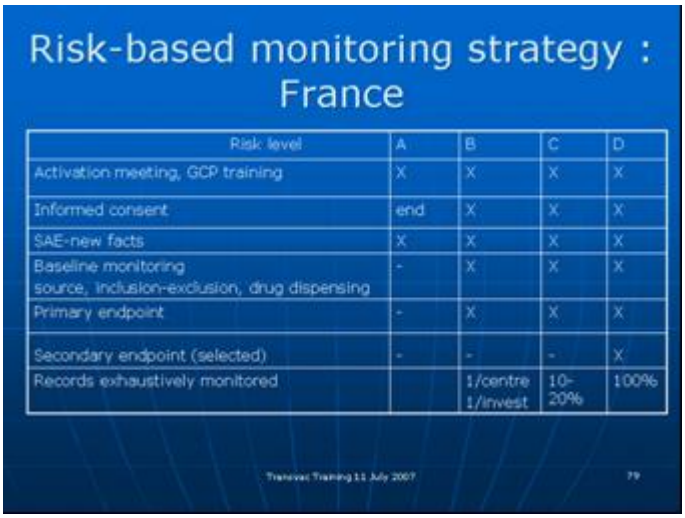
- -Resolve any pending issue
- -Verify the trial master file
- -Collect essential documents
- -Prepare archiving

10.3 Other monitoring strategies

There is no single monitoring strategy and different monitoring strategies can be used either in industry-sponsored or in investigator initiated trials.

Study-specific monitoring plan should be defined in advance based on risk assessment and study management based on the hazard to the participants, hazard to the study, hazard to the institution/company, and hazard to the public health.

For example: alternative monitoring procedures based on the risk assessment have been developed in France in the AP-HP (scheme) or in Germany. Shown is the strategy for France:



11. Data protection

11.1 Aspects

Data protection has several aspects:

- Right to privacy with respect to the processing of personal data
- Confidentiality
- Security

11.2 Definitions

11.2.1 personal data

any information relating to an identified or identifiable natural person; an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity

11.2.2 sensitive personal data

all information relating to an individual's health, ethnicity, religion or political beliefs

11.2.3 processing of personal data

any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission

11.3 Prerequisite

There exist several prerequisites for proper data protection in clinical research:

- informed consent (specific information given on the treatment of data such as identity of the controller, purpose of the processing, data concerned, existence of the right of access to and the right to rectify)
- review and approval (Ethics committees, supervisory authority)
- appropriate technical and organisational measures to protect personnel data (accidental or unlawful destruction or accidental loss, alteration, unauthorised disclosure or access, unlawful forms of processing)

11.4 Transfer to third countries

The transfer of data is only possible if an adequate level of protection can be ensured.

12. Investigational medicinal product (IMP) in Europe

12.1 What is an IMP?

The **Investigational Medicinal Product** is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation be used or assembled (formulated or packaged) in a way different from the authorised form or when used for an unauthorised indication or when used to gain further information about the authorised form

12.2 Non-Investigational Medicinal Product

What is not an IMP (NIMP= Non Investigational Medicinal Product):

- A rescue medication (used to manage an emergency situation)
- *except in Spain, NDL, Italy consider these products as IMP if not authorised in the indication in the MS
- Challenge agents (product given to produce a physiological response that is necessary before the pharmacological effect of the IMP can be assessed)
- *except in Ireland, Norway, Spain, NDL, Italy, Germany consider as IMP if not authorised in the indication in the MS
- Medicine used to assess primary endpoints in the clinical trials
- *except in Ireland, NDL, Spain, Italy, Sweden, Germany consider as IMP if not authorised in the indication in the MS
- Concomittant medicinal products systematically prescribed to the study subject
- Background treatment (except if protocol addresses questions on this treatment)

12.3 Regulation

There exist regulations for IMP: IMP should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and used in accordance with the approved protocol. Specific regulation exist for IMP genetically modified organisms. The verification of the compliance with the provisions of GMP and GCP is done through inspections by the CA

13. First-in-men

First-in-men (FIM) trials are a special challenge.

13.1 Properties of First-in-men trials

The **objectives** of these studies are:

- Assess initial safety and tolerability
- Define and describe the pharmacokinetics and pharmacodynamics (continue through out the development, include subpopulations)
- Explore drug metabolism and drug interactions
- Estimate the activity

The characteristic **properties** of FIM are:

- Non therapeutic
- Healthy volunteers or certain type of patients
- with an appropriate clinical environment (immediate access to intensive care and treatment facilities)
- with a adequate staff (appropriate training and expertise)

The **prerequisite** are the following:

- results of non clinical studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in human
- emerging animal toxicological data and clinical data should be reviewed and evaluated by experts to assess their implication for the safety of the trial subject
- calculation of the first dose in man is based on No Observed Adverse Effect Level (NOAEL) determined in non clinical safety studies
- the investigational medicinal product (IMP) used for the proposed clinical trial should be comparable to that used in the toxicity studies in terms of quantitative and qualitative impurity profile

- a critical analysis of the available non-clinical data should be provided, ensuring that an appropriate safety assessment was performed allowing administration to humans or justifying the lack of data in the opposite case.

