UniversityHospital Zurich

Clinical Trials Center (CTC)

Planning Clinical Trials
Clinical Neuroscience FS2018

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Clinical Trials Center / Research and Education Office

UniversityHospital
Zurich

Clinical Neuroscience – Planning Clinical Trials

Clinical Trials Center

General remarks clinical trials and definitions

Historical development of drug regulation

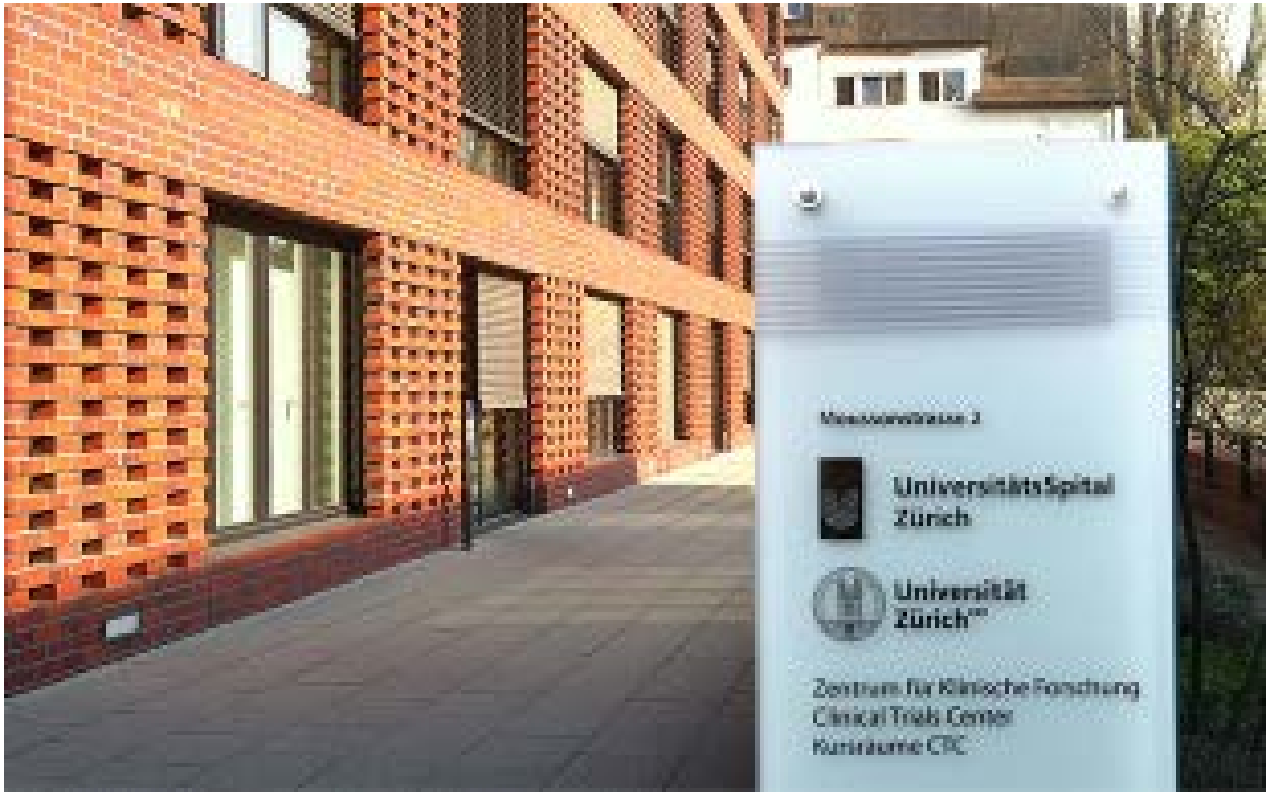
Regulatory aspects

ICH – Good Clinical Practice

Workshop Planning a Clinical Trial

Clinical Trials Center – CTC

Head: Prof. Dr. med. Gabriela Senti



Clinical Trials Center

Regulatory Affairs	Monitoring	Data Management	Clinical Research Ward	Quality Management	Education & Training
Consulting for: Study design	Site Management	Database Management System	Study Nurses / Study Coordinators CTC	Quality Management System (QMS)	Pharmaceutical Medicine SMA (Cat. A)
Submissions to Ethics Committee / Swissmedic	SOP & WI Training Support IIT Responsibilities	Electronic CRF Data import	Investigators CTC	Quality Assurance Audits	GCP Training
Insurances	Site recruitment	Data validation Plausibility check	Infrastructure	QM Consulting	Certificates of Advanced Studies UZH
Study documents	Monitoring	Data storage	Research collaborations	Platform for Clinical Research Guidelines	International Associations

Investigator Initiated Trials (IIT)
IIT with industry support
Industry-sponsored studies

Projects of the University Hospital and UZH Clinics

Projects of collaboration partners

SIWF ISFM FMH

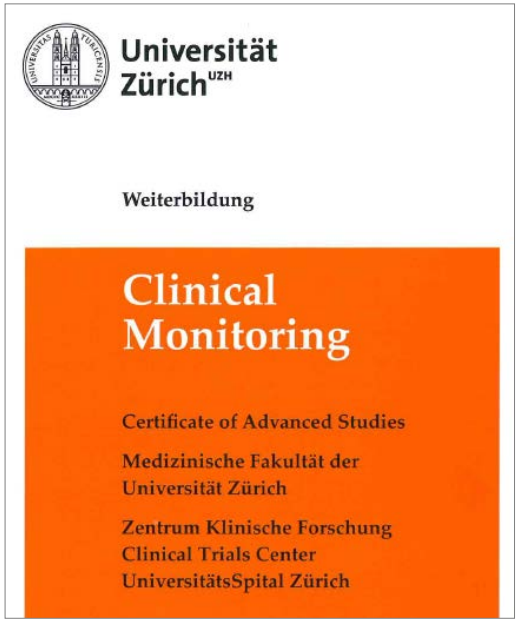
Facharzt für Pharmazeutische Medizin

sgpm asmp
Schweizerische Gesellschaft für Pharmazeutische Medizin
Association Suisse de Médecine Pharmaceutique

