Medizinische Universität Graz

Dr.sci.med./PhD - Programme

Scientific Basics

Ethics Committee

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Agenda

- Subjects of medical research
- EU-Directives
- Trials on medicinal products (drugs)
  - Austrian Drug Law, definitions, ICH-GCP, prerequisites
- Trials on medical devices
  - Austrian Medical Devices Law, definitions, prerequisites, "essential requirements"
- Other medical research
- International Standards
  - Declaration of Helsinki, CIOMS-Guidelines, WHO-Guidelines
- Ethics Committee
  - Composition, duties and responsibilities, elements of the assessment, development of Ethics Committees in Austria

Medical Research – Subjects

- **Medicinal products (drugs)**
  Drug Law ("Arzneimittelgesetz", AMG), ICH-GCP-Guideline
  → comprehensive regulations
- **Medical devices**
  Law on Medical Devices ("Medizinproduktegesetz," MPG),
  EN-ISO-Norm 14155 → comprehensive regulations
- **New medical methods**
  Federal Hospital Act ("Kranken- und Kuranstaltengesetz", KAKuG) – not directly applicable → laws of the Federal States
  → Requirement to seek the opinion of an Ethics Committee
  Ethical Standards
- **Applied medical research in human subjects**
  University Act ("Universitätsgesetz", UG 2002)
  → Requirement to seek the opinion of an Ethics Committee
  Ethical Standards

Relevant EU-Directives

- **Directive 2001/20/EC "Clinical Trials Directive"**
  Harmonisation: Clinical trials on medicinal products
  One Ethics Committee opinion per member state for multicentre trials
  → implemented in the Drug Law (AMG)
- **Directive 2005/28/EC "Good Clinical Practice Directive"**
  Complement to the 2001/20/EC: "Good Clinical Practice"-Guidelines, manufacturing, importing, inspections, etc.
  → implemented in the Drug Law (AMG), decrees in preparation
- **Directive 90/385/EEC "Active Implantable Devices"***
  Directive 93/42/EEC "Medical Devices"*
  Directive 98/79/EC "In-Vitro Diagnostics"
  * Amended by the Directive 2007/47/EC
  Comprehensive regulations for medical devices, CE-marking, free movement of goods, clinical evaluation / clinical investigation, vigilance system, etc. → implemented in the Law on Medical Devices (MPG) (revision overdue but still pending)

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Legal Status of EU-Documents

- **Regulations ("*Verordnungen*")**
  - apply directly to each member state, overrule national law
- **Directives (*"Richtlinien"*)**
  - binding for each member state regarding the objectives, to be implemented in national law
  - If not implemented on the due date ➔ directly applicable law
- **Guidelines ("*Leitlinien*")**
  - not mandatory, deviations – e.g. due to scientific or technological progress/improvements – possible ➔ justification to be documented
- **Guidance Documents ("*Anleitungen*")**
  - Explanations on Directives and hints for the implementation, may become binding if referenced – e.g. in laws

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International Standards - ICH GCP

International Conference on Harmonization (ICH)

ICH Topic E 6 Guideline for Good Clinical Practice

Step 5, Consolidated Guideline 1.5.96

NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE

(CPMP/ICH/135/95) – EU: **3CC1a**

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

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ICH GCP

INTRODUCTION (continued)

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ICH GCP – Chapters

1. **GLOSSARY**
2. **THE PRINCIPLES OF ICH GCP**
3. **INSTITUTIONAL REVIEW BOARD / INDEPENDENT ETHICS COMMITTEE (IRB/IEC)**
4. **INVESTIGATOR**
5. **SPONSOR**
6. **CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)**
7. **INVESTIGATOR'S BROCHURE**
8. **ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL**

ICH GCP – Principles

2. THE PRINCIPLES OF ICH GCP

2.1 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).

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (EC) approval/favourable opinion.