13.2 Data of First-in-men trials

The following data should be clearly presented:

- the kinds of toxicities observed: target organs or functions, reversibility
- the No Observed Effect Level (NOEL) and/or the No Observed Adverse Effect Level (NOAEL)
- doses proposed in the clinical trials and their justification
- the parameters to be monitored during the clinical trials considering the available non clinical data

13.3 Risks in First-in-men trials

Following the catastrophic systemic failure that occurred in the first-in-man clinical trial of TGN1412 in March 2006 (Immunomodulatory drug designed as an orphan medical product by EMEA) a new guideline on requirements for first-in man clinical trials for potential high-risk medicinal products has been issued and is under consultation.

This concern:

- High-risk medicinal products (chemical and biological medicinal products)
- Gene and cell therapy medicinal products excluded to be covered by specific guidelines

It contains an additional approach to dose calculation (Minimal Anticipated Biological Effect Level= MABEL= anticipated dose level leading to a minimal biological effect level in humans, MABEL calculation should utilise all relevant in vitro and in vivo available information from PK/PD data). When NOAEL, MABEL give different estimations of the first dose in man, the lowest value should be used.

13.4 Protocol content

The protocol should contain the following information:

- Study population: healthy subjects or patients
- Route and rate of administration
- Number of subjects per cohort
- Precautions to apply between doses within a cohort: an initial sequential dose administration design should be employed within each cohort
- Precautions to apply between cohorts: all the results from all subjects of the first cohort (and of subsequent cohorts) need to be carefully considered before administration of the first dose of the next cohort.

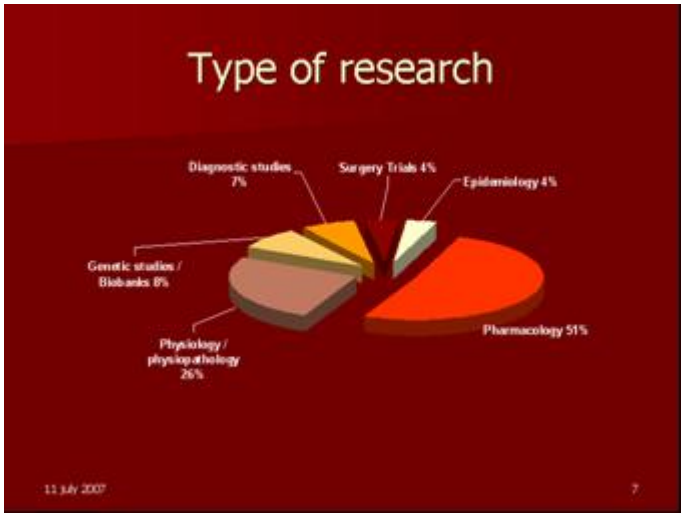
- PK and PD data from the previous cohorts should be compared to known non-clinical PK, PD and safety information. Any observed responses should be compared to the responses that were anticipated. Unanticipated responses may require a revised dose escalation.
- Administration in the next cohort should not occur before all the participants in the previous cohort have been treated and data/results from these participants reviewed.
- -Dose escalation scheme: pharmacodynamic aspects including the shape of dose-response curve from non-clinical studies should be taken into account.
- Interval between dosing subjects within the same cohort
- Dose escalation increments
- -Transition to next dose cohort
- Monitoring for adverse events/reactions
- Stopping rules and decision making process
- Defining responsibilities for decisions with respect to subject dosing and dose escalation
- Site of the clinical trial: staff, facilities (intensive care unit)
- Long term monitoring

14. The infrastructures of clinical research

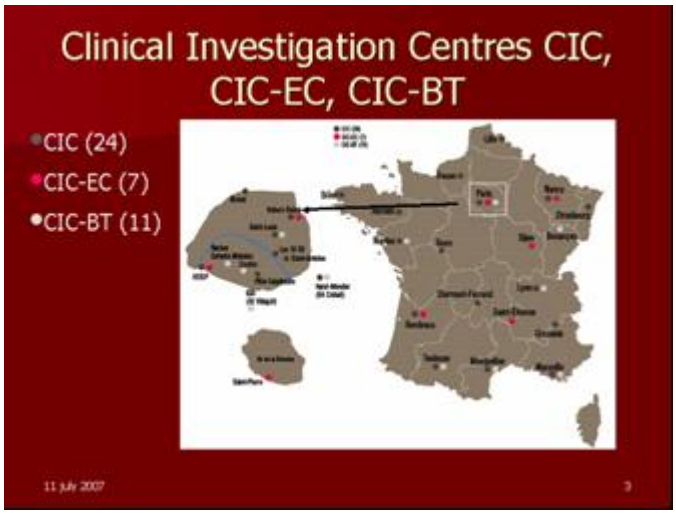
14.1 Infrastructure in France: Centres and networks