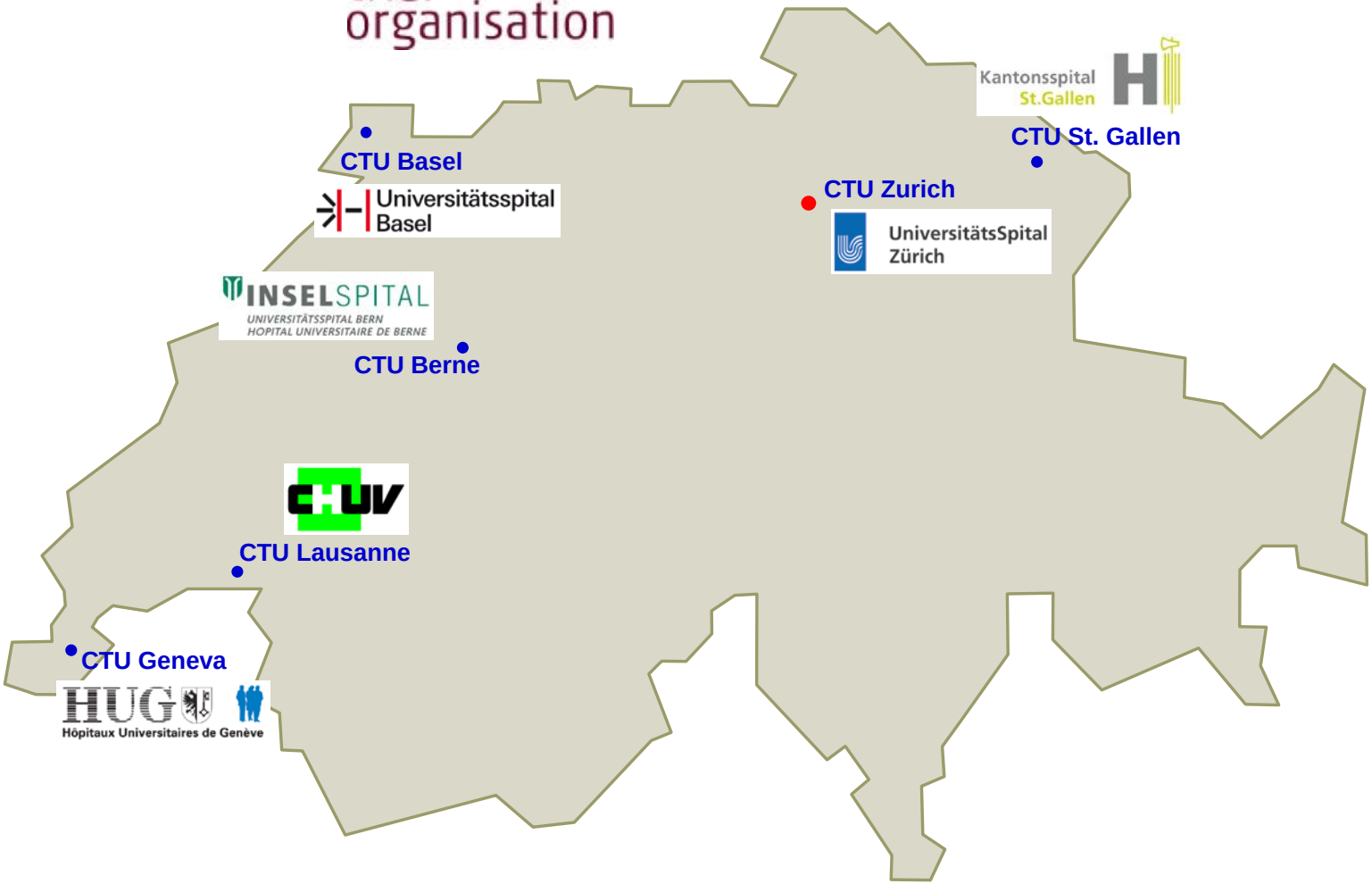
SwAPP | Swiss Association of Pharmaceutical Professionals

Certificate of Advanced Studies CAS

since 2017



swiss clinical trial organisation



International Clinical Trial Center Network - ICN

ICN International Clinical Trial Center Network

www.ICN-connect.org

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Clinical trial (HRA Art. 3)

Definition

→ Research project in which persons are prospectively assigned to a health-related intervention in order to investigate its effects on health or on the structure and function of the human body

Health-related intervention

→ Preventive, diagnostic, therapeutic, palliative or rehabilitative action / measure that is investigated in a clinical trial

Roles

Sponsor

- Individual/company/institution that takes responsibility for initiation, management, and financing

Investigator

- Person responsible for conduct of the clinical trial at a trial site

Principal Investigator (PI)

- If a trial is conducted by a team the responsible leader may be called PI (others: Sub-Investigators)

Types of clinical trials

Sponsor

- Pharmaceutical industry / Investigator Initiated Trials

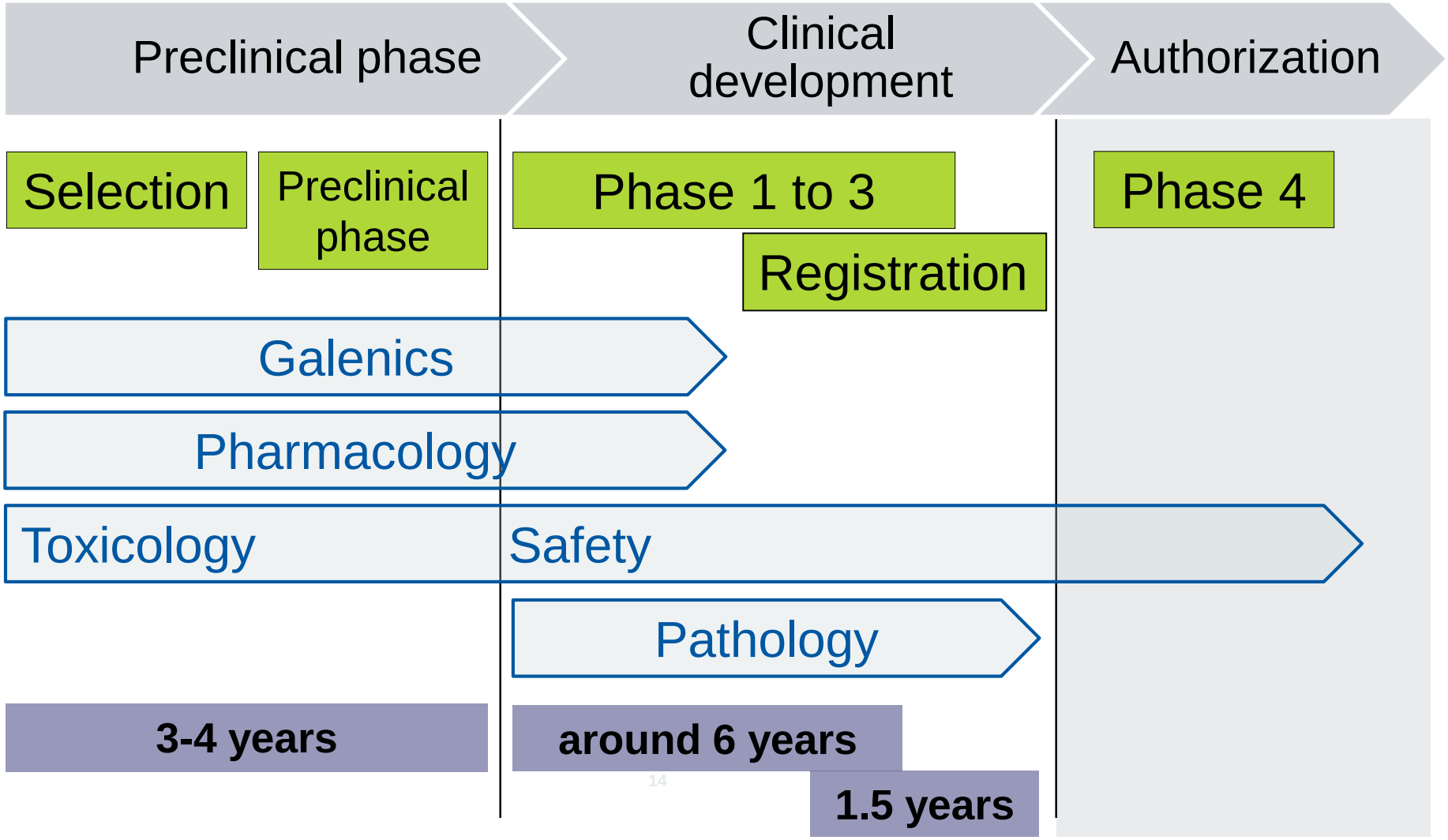
Types

- Trials with IMP / medical devices
- Epidemiological / observational trials (non-interventional)
- Clinical trials in other areas (e.g. surgery techniques)