ICH-GCP – Structure of a trial protocol

1. General Information
2. Background Information
3. Trial Objectives and Purpose
4. Trial Design
5. Selection and Withdrawal of Subjects
6. Treatment of Subjects
7. Assessment of Efficacy
8. Assessment of Safety
9. Statistics
10. Direct Access to Source Data/Documents
11. Quality Control and Quality Assurance
12. Ethics
13. Data Handling and Record Keeping
14. Financing and Insurance
15. Publication Policy
16. Supplements

ICH GCP – Independent Ethics Committee

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

- trial protocol(s)/amendment(s)
- written informed consent form(s) and consent form updates that the investigator proposes for use in the trial
- subject recruitment procedures (e.g. advertisements)
- written information to be provided to subjects

ICH GCP – Independent Ethics Committee

3.1.2 The IRB/IEC should obtain the following documents (continued):

- Investigator's Brochure (IB)
- available safety information
- information about payments and compensation available to subjects
- the investigator's current curriculum vitae and/or other documentation evidencing qualifications

  and
- any other documents that the IRB/IEC may need to fulfil its responsibilities.

ICH GCP – Independent Ethics Committee

3.1.2 (continued):

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval/negative opinion;

and

- termination/suspension of any prior approval/favourable opinion.

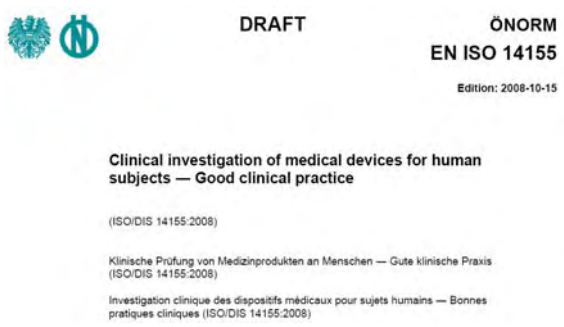
Norm EN ISO 14155-1

- **Clinical investigation of medical devices for human subjects**
  Part 1: General requirements (ISO 14155-1:2003)
  - Justification of the clinical investigation
  - Ethical considerations
  - General requirements
  - Documentation
  - Sponsor
  - Monitor
  - Clinical investigator
  - Final report
  - Appendices
    - Procedure for the bibliography
    - Notification of the Ethics Committee
    - Structure of the final report

Norm EN ISO 14155-2

- **Clinical investigation of medical devices for human subjects**
  Part 2: Clinical investigation plan (ISO 14155-2:2003)
  - Identification and description of the medical device to be investigated
  - Preliminary investigations and justification of the study
  - Objectives of the Clinical Investigation
  - Design of the Clinical Investigation
  - Statistical considerations
  - Deviations from and amendments to the Clinical Investigation Plan
  - Adverse events
  - Early termination or suspension of the investigation
  - Publication policy
  - Case report forms

ÖNORM EN ISO 14155:2008 10 15 – Draft


DRAFT

ÖNORM
EN ISO 14155

Edition: 2008-10-15

Clinical investigation of medical devices for human subjects — Good clinical practice

(ISO/DIS 14155:2008)

Klinische Prüfung von Medizinprodukten an Menschen — Gute klinische Praxis (ISO/DIS 14155:2008)

Investigation clinique des dispositifs médicaux pour sujets humains — Bonnes pratiques cliniques (ISO/DIS 14155:2008)

Complete revision, largely approximated to the ICH-GCP

Definition – Medicinal Product (§ 1 AMG)

- (1) **"Medicinal Products"** mean substances or preparations of substances, which, when applied to, or in, the human or animal body, have in the common opinion the purpose, or are due to the modality of the placing on the market meant to
  - heal, alleviate, prevent, or detect diseases, suffering, bodily injuries, or pathological disturbances,
  - identify the composition, the status, or the functions of the body or the psychic condition,
  - replace active substances or body fluids produced by the human or animal body,
  - hold off, eliminate, or disarm pathogens, parasites, or exogenous substances, or
  - manipulate the composition, the status, or the functions of the body or the psychic condition.