Two different infrastructures exist in France. The Clinical Investigation Centres (CIC) and the Clinical Trials Units (CTUs)

The CIC are hospital-based facilities, steered by INSERM and University Hospitals
They perform translational, phase I-IV, mechanism of disease studies. The studies can either be academic or industry sponsored.



Some Investigation Centres are specialised in epidemiology or biotherapy. The others are plurithematic.



The Clinical Investigation Centres are composed of professional staff (10-25) trained to clinical research including physicians (who can act as investigators), study nurses, clinical research

assistants, project managers, technical staff, pharmacists. They are created following competitive call and undergo scientific and financial evaluation every 4 years. They are also audited (system or study audits). The CIC network promotes the harmonisation (procedures, information tools) and facilitates the scientific collaboration and multicentre studies.

The Clinical Trials Units (CTUs) ate not hospital-based. They perform epidemiological and biostatistical support to clinical trials and Phase II-IV, diagnostic and prognostic studies, cost-effectiveness studies. The studies can either be academic or industry sponsored.

14.2 ECRIN, an integrated infrastructure for clinical trials in the EU

ECRIN (European Clinical Research Infrastructures Network) is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of clinical research centres and clinical trial units. ECRIN participants are currently Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, Switzerland, and the United Kingdom, with the participation of the European Organisation for Research and Treatment of Cancer (EORTC), and the contribution of the European Forum for Good Clinical Practice (EFGCP). ECRIN plans extension to national infrastructures networks in other member states, and stimulates the set-up of new national networks able to provide support to clinical research in any medical field for further connection to ECRIN.

14.2.1 The European network

There exist now 12 ECRIN members.

14.2.2 Development of the ECRIN programme

The ECRIN project consists of **three steps**:

ECRIN-1

The first step (**ECRIN-RKP) (1**) was supported by a FP6 grant (health priority, 2004-2005) and resulted in a survey on clinical research in the participating countries, leading to compare the regulation, tools and practice, hence to identify the bottlenecks to multinational clinical research National reports, comparative analyses are available on the www.ecrin.org website.

ECRIN-2

Based on the outcome of the first programme, the ongoing second step (**ECRIN-TWG**), also funded by the FP6 (health priority, 2006-2008), consists of designing an infrastructure able to provide support to EU-wide clinical studies.
In this phase seven transnational working groups are in charge of defining guidelines, procedures and tools to support multinational studies, in any medical field, in any patient population, and for any type of study including medicinal trials, medical device or surgery trials, diagnostic or prognostic studies, genetic studies and studies on the mechanism of disease. These working groups cover:

1. interaction with ethics committees,
2. interaction with competent authorities and regulatory affairs,
3. adverse event reporting,
4. data management,
5. study monitoring,
6. quality assurance,
7. education

These tasks are supported by European correspondents embedded in the national network of each member state, and coordinated by a multinational Coordination Team.

ECRIN-3

Competence and know-how accumulated by the Coordination Team and European correspondents in each participating country will allow ECRIN, during the next step of its development, to provide integrated support to multinational studies during the third phase of

ECRIN, which is intended to start in 2008 as a **FP7 infrastructure** providing a set of 'one-stop shop' services to investigators and sponsors in multinational studies:

1 - support in the interaction with ethics committees
2 - support in the interaction with competent authorities and in regulatory affairs
3 - support in adverse event reporting
4 - support in drug dispensing
5 - support in the circulation of biological samples
6 - support in study monitoring
7 - data management.