Marketing authorization

- Process of reviewing and assessing a dossier by (competent) regulatory authority
- Assessment based on quality, efficacy and safety criteria
- Finalized by granting a marketing authorization (product license).
- Legislative framework defines the requirements necessary for application

Drug development



UniversityHospital Zurich

Phase I – III studies

	Phase I	Phase II	Phase III
	Non-therapeutic	Therapeutic-exploratory	Therapeutic-confirmatory
Goal	Safety Pharmacology Interactions	Dose-finding Efficacy Safety	Efficacy Safety Tolerability
Design / method	Open-label / controlled, single dose / repeated dose	Open-label / controlled, various designs	Randomized, controlled, blinded
Subjects	12 – 20 volunteers	20 – 200 homogeneous	200 – 10000 heterogeneous
Obs. period	Hours / days	Weeks / months	Months / years

Phase IV studies

	Phase IV
	Post-Authorization Post-Authorization Efficacy / Safety Study (PAES, PASS)
Goal	Efficacy (e.g. interactions with concomitant medication) Long-term safety (very rare side effects, < 1/10000)) Pharmaeconomics (marketing studies)
Design / method	often observational (non-clinical), IITs (only for authorized indications, doses and dosage forms)
Subjects	10000 – … heterogeneous
Obs.period	years

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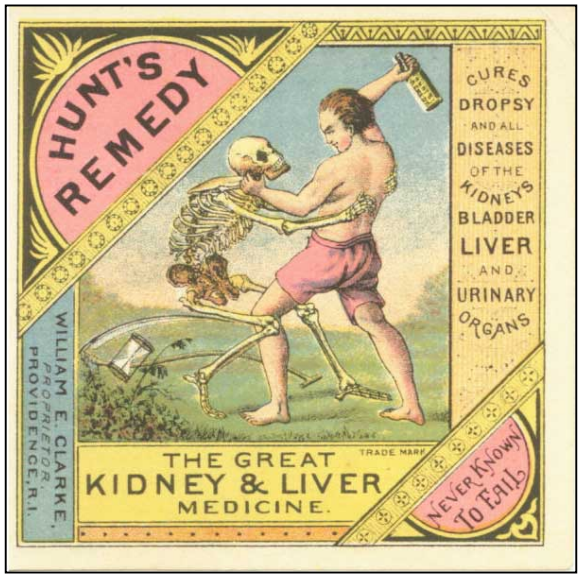
U.S. Food and Drug Legislation

Patent Medicine

- 17th -19th century



- 1906 – Pure Food and Drug Act
- 1931 – Founding of the Food and Drug Administration (FDA)

The Sulfanilamide Tragedy – 1937

Dr. Massengill's Elixir Sulfanilamide

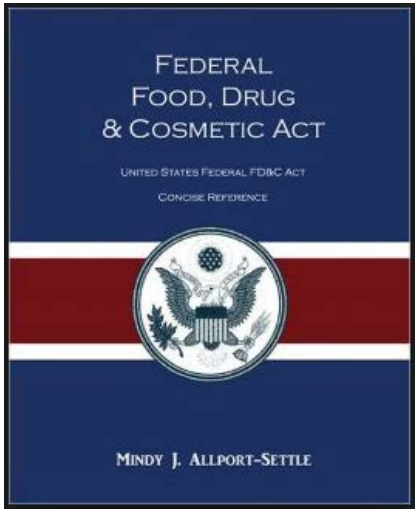
- Antibiotic syrup
- Use of diethylene glycol (antifreeze agent) as a solvent
- Consequence: 107 people died
- But no violation of existing laws (correct labeling !!!)

➢ Federal Food, Drug and Cosmetic Act

U.S. Food and Drug Legislation

Federal Food, Drug, and Cosmetic Act – 1938

- As a consequence of the sulfanilamide tragedy
- Marketing authorization by the FDA: NDA – «New Drug Application»
- Requires proof of safety of a medicinal product
- Demands directions for the use of medicinal products



Research abuse during Nazi time

Experiments on concentration camp prisoners

- Height experiments: simulation fall from 21,000 m
- Hypothermia experiments: immersion in ice water
- Seawater experiments: replacement for drinkable water
- Typhus fever experiments: vaccine trials
- Experiments on bone, muscle and nerve regeneration, bone marrow transplants
- Euthanasia program: "Eugenics"

➢ Nuremberg Doctors Trial (conviction of concentration camp doctors)

The Nuremberg Code – 1947

Basic principles for the protection of study subjects

- Voluntary participation (no persuasion / arbitrariness / compulsion)
- Results for the benefit of the society
- Avoid of unnecessary physical and mental suffering
- Scientifically qualified personnel
- Trials involving humans have to be based on animal tests and scientific knowledge

The Thalidomide Tragedy – 1958-1961

Thalidomide

- 1958: authorized in Germany for the treatment of sleep disorders and nausea in pregnant women
- Consequence: more than 10000 newborns worldwide with deformed extremities

- USA – 1962: Drug Amendment
- EU – 1965: Directive 65/65/EEC
- Germany – 1978: Pharmaceuticals Market Reorganisation Act

Drug Amendment – 1962 (Kefauver Harris Amendment)

Requirements for the authorization of new drugs in the US

- Proof of efficacy and safety in clinical trials
- Disclosure of benefit and risks
- Report of adverse drug reactions to the FDA (vigilance system)

Directive 65/65/EEC – 1965

First European pharmaceutical directive

- Uniform standards for the authorization of medicinal products within the EEC (European Economic Community)

Further unethical experiments in the USA with vulnerable persons

“Jewish Chronic Disease Hospital Study” - 1963

- Injection of living tumor cells in senile patients
- No information of the patients (ability to judge)

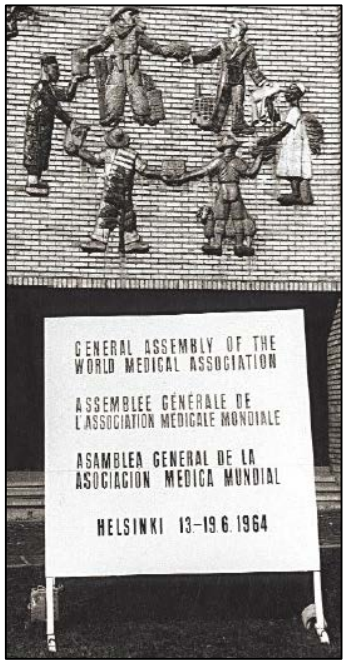
“Willowbrook State School Experiment” - 1963-1966

- Infection of mentally disabled children with Hepatitis A
- To study the antibody reaction