Definition – Medicinal Product (§ 1 AMG)

- (2) As medicinal products are considered
  - items, which contain a medicinal product, or on which a medicinal product is superimposed, and that are intended to be applied on, or in, the human or animal body, and
  - substances or preparations of substances, which do not possess the attributes of section 1, inasmuch as they are meant for the manufacturing of medicinal products.
- (3) No medicinal products are
  - foods according to article 2 clause 1 and 2 of the regulation (EC) No. 178/2002, inasmuch as they do not have in the common opinion the purpose, or are not due to the modality of the placing on the market meant to, fulfil the purpose of section1, number 1 to 4,
  - …
  - …

Definition – Medicinal Product (§ 1 AMG) org.

- (1) **"Arzneimittel"** sind Stoffe oder Zubereitungen aus Stoffen, die nach der allgemeinen Verkehrsauffassung dazu dienen oder nach Art und Form des Inverkehrbringens dazu bestimmt sind, bei Anwendung am oder im menschlichen oder tierischen Körper
  - Krankheiten, Leiden, Körperschäden oder krankhafte Beschwerden zu heilen, zu lindern, zu verhüten oder zu erkennen,
  - die Beschaffenheit, den Zustand oder die Funktionen des Körpers oder seelische Zustände erkennen zu lassen,
  - vom menschlichen oder tierischen Körper erzeugte Wirkstoffe oder Körperflüssigkeiten zu ersetzen,
  - Krankheitserreger , Parasiten oder körperfremde Stoffe abzuwehren, zu beseitigen oder unschädlich zu machen oder
  - die Beschaffenheit, den Zustand oder die Funktionen des Körpers oder seelische Zustände zu beeinflussen.

Definition – Medicinal Product (§ 1 AMG) org.

- (2) Als Arzneimittel gelten
  - Gegenstände, die ein Arzneimittel enthalten oder auf die ein Arzneimittel aufgebracht ist, und die zur Anwendung am oder im menschlichen oder tierischen Körper bestimmt sind, und
  - Stoffe und Zubereitungen aus Stoffen, die die Merkmale des Abs. 1 nicht aufweisen, sofern sie dazu bestimmt sind, für die Herstellung von Arzneimitteln verwendet zu werden.
- (3) Keine Arzneimittel sind
  - Lebensmittel gemäß Art. 2 Abs. 1 und 2 der Verordnung (EG) Nr. 178/2002, sofern sie nicht nach der allgemeinen Verkehrs-auffassung dazu dienen oder nach Art und Form des In-Ver-kehr-Bringens dazu bestimmt sind, die Zweckbestimmungen des Abs. 1 Z 1 bis 4 zu erfüllen,
  - …
  - …

Definition – Clinical trial (§ 2a AMG)

- (1) **"Clinical trial"** means a systematic investigation of a medicinal product in a trial subject, which is carried out with the aim,
  - to discover or verify the effects of investigational medicinal products,
  - to identify any adverse reactions to investigational medicinal products, or
  - to study absorption, distribution, metabolism and excretion of investigational medicinal products.

  This includes clinical trials carried out in either one site or multiple sites, in one or more than one contract party of the European Economic Area.
  No clinical trial is a non-interventional trial ("Anwendungs-beobachtung") in terms of section 3.

Definition – Clinical trial (§ 2a AMG)

- (2) **"Multi-centre clinical trial"** is a clinical trial conducted according to a single protocol
  - at more than one site, and therefore
  - by more than one investigator,
  - whereas the centres may be located in one or more than one contract party of the European Economic Area, or
  - in contract parties and third countries.
- Comment:
  - The leader of a multi-centre clinical trial is designated as "*Coordinating Investigator*".

Definition – Clinical trial (§ 2a AMG) org.

- (1) **"Klinische Prüfung"** ist eine systematische Untersuchung eines Arzneimittels an einem Prüfungsteilnehmer, die mit dem Ziel durchgeführt wird,
  - Wirkungen von Prüfpräparaten zu erforschen oder nachzuweisen,
  - Nebenwirkungen von Prüfpräparaten festzustellen, oder
  - die Resorption, die Verteilung, den Stoffwechsel und die Ausscheidung von Prüfpräparaten zu untersuchen.