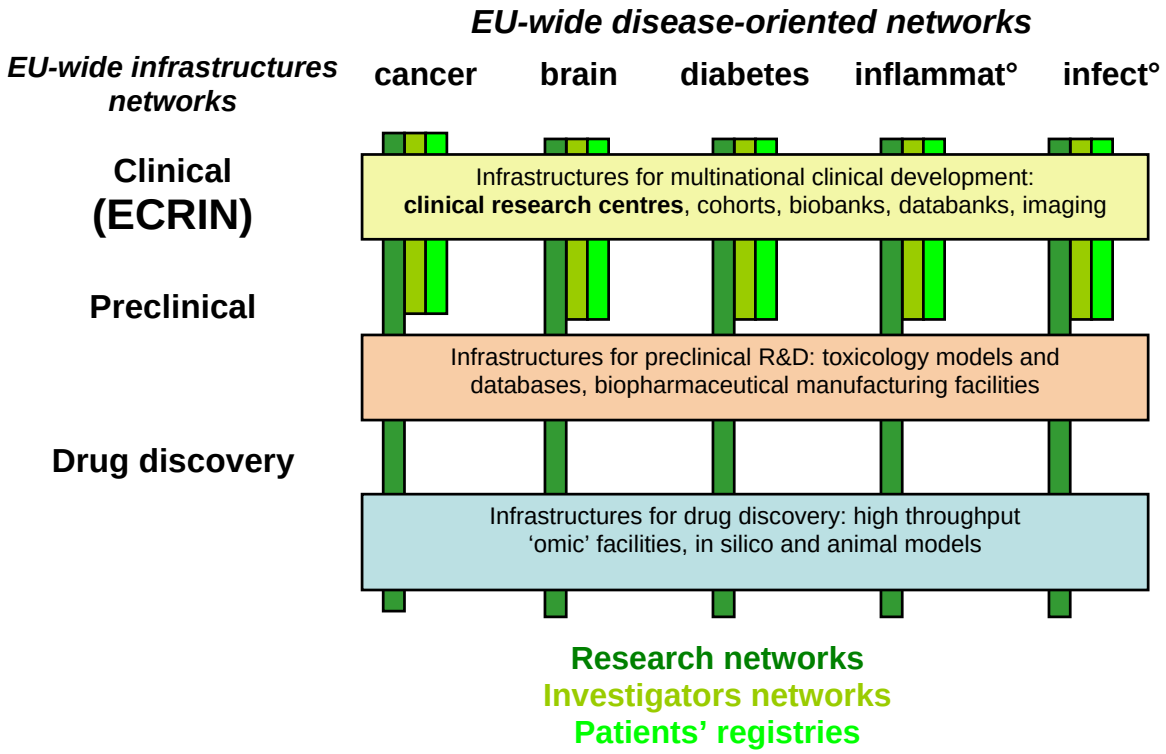
In addition, consulting will be provided to investigators and to sponsors before the clinical trial (including on regulation and ethics, centre selection, patients recruitment, cost evaluation, funding opportunities, insurance).

14.2.3 Potential applications

Users of this integrated and distributed EU clinical research infrastructure will be disease-oriented scientific networks, clinical research projects sponsored by public institutions, SMEs or pharmaceutical companies, and public-private partnership programs.

The FP7 **Innovative Medicines Initiative** (IMI) (www.imi-europe.org) project requires integrated infrastructures for drug development at the drug discovery, preclinical and clinical steps. As IMI will support public-private partnership research at the precompetitive step, clinical research will mainly focus on the identification and validation of biomarkers predictive for efficacy or safety, and on post-marketing studies.

Typically this precompetitive research will be sponsored by academic institutions, which currently lack the capacity to act as a sponsor for clinical studies at the EU level. This project is therefore critical for the implementation of the IMI strategic research agenda. In addition, tools provided by ECRIN will help connect the national **disease-oriented networks** across the borders, particularly in the fields covered by IMI (cancer, brain, metabolism-diabetes, inflammation, and infectious diseases).



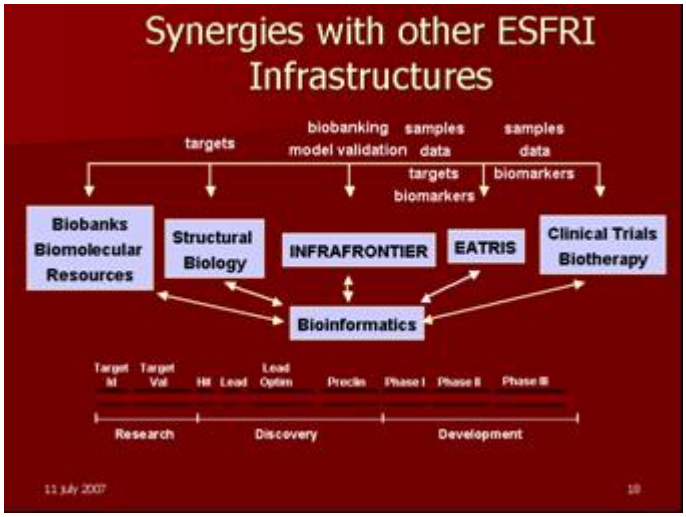
Europe-wide infrastructures and disease-oriented networks in drug development. From (2)