Declaration of Helsinki – 1964

Purpose

- Key document detailing ethical principles for medical research involving humans
- Adaptation of the Nuremberg Code to the current research situation
- Authors: World Medical Association (WMA)
- Last revision: 2013 (Fortaleza, Brasil)



Declaration of Helsinki – 1964

Principles

- Integrity of the study subjects
- Informed and voluntary consent to participation
- Positive benefit-risk ratio
- Comprehensive written research protocol
- Prior assessment by an independent Ethics Committee
- Registration in a publicly accessible database
- Special conditions for research involving vulnerable persons
- Conditions for the use of placebo
- Also publication of negative results

Tuskegee study – 1932-1973 (USA)

Syphilis study

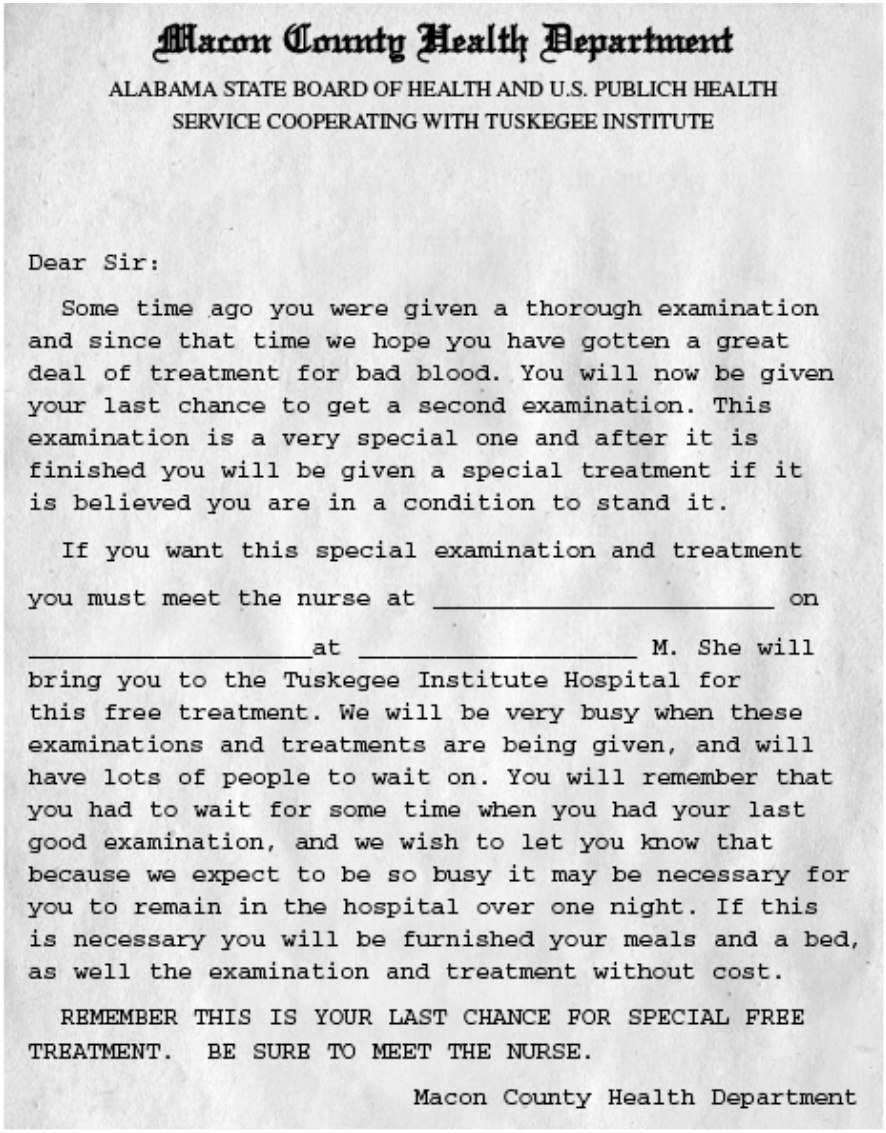
- Assessment of the natural course of the disease
- Trial of the "United States Public Health Service"
- Test subjects: exclusively Afro-Americans from a poor background

Tuskegee study

Deficiencies

- False Advertising (e.g. with lumbar puncture and blood samples as so-called "free treatment“)
- No declaration of informed consent
- No therapeutic benefit
- Intentional deprivation of a potential therapy (treatment with penicillin available from 1947 onwards)
- Many deaths due to disease symptoms

Tuskegee study



Macon County Health Department

ALABAMA STATE BOARD OF HEALTH AND U.S. PUBLICH HEALTH SERVICE COOPERATING WITH TUSKEGEE INSTITUTE

Dear Sir:

Some time ago you were given a thorough examination and since that time we hope you have gotten a great deal of treatment for bad blood. You will now be given your last chance to get a second examination. This examination is a very special one and after it is finished you will be given a special treatment if it is believed you are in a condition to stand it.

If you want this special examination and treatment you must meet the nurse at _____ on _____at _____ M. She will bring you to the Tuskegee Institute Hospital for this free treatment. We will be very busy when these examinations and treatments are being given, and will have lots of people to wait on. You will remember that you had to wait for some time when you had your last good examination, and we wish to let you know that because we expect to be so busy it may be necessary for you to remain in the hospital over one night. If this is necessary you will be furnished your meals and a bed, as well the examination and treatment without cost.

REMEMBER THIS IS YOUR LAST CHANCE FOR SPECIAL FREE TREATMENT. BE SURE TO MEET THE NURSE.

Macon County Health Department

This letter is reproduced from an educational website at the University of Illinois's Poynter Center for the Study of Ethics and American Institutions (http://poynter.indiana.edu/sas/lb/facts.html.)

Tuskegee study

Disclosure

- Uncovering in a newspaper article in 1972 resulted in termination of the study

- 1974 National Research Act

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

National Research Act – 1974

Purpose

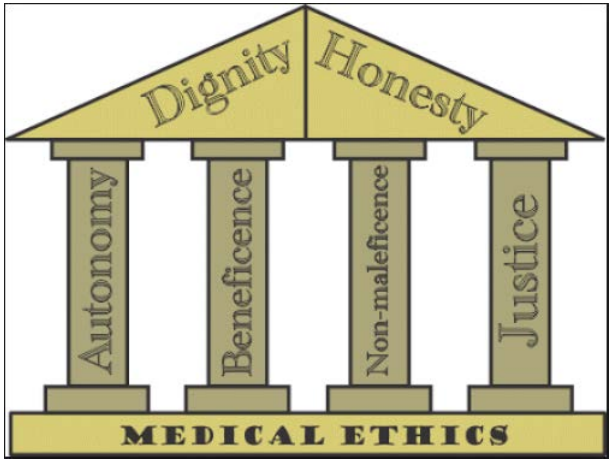
- Informed consent becomes mandatory
- Research projects have to be reviewed and given a positive vote by Ethics Committees (Institutional Review Boards, IRBs)

➢ Establishment of the «National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research» (Task: Identification of the basic ethical principles for biomedical research)

Basic principles of medical ethics – 1977

«Classical principles of biomedical ethics»

- Respect for Autonomy: free power of choice
- Beneficence: welfare
- Non-maleficence: avoiding all harm
- Justice: fair distribution of healthcare services



History of GCP

UZH, 01.12.2003

Untersuchungs- Ergebnisse zu den Impfstudien der Dermatologischen Universitätsklinik

Das international beachtete Forschungsprojekt der Dermatologischen Klinik des UniversitätsSpitals Zürich zur Entwicklung einer Impftherapie gegen den schwarzen Hautkrebs steht seit längerem in der Diskussion. Die nach Sistierung der Impfstudien Anfang Jahr durch Universitätsleitung und Spitalleitung eingeleiteten Abklärungen sind abgeschlossen, die Ergebnisse liegen vor. Erste Massnahmen wurden bereits getroffen, weitere sind geplant, um die Qualität der klinischen Forschung laufend zu erhöhen.