  Dies umfasst klinische Prüfungen, die in einem oder mehreren Prüfzentren in einer oder mehreren Vertragsparteien des Europäischen Wirtschaftsraumes durchgeführt werden.
  Keine klinische Prüfung ist eine Anwendungsbeobachtung im Sinne des Abs. 3.

Definition – Clinical trial (§ 2a AMG) org.

- (2) **"Multizentrische klinische Prüfung"** ist eine nach einem einzigen Prüfplan durchgeführte klinische Prüfung, die
  - in mehr als einem Prüfzentrum erfolgt und daher
  - von mehr als einem Prüfer vorgenommen wird,
  - wobei die Prüfzentren sich in einer einzigen oder in mehreren Vertragsparteien des Europäischen Wirtschaftsraumes oder
  - in Vertragsparteien und Drittländern befinden können.
- Anmerkung:
  - Der Leiter einer multizentrischen Prüfung wird als koordinierender Prüfer (*Coordinating Investigator*) bezeichnet.

Research on medicinal products - Phases

- **Phase I**
  First application in man (mostly in healthy volunteers), pharmakokinetics und –dynamics, safety
- **Phase II**
  therapeutic pilot studies in small numbers of patients, dose finding, dose-response-relation
- **Phase III**
  larger collectives, broad application, benefit/risk assessment, adverse effects, therapeutic effects (comparative),
  Aim: marketing authorisation
- **Phase IV**
  after placing on the market, surveillance, assessment of the therapeutic benefit (effectiveness) and safety
- **Non-interventional trial ("Anwendungsbeobachtung")**
  observations and record keeping, no intervention, no change of the routine patient care

Research on medicinal products

- **Phase I to IV**
  - EudraCT-number and -form (+ complete documentation of pre-clinical and clinical data)
  - Non-prohibition by the competent authority
  - In case of gene therapy, somatic cell therapy and medicinal products containing genetic modified organisms → explicit approval by the competent authority
  - Ethics Committee
- **Non-interventional trial ("Anwendungsbeobachtung")**
  - At present: no requirements
  - The Drug Law provides for a decree → notification requirement (still pending)

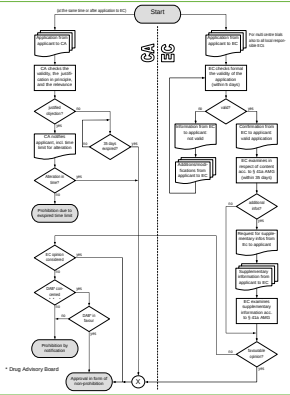
Required documents – CA - EC

CA	EC		INFORMATION PROVIDED	
		1	**General**	
☒	☐	**1.1**	Receipt of confirmation of EudraCT number	☐
☒	☒	**1.2**	Covering letter	☐
☒	☒	**1.3**	Application form	☐
☒	☒	**1.4**	List of Competent Authorities within the Community to which the application has been submitted and details of decisions	☐
☒	☐	**1.5**	Copy of ethics committee opinion in the MS concerned when available	☐
☒	☐	**1.6**	Copy/summary of any scientific advice	☐
☒	☐	**1.7**	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	☐
		2	**Subject related**	
☒	☒	**2.1**	Informed consent form	☐
☒	☒	**2.2**	Subject information leaflet	☐
☒	☒	**2.3**	Arrangements for recruitment of subjects	☐
		3	**Protocol related**	
☒	☒	**3.1**	Clinical trial protocol with all current amendments	☐
☐	☒	**3.2**	Summary of the protocol in the national language	☐
☒	☒	**3.3**	Peer review of trial when available	☐
☐	☒	**3.4**	Ethical assessment made by the principal/coordinating investigator, if not given in the application form or protocol	☐
		4	**IMP related**	
☒	☒	**4.1**	Investigator's brochure	☐
☒	☐	**4.2**	Investigational Medicinal Product Dossier (IMPD)	☐
☒	☐	**4.3**	Simplified IMPD for known products (see table 1)	☐
☒	☐	**4.4**	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	☐
☐	☐	**4.5**	Outline of all active trials with the same IMP	☐
		4.6	If IMP manufactured in E.U. and if no marketing authorisation in EU:	
☒	☐	**4.6.1**	Copy of the manufacturing authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization	☐