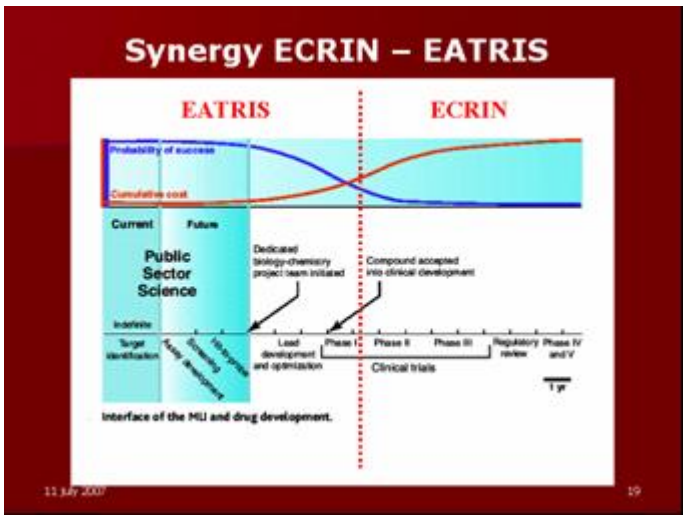
14.2.4 International Clinical Trials Day

ECRIN promotes the active participation of patients and citizens, and transparency in clinical research. For this purpose ECRIN has launched a yearly communication event (May 20, the International Clinical Trials Day) on the challenges raised by clinical research.

In May 2006, the International Clinical Trials Day resulted in forums with patients and citizens in various European cities, allowing discussion on transparency, on patients protection, information, education, and on their participation in clinical trials. In addition, a workshop and press conference in Brussels under the auspices of the European Commission celebrated this event.

14.3 Synergies with other ESFRI Infrastructures





14.4 Funding of clinical research

Public funding in France:

- to centres and networks : national (Ministry of health, INSERM) & local (University hospitals, regions)
- to clinical research projects : Ministry of health (PHRC), INCa, INSERM, ANRS, ANR (agence nationale de la recherche)

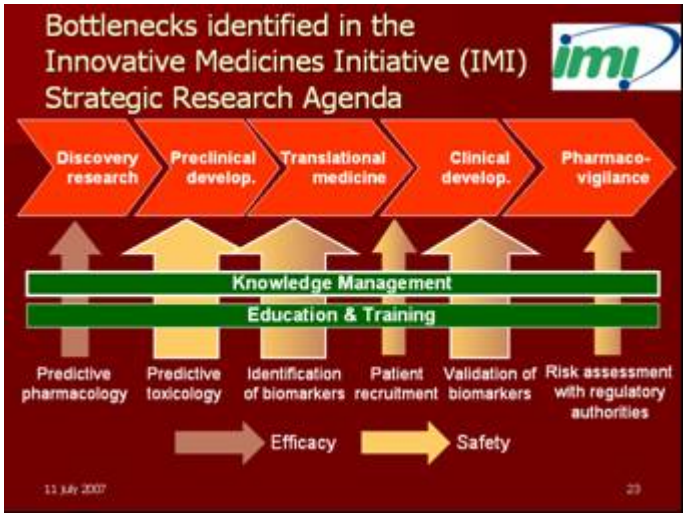
Public funding in the EU:

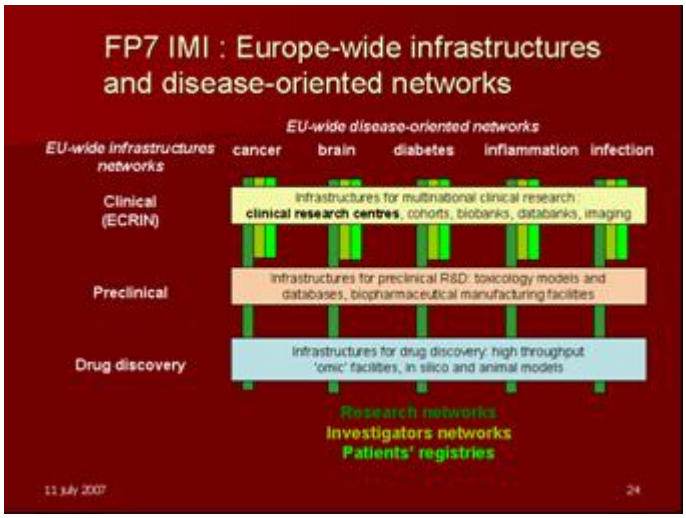
- National funding to clinical research projects : Italy, Germany, Spain, MRC
- National funding to the infrastructure : Germany, UKCRN, Wellcome Trust
- integration / coordination of national funding ?