Melanoma study, USZ 2003

- Insufficient description of treatments, assessments and methods
- Study treatment of patients outside the study
- Missing Informed Consent Forms
- Non-GMP conform study drug
- Healing promises
- Missing CRFs

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USA / Europe

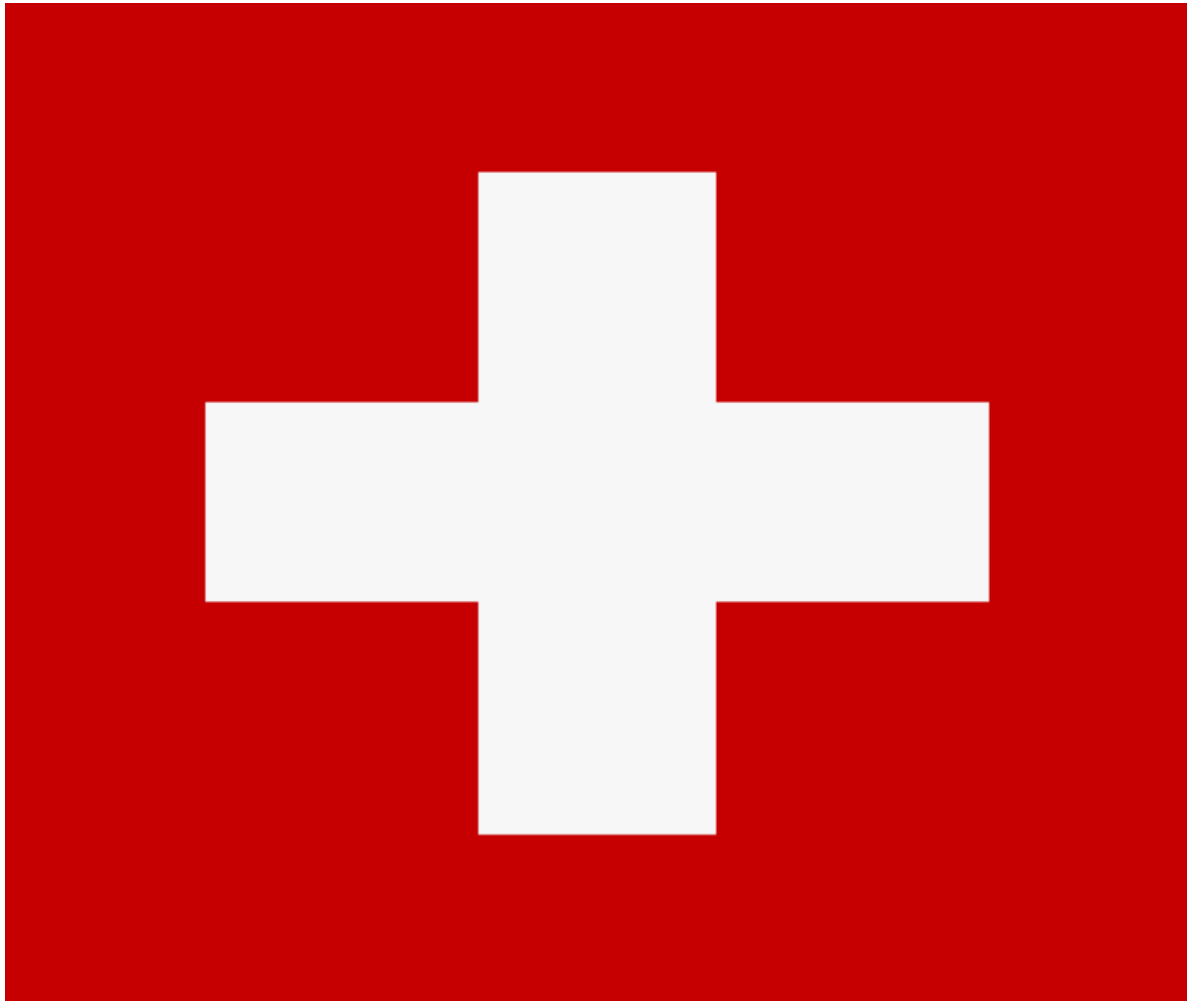
USA – Food and Drug Administration (FDA)

- Belongs to the Department of Health and Human Services
- Center for Drug Evaluation and Research (CDER)

Europe – European Agency for the Evaluation of Medicinal Products (EMA)

- Committee for Medicinal Products for Human Use (CHMP)

Switzerland



swissmedic

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

News & Updates | Legal matters, standards | Contact | Support & Help

Human medicines | Veterinary medicines | Complementary & herbal medicines | Medical devices | Services & lists | About us

Close

Clinical trials
Clinical trials on medicinal products

Licensing
Authorisations
Special authorisation
Microbiological Laboratories

Authorisations
Information
Guidance document
Human Medicines Expert Committee (HMEC)
The Swissmedic publication platform
Authorised medicinal products with new active substances

Special categories
Authorised narcotics
Blood and blood components
Medicines for children
Transplant products

Market surveillance
Pharmacovigilance
Focus topics
Risk Management (PSURs, PV Planning)
Healthcare Professional Communications
Haemovigilance
Quality defects and batch recalls
Out-of-Stock
Medicinal products from the Internet
Advertising of medicinal products

Human medicines

Medicinal products may only be distributed in Switzerland if they are authorised by Swissmedic. The Swiss Agency for Therapeutic Products, is involved in the entire life cycle of a medicinal products because of its mandated areas of responsibility in the sectors of licensing and the authorisation and monitoring of medicinal products.