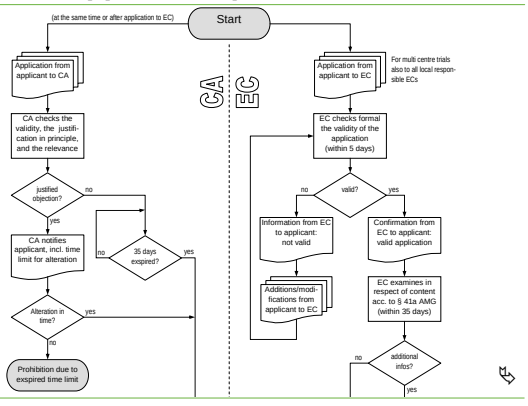
Required documents – CA - EC

		4.7	If IMP not manufactured in E.U. and if no marketing authorisation in EU:
☒	☐	**4.7.1**	Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP, or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality
☒	☐	**4.7.2**	Certification of GMP status of active biological substance
☒	☐	**4.7.3**	Copy of the importers manufacturing authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization
		4.8	Certificate of analysis for test product in exceptional cases :
☒	☐	**4.8.1**	Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected
☒	☐	**4.9**	Viral safety studies when applicable.
☐	☐	**4.10**	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals
☒	☐	**4.11**	TSE Certificate when applicable
☐	☐	**4.12**	Examples of the label in the national language
		5	**Facilities & staff related**
☐	☒	**5.1**	Facilities for the trial
☒	☒	**5.2**	CV of the coordinating investigator in the MS concerned (for multicentre trials)
☒	☒	**5.3**	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)
☐	☒	**5.4**	Information about supporting staff
		6	**Finance related**
☒	☒	**6.1**	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial
☒	☒	**6.2**	Any insurance or indemnity to cover the liability of the sponsor or investigator
☒	☒	**6.3**	Compensation to investigators
☒	☒	**6.4**	Compensation to subjects
☐	☒	**6.5**	Agreement between the sponsor and the trial site
☐	☐	**6.6**	Agreement between the investigators and the trial sites
☒	☒	**6.7**	Certificate of agreement between sponsor and investigator when not in the protocol

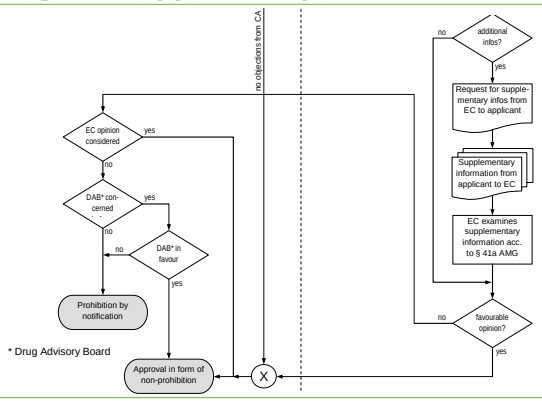
Drug Law: Application procedures CA - EC



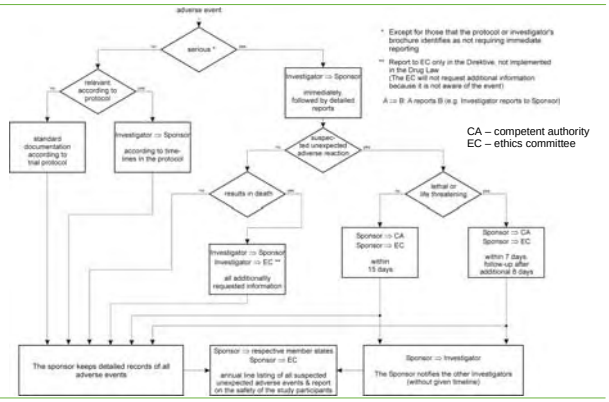
Drug Law: Application procedures CA - EC