EU funding:

- Health priority: public, public-private
- IMI

Bottlenecks identified in the Innovative Medicines Initiative (IMI) Strategic Research Agenda





14.5 Cost of clinical research

- Cost evaluation based on the protocol
- Charge for 'overhead' expenses compared to usual care
- Hospital stay, intervention (drug, surgery), investigation (imaging, biological assessment), human resources

Academic vs. industry cost evaluation

15. Biotherapy

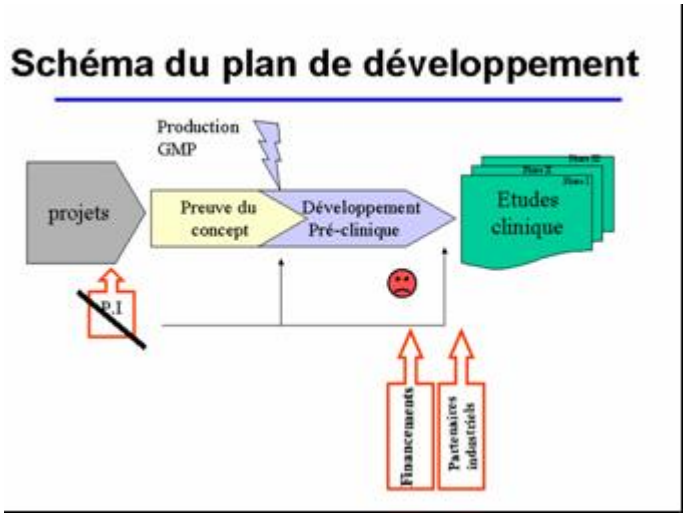
« Biothérapies » means:

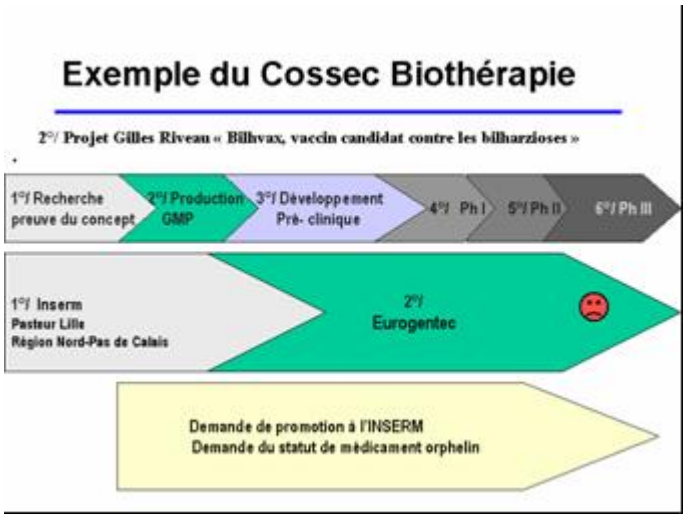
- Biomédicaments
- Thérapie cellulaire
- Thérapie génique

Thérapie cellulaire et génique

•Différences avec les médicaments:

- Thérapie cellulaire: produits « sur mesure » pour un patient donné.
- Pas le même shéma de développement clinique
- Peu d'industriels, pas d'AMM.





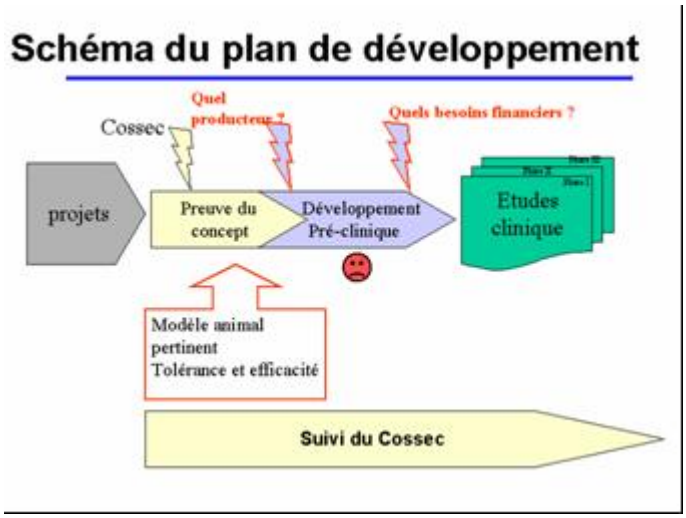
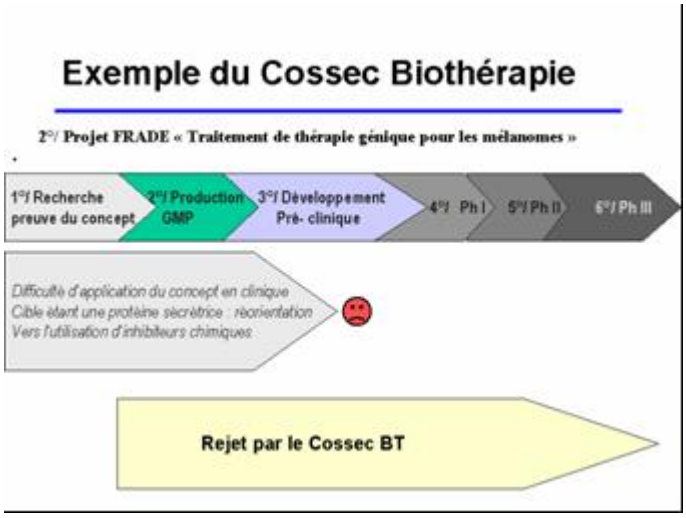