Direct links
- Authorized medicines
- Documents and Forms
- Medicinal product information
- eGov Services
- Submissions

Swissmedic

Core competencies

- Authorisation of medicinal products
- Licences for manufacturing and wholesale, and inspections
- Market monitoring of medicinal products and medical devices
- Establishing standards
- Clinical trials and laboratory testing regarding the quality of medicines
- Information

Swiss regulations

Federal Act on Medicinal Products and Medical Devices
(Therapeutic Products Act, TPA)

of 15 December 2000 (Status as of 1 January 2014)

Federal Act
on Research involving Human Beings
(Human Research Act, HRA)

of 30 September 2011 (Status as of 1 January 2014)

Purpose of the HRA (Art. 1)

For research involving human beings

- to protect the dignity, privacy and health
- to create favourable conditions
- to help to ensure the quality
- to ensure the transparency

Scope of the HRA (Art. 2 and 3)

Research

Method driven search for generalizable knowledge concerning

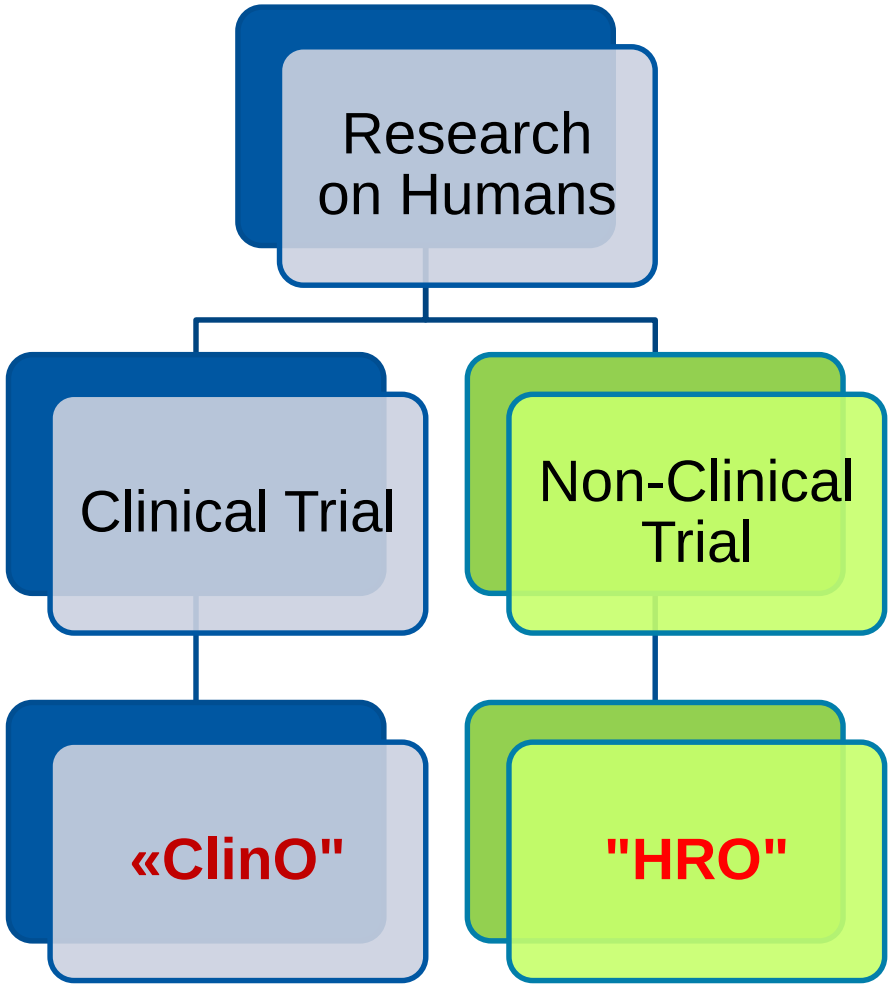
- human diseases (clinical trials with e.g. medicinal products, psychology, surgery, transplantation, nursing etc.) and
- the structure and function of the human body (anatomy, physiology, genetics etc.)

Research objects (Art. 2)

The HRA applies for research with:

- Persons
- Health-related personal data
- Biological material
- Deceased persons
- Embryos and foetuses

Ordinances of the HRA

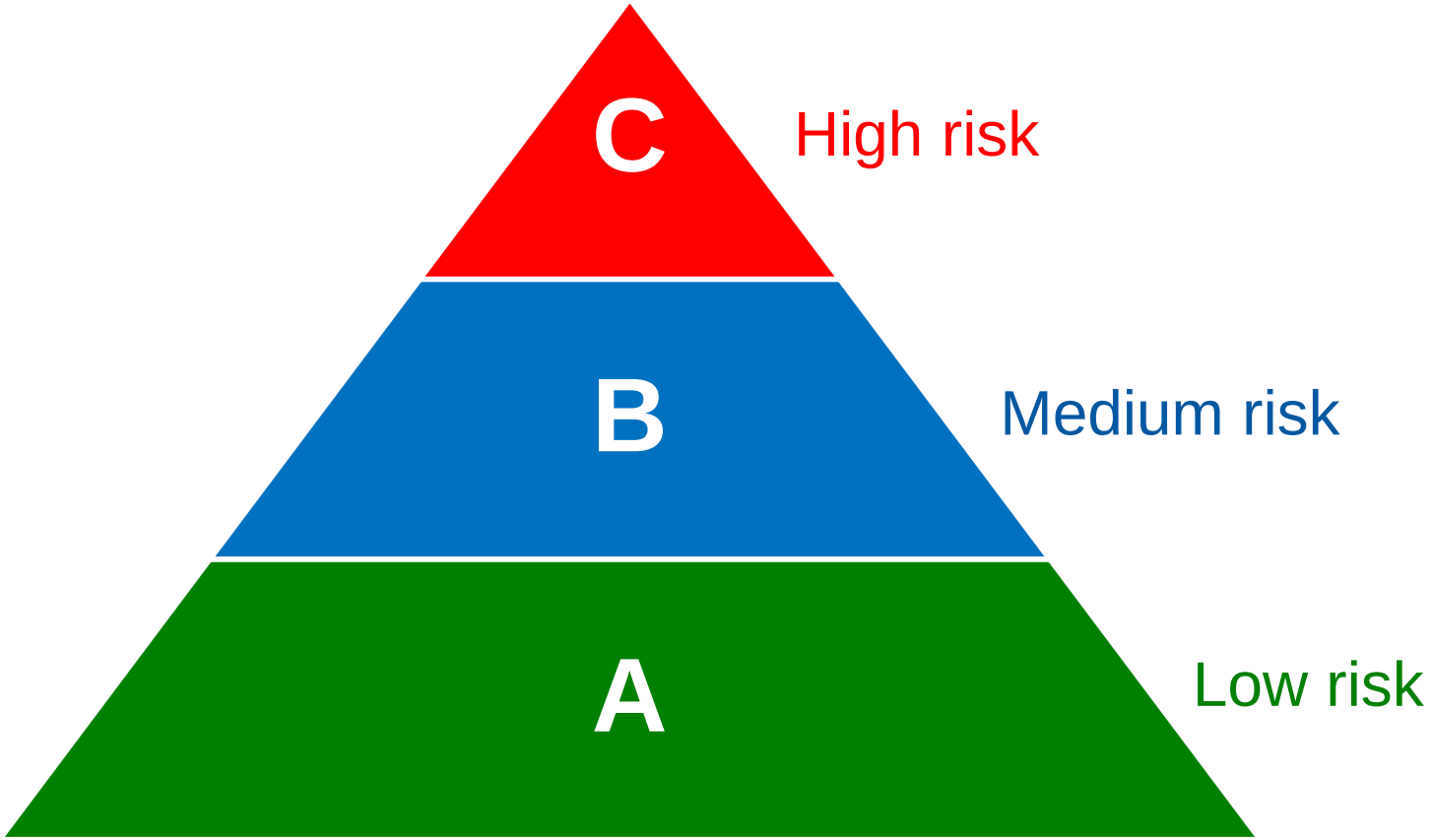


Health-related Intervention

Personal data / Biological material

Risk-based categorization of research

Risk Categorization



Risk-based categorization – Drugs and transplantation products

A	B	C
• Swissmedic approved • Use according to prescribing information • deviation from prescribing information according to predefined criteria	• Swissmedic approved • deviation from prescribing information outside of predefined criteria	• No Swissmedic approval

Regulatory consequences – Drugs and transplantion products

A	B	C
• Approval by Ethical Committee • Simplified submission document • Simplified Safety Reporting • Reduced indemnification obligation	• Approval by Ethical Committee and Swissmedic • Simplified submission document • Simplified Safety Reporting	• Approval by Ethical Committee and Swissmedic

Risk-based categorization – Research projects

A

- Measures for sampling of biological material or collection of health-related personal data from persons entailing only minimal risks and burdens

B

- Measures for sampling of biological material or collection of health-related personal data from persons entailing more than minimal risks and burden

Which research needs approval?