Drug Law: Application procedures CA - EC

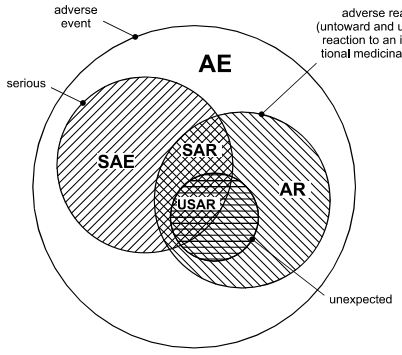


Trials on medicinal products – safety reporting



CA – competent authority
EC – ethics committee

Definition – "SUSAR"



AE	adverse event
AR	adverse reaction
SAE	serious adverse event
SAR	serious adverse reaction
USAR	unexpected serious adverse reaction
SUSAR	suspected unexpected serious adverse reaction

In German: "Mutmaßliche unerwartete schwerwiegende Nebenwirkung – MUSNW"

Definition – Medical device (§ 2 MPG)

(1) **"Medical device"** means any

- instrument, apparatus, appliance,
- software, material or other article,

whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process, or
- control of conception

Definition – Medical device (§ 2 MPG)

and which does not achieve its principal intended action in or on the human body by

- pharmacological, immunological

  or

- metabolic

  means,

but which may be assisted in its function by such means.

A newly conditioned medical device is considered equal to a new device.

Definition – Medical device (§ 2 MPG) org.

(1) **"Medizinprodukte"** sind alle einzeln oder miteinander verbunden verwendeten

- Instrumente, Apparate, Vorrichtungen,
- Stoffe oder andere Gegenstände,

einschließlich der für ein einwandfreies Funktionieren des Medizinproduktes eingesetzten Software, die vom Hersteller zur Anwendung für Menschen bestimmt sind zur

- Erkennung, Verhütung, Überwachung, Behandlung oder Linderung von Krankheiten,
- Erkennung, Überwachung, Behandlung, Linderung oder Kompensierung von Verletzungen oder Behinderungen,
- Untersuchung, Veränderung oder zum Ersatz des anatomischen Aufbaus oder physiologischer Vorgänge, oder
- Empfängnisregelung

Definition – Medical device (§ 2 MPG) org.

und deren bestimmungsgemäße Hauptwirkung im oder am menschlichen Körper weder

- durch pharmakologische oder immunologische Mittel

noch

- metabolisch

erreicht wird,

deren Wirkungsweise aber durch solche Mittel unterstützt werden kann.

Dem neuen steht ein als neu aufbereitetes Medizinprodukt gleich.

Definition – Accessory (§ 2 MPG)

(2) **"Accessories"** for a medical devices mean

- articles,
- substances,
- preparations of substances as well as
- software,

which whilst not being a device is intended specifically by its manufacturer,

- to be used together with a device, … or
- to support the use of the device in accordance with the use intended by the manufacturer of the device.

Accessory is to be considered as a medical device!

Definition – Accessory (§ 2 MPG) org.

(2) **"Zubehör"** für ein Medizinprodukt sind

- Gegenstände,
- Stoffe,
- Zubereitungen aus Stoffen sowie
- Software,

die selbst keine Medizinprodukte sind, nach ihrer vom Hersteller ausdrücklich festgelegten Zweckbestimmung aber dazu bestimmt sind,

- zusammen mit einem Medizinprodukt verwendet zu werden, … oder
- die für das Medizinprodukt festgelegte Zweckbestimmung zu unterstützen.

Zubehör gilt selbst als Medizinprodukt!

Definition – In vitro diagnostic MD (§ 2 MPG)

(5) **"In vitro diagnostic medical device"** means any medical device which

- is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of
  - providing information concerning a physiological or pathological state, or concerning a congenital abnormality, or
  - to determine the safety and compatibility with potential recipients, or
  - to monitor therapeutic measures.

Definition – In vitro diagnostic MD (§ 2 MPG) org.