Schéma du plan de développement
Cossec
Quel producteur ?
Quels besoins financiers ?
projets
Preuve du concept
Développement Pré-clinique
Etudes clinique
Modèle animal pertinent
Tolérance et efficacité
Suivi du Cossec


Exemple du Cossec Biothérapie
2°/ Projet FRADE « Traitement de thérapie génique pour les mélanomes »
1°/ Recherche preuve du concept
2°/ Production GMP
3°/ Développement Pré- clinique
4°/ Ph I
5°/ Ph II
6°/ Ph III
Difficulté d'application du concept en clinique
Cible étant une protéine sécrétrice : réorientation
Vers l'utilisation d'inhibiteurs chimiques
Rejet par le Cossec BT

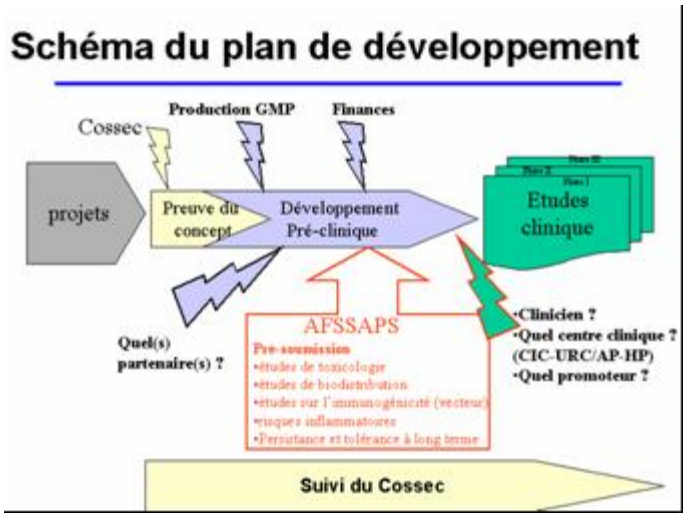


Schéma du plan de développement
Cossec
Production GMP
Finances
projets
Preuve du concept
Développement Pré-clinique
Etudes clinique
Quel(s) partenaire(s) ?
AFSSAPS
Pré-soumission
•études de toxicologie
•études de biodistribution
•études sur l'immunogénicité (vecteur)
•risques inflammatoires
•Persistance et tolérance à long terme
•Clinicien ?
•Quel centre clinique ? (CIC-URC/AP-HP)
•Quel promoteur ?
Suivi du Cossec

Exemples du Cossec Biothérapie

2°/ **Projet Jean-Michel Heard « Traitement de thérapie génique pour les maladies neurodégénératives Hurler et San Filipo »**

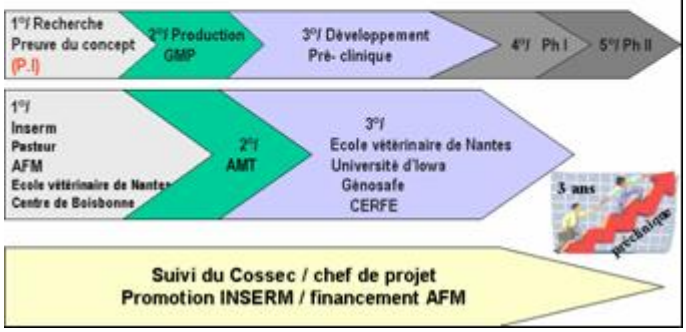
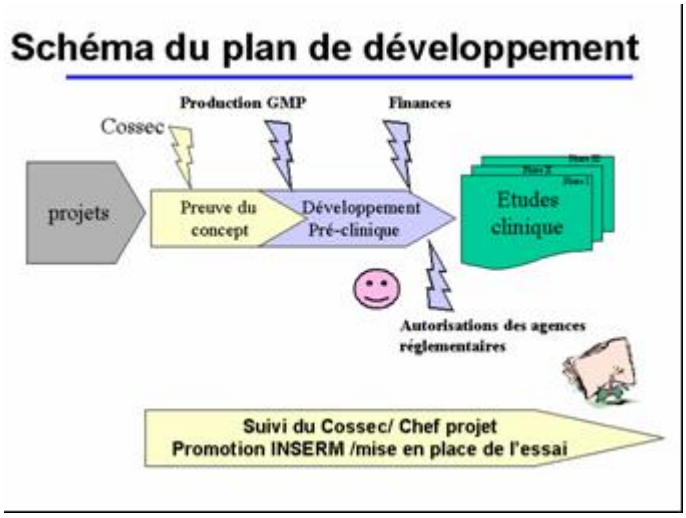
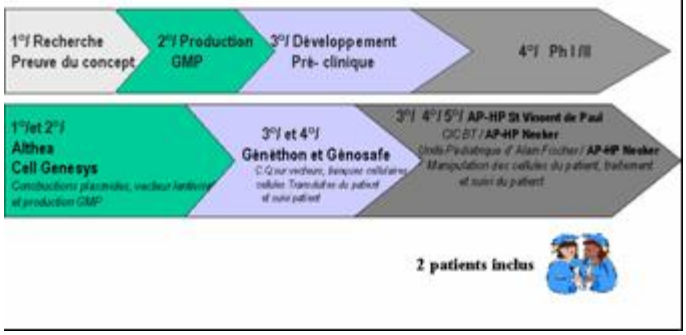