Approval by

- Ethical Committee and
- Swissmedic and/or FOPH*
  → depending on risk category / *irradiation burden

Required for

- All research projects on humans
- Re-use of biological specimens and health-related personal data

Division of tasks between Ethical Committees and Swissmedic

Swissmedic

Safety of the medicinal product

Risk assessment

Composition and Quality

…

→ **GMP** compliance

EC

Categorisation

Scientific relevance and methodology

Risk-benefit ratio

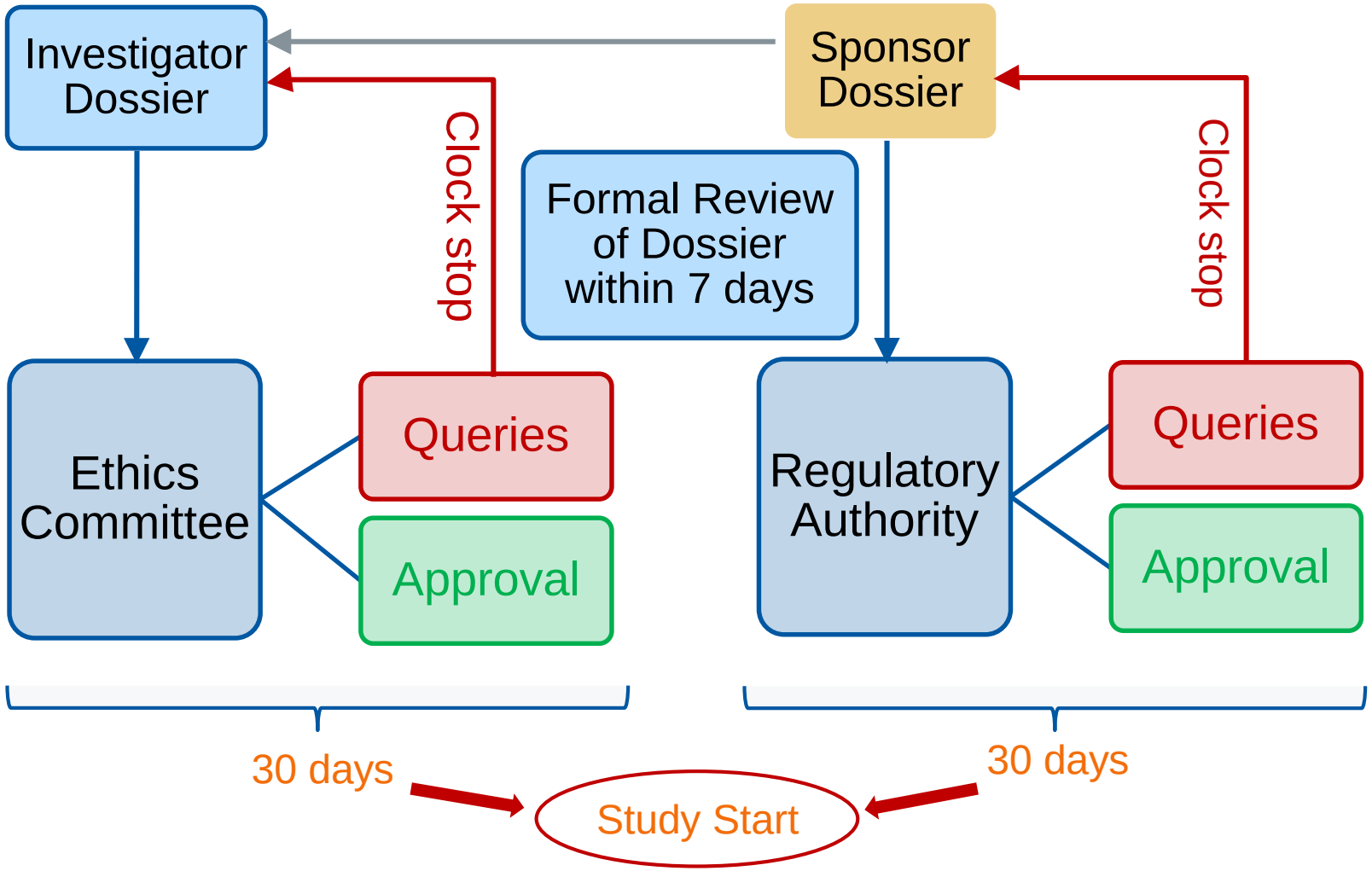
Participant selection criteria

PI/IC procedeures

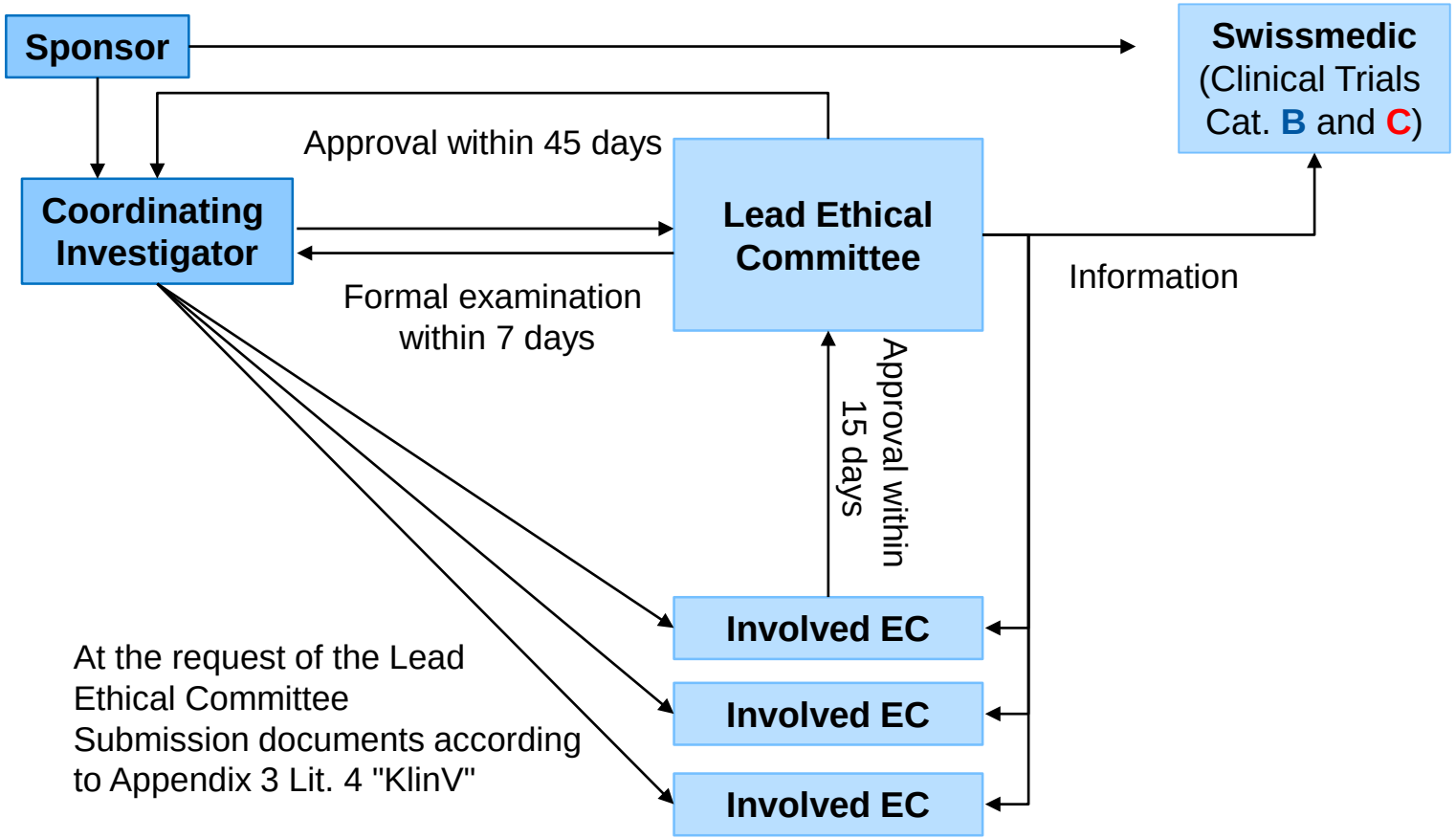
…

→ **GCP** compliance

Approval process



Multicenter Clinical Trials



Registration of Clinical Trials

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

World Health Organization

Primary registries

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ICH – Composition

Europa	European Comission (EC)	European Federation of Pharmaceutical Industries and Associations (EFPIA)
Japan	Ministry of Health, Labour and Welfare of Japan (MHLW)	Japan Pharmaceutical Manufacturers Association (JPMA)
USA	Food and Drug Administration (FDA)	Pharmaceutical Research and Manufacturers of America (PhRMA)
Canada	Health Canada	
Switzerland	Swissmedic	
Brasil	Agência Nacional de Vigilância Sanitária (ANVISA)	
South Korea	Ministry of Food and Drug Safety (MFDS)	
		The International Generic and Biosimilar Medicines Association (IGBA)
		The World Self-Medication Industry (WSMI)
		The Biotechnology Innovation Organisation (BIO)

2015

2016

Members with observer status – 22 institutions

Representatives on all continents – Examples

- World Health Organisation (WHO)
- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)
- Council for International Organizations of Medical Sciences (CIOMS)
- The Medicine Control Council (MCC, South Africa)
- Therapeutic Goods Administration (TGA, Australia)

Goals of the ICH

Harmonization of the requirements concerning drug trials
and
authorization documents

Efficient research and development processes:
prevention of repetitions,
optimal utilization of resources

More rapid access of patients to new medicinal products
while upholding the standards for
safety, quality and efficacy

Topics of the ICH guidelines

Quality

Chemical and pharmaceutical quality control

Examples:

- Q1 Stability Testing
- Q3 Impurity Testing
- **Q7 Good Manufacturing Practice (GMP)**
- Q9 Quality Risk Management
- Q10 Pharmaceutical Quality System

Topics of the ICH guidelines

Quality	Safety
Chemical and pharmaceutical quality control	Preclinical trials in vitro / in vivo
Examples: ▪ Q1 Stability Testing ▪ Q3 Impurity Testing ▪ **Q7 Good Manufacturing Practice (GMP)** ▪ Q9 Quality Risk Management ▪ Q10 Pharmaceutical Quality System	Examples: ▪ S1 Carcinogenicity Testing ▪ S2 Genotoxicity Testing ▪ S5 Reproductive Toxicology

Topics of the ICH guidelines

Quality 	Safety 	Efficacy 