(5) **"Medizinprodukt für die in-vitro-Diagnose"** oder **"In-vitro-Diagnostikum"** ist jedes Medizinprodukt, das

- einzeln oder kombiniert nach der vom Hersteller festgelegten Zweckbestimmung als Reagens, Reagenzprodukt, Kalibriermaterial, Kontrollmaterial, Kit, Instrument, Apparat, Gerät oder System zur in-vitro-Untersuchung von aus dem menschlichen Körper stammenden Proben, einschließlich Blut- und Gewebespenden, verwendet wird, und
- allein oder überwiegend dazu dient,
  - Informationen über physiologische oder pathologische Zustände oder angeborene Anomalien zu geben oder
  - die Unbedenklichkeit und die Verträglichkeit bei den potentiellen Empfängern zu prüfen, oder
  - eine therapeutische Maßnahme zu überwachen.

Definition – Intended purpose (§ 2 MPG)

- (9) **"Intended Purpose"** means the use for which the device is intended according to the data supplied by the manufacturer on the labeling, in the instructions and/or in promotional materials.

- Comment:
  - The manufacturer defines by the declaration of the intended purpose whether or not the product is a medical device.
  - The appearance of the product may possibly not tell:
  - A bicycle ergo meter (medical device) might for example also be an exercise machine (household appliance). In that case it must not be used for medical purposes in health care facilities.

Definition – Intended purpose (§ 2 MPG) org.

- (9) **"Zweckbestimmung"** ist jene Verwendung, für die das Medizinprodukt nach den Angaben des Herstellers in der Kennzeichnung, der Gebrauchsanweisung oder dem Werbe-material bestimmt ist.

- Anmerkungen:
  - Der Hersteller legt mit der Angabe der Zweckbestimmung fest, ob es sich um ein Medizinprodukt handelt.
  - Dem Produkt selbst sieht man das unter Umständen nicht an:
  - Ein Fahrrad-Ergometer (Medizinprodukt) könnte z.B. auch ein Heimtrainer (Haushaltsgerät) sein. In diesem Fall dürfte es nicht in Einrichtungen des Gesundheitswesens für medizini-sche Zwecke verwendet werden.

Definition – Clinical investigation (§ 3 MPG)

(2) **"Clinical investigation"** means a systematic investigation of a medical device – with the exception of in vitro diagnostic devices – in a trial subject, which is carried out with the aim

- to evaluate the performance of the medical device, or to verify that, under normal conditions of use, the performance of the device conform to those given by the manufacturer or any other sponsor,
- to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device, or
- to determine mechanisms of action and adequate clinical fields of application of the medical device,

in order to investigate the safety and efficacy of the medical device.

Definition – Clinical investigation (§ 3 MPG) org.

(2) **"Klinische Prüfung"** ist eine systematische Untersuchung eines Medizinproduktes, ausgenommen In-vitro-Diagnostika, an Ver-suchspersonen, mit dem Ziel,

- die Leistungsdaten des Medizinproduktes zu ermitteln oder zu überprüfen, ob die Leistungen des Medizinproduktes bei normalen Einsatzbedingungen den vom Hersteller oder sonstigen Sponsor angegebenen Leistungsdaten entsprechen,
- etwaige bei normalen Einsatzbedingungen auftretende Neben-wirkungen nach Art, Schwere und Häufigkeit im Hinblick darauf zu ermitteln, ob diese unter Berücksichtigung der vorgegebenen Leistungen vertretbare Risken darstellen, oder
- Wirkungsmechanismen und geeignete klinische Einsatzgebiete des Medizinproduktes zu ermitteln,

um damit die Sicherheit und Wirksamkeit des Medizinproduktes zu untersuchen

Definition – Performance evaluation (§ 3 MPG)

(2a) **"Performance evaluation"** means a systematic investigation of an in vitro diagnostic medical device in laboratories for medical analyses or in other appropriate environments on samples of trial subjects, including blood and tissue donations, with the aim

- to evaluate the performance of the in vitro diagnostic medical device, or to verify that, under normal conditions of use, the performance of the device conform to those given by the manufacturer or any other sponsor,
- to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device, or
- to determine detection possibilities and adequate clinical fields of application of the in vitro diagnostic medical device.

Definition – Performance evaluation (§ 3 MPG) org.