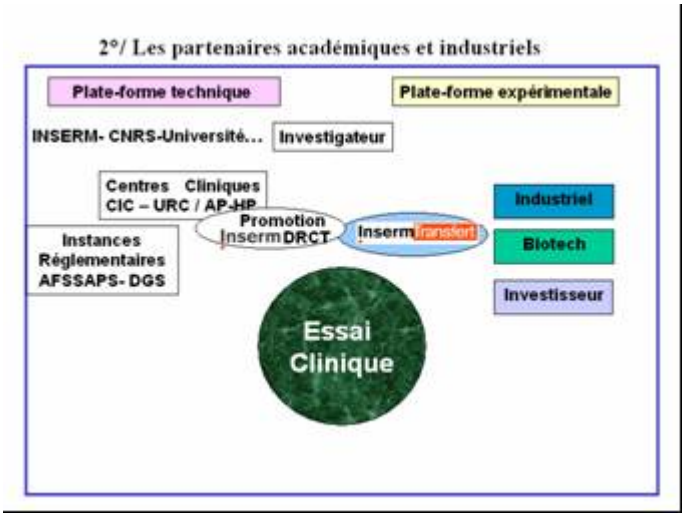
Schéma du plan de développement



Exemples du Cossec Biothérapie

1°/ **Projet Patrick Aubourg « Traitement de l'Adrénoleucodystrophie lié à l'X de l'enfant par transfert ex-vivo du gène ALD dans les cellules CD34+ » - Promoteur INSERM**





- Similitudes
  - Souhait de l'Afssaps d'encadrer : qualité, reproductibilité et sécurité.
  - Thérapie cellulaire et génique
- Thérapie par cellules génétiquement modifiées:
  - Phase de la preuve du concept
  - Ce ne sont pas des médicaments
  - Plus proche de la greffe d'organe et de tissus
- Thérapie génique in vivo :
  - Phase de la preuve du concept
  - Plus proche du médicament (macromolécules).

Schéma du plan de développement
Exemple du Cossec Biothérapie

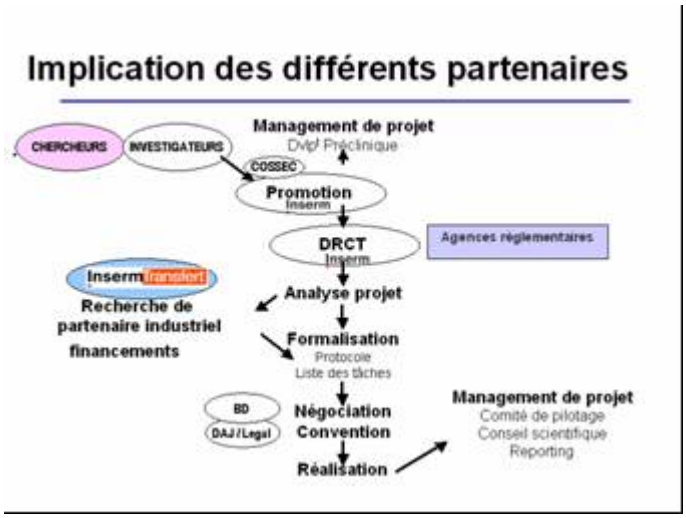


Schéma du plan de développement
Exemple du Cossec Biothérapie

Schéma du plan de développement

Exemples du Cossec Biothérapie

Schéma du plan de développement
Exemples du Cossec Biothérapie