Chemical and pharmaceutical quality control	Preclinical trials in vitro / in vivo	Conduct of clinical trials
<u>Examples:</u> ▪ Q1 Stability Testing ▪ Q3 Impurity Testing ▪ **Q7 Good Manufacturing Practice (GMP)** ▪ Q9 Quality Risk Management ▪ Q10 Pharmaceutical Quality System	<u>Examples:</u> ▪ S1 Carcinogenicity Testing ▪ S2 Genotoxicity Testing ▪ S5 Reproductive Toxicology	<u>Examples:</u> ▪ E2A Clinical Safety Data Management ▪ E3 Clinical Study Reports ▪ **E6 Good Clinical Practice (GCP)** ▪ E8 General Considerations for Clinical Trials ▪ E9 Statistical Principles for Clinical Trials

Topics of the ICH guidelines

Quality 	Safety 	Efficacy 	Multidisciplinary 
Chemical and pharmaceutical quality control	Preclinical trials in vitro / in vivo	Conduct of clinical trials	Topics, that do not match the Q, S, E category
<u>Examples:</u> ▪ Q1 Stability Testing ▪ Q3 Impurity Testing ▪ Q7 Good Manufacturing Practice (GMP) ▪ Q9 Quality Risk Management ▪ Q10 Pharmaceutical Quality System	<u>Examples:</u> ▪ S1 Carcinogenicity Testing ▪ S2 Genotoxicity Testing ▪ S5 Reproductive Toxicology	<u>Examples:</u> ▪ E2A Clinical Safety Data Management ▪ E3 Clinical Study Reports ▪ E6 Good Clinical Practice (GCP) ▪ E8 General Considerations for Clinical Trials ▪ E9 Statistical Principles for Clinical Trials	<u>Examples:</u> ▪ M1 MedDRA Terminology (Medical Dictionary for Regulatory Activities Terminology) ▪ M4 Organisation of the Common Technical Document (CTD)

Good Clinical Practice – GCP

What is GCP?

- International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Good Clinical Practice – GCP

What is GCP?

- International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Compliance provides assurance that

- rights, safety and well-being of trial subjects are protected
- consistent with the principles of the Declaration of Helsinki,
- the clinical trial data are credible

Responsibilities (ICH-GCP)

Sponsor

- Initiation, management and/or financing of the clinical study
- Selection of the investigational sites
- Study oversight
- Data integrity
- Reporting of to regulatory authorities
- IMP: production, shipment, packaging, labelling, specifications
- Quality control and assurance

Responsibilities (ICH-GCP)

Investigator

- Proper conduct of the study at the investigational site according to the protocol and documentation
- Recourses (team, training, …)
- Obtaining approval of IEC before study start
- Obtaining informed consent of study subjects
- All study-specific medicinal decisions
- Correct handling of the IMP, drug accountability
- Safety reporting

Responsibilities (ICH-GCP)

Ethical Committees

- Ensure the protection of the rights, safety and well-being of the study subjects
- Evaluation of a clinical study within a reasonable time
- Evaluation of the investigator’s qualification
- Continuous supervision of the ongoing clinical studies

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