(2a) **"Leistungsbewertungsprüfung"** ist eine systematische Untersuchung eines In-vitro-Diagnostikums in medizinischen Laboratorien oder sonstigen geeigneten Einrichtungen an Proben von Versuchspersonen, einschließlich Blut- und Gewebespenden, mit dem Ziel,

- die Leistungsdaten des In-vitro-Diagnostikums zu ermitteln oder zu überprüfen, ob die Leistungen des In-vitro-Diagnostikums bei normalen Einsatzbedingungen den vom Hersteller oder sonstigen Sponsor angegebenen Leistungsdaten entsprechen,
- etwaige bei normalen Einsatzbedingungen auftretende Risken nach Art, Schwere und Häufigkeit im Hinblick darauf zu ermitteln, ob diese unter Berücksichtigung der vorgegebenen Leistungen vertretbare Risken darstellen, oder
- Nachweismöglichkeiten und geeignete medizinische Einsatzgebiete des In-vitro-Diagnostikums zu ermitteln.

Research on medical devices

- **MD without CE-Mark – clinical evaluation**
  Within the scope of the conformity assessment procedures to obtain the CE-Mark
  - Proof of the fulfilment of the "essential requirements"
  - Risk analysis
  - Non-prohibition by the competent authority
  - Ethics Committee
- **MD with CE-Mark – new indication (intended purpose)**
  - "Essential requirements" (related to the new indication)
  - Risk analysis (related to the new indication)
  - Non-prohibition by the competent authority
  - Ethics Committee
- **MD with CE-Mark – according to the intended purpose**
  - Ethics Committee (no insurance required)

Essential requirements (MDD)

- No unacceptable risks and side effects
- The claimed performance has to be provided
  - during the whole life cycle
  - under the declared environmental conditions
- Integrated safety
  - electrical
  - mechanical
  - thermal
  - Software
  - Handling
  - Infection
  - Supply

Essential requirements (MDD)

- Measuring accuracy, reliability
- Infection and contamination protection
- Emission protection
  - Radiation, radio interference suppression, leakages
- Immission protection
  - electromagnetic, mechanical, humidity
- Biocompatibility
- Package, transportation, storage
- Quality assurance
- Information
  - Instruction manual, device labelling, further documentation

Other medical research

- **International ethical standards**
  - Declaration of Helsinki
  - CIOMS-Guidelines
- **Law on Genetic Engineering ("Gentechnikgesetz")**
  - Protection of genetic information
  - Handling of samples
  - Storage of samples and data – bio banks
  - Genetic counselling
- **University Act ("Universitätsgesetz 2000")**
  - "applied medical research in human beeings"
- **Data Protection Act ("Datenschutzgesetz 2000")**
- **Principles of ICH-GCP**
  - as far as applicable

Ethical standards – Deklaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964,
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004
(Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

Deklaration of Helsinki

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of **ethical principles for medical research involving human subjects**, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

Deklaration of Helsinki

4. The Declaration of Geneva of the WMA binds the physician with the words, "**The health of my patient will be my first consideration**," and the International Code of Medical Ethics declares that, "**A physician shall act in the patient's best interest when providing medical care**."
5. Medical progress is based on **research** that ultimately must include **studies involving human subjects**. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

Deklaration of Helsinki

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments).

   Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to **ethical standards** that promote respect for all human subjects and protect their health and rights.

Deklaration of Helsinki

Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. It is the **duty of physicians** who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

Deklaration of Helsinki

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be **clearly described** in a **research protocol**.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed.

Deklaration of Helsinki

The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a **research ethics committee** before the study begins.

    This committee must be **independent** of the researcher, the sponsor and any other undue influence.

Deklaration of Helsinki

It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies.

The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications.

Deklaration of Helsinki

Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

The **responsibility for the protection of research subjects** must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

Deklaration of Helsinki

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed.
    Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

Deklaration of Helsinki

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be **voluntary**. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

Deklaration of Helsinki

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study.

    The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.

    Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

Deklaration of Helsinki

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing.

If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse.

There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Deklaration of Helsinki

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

Deklaration of Helsinki

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population.

In such circumstances the physician should seek informed consent from the legally authorized representative.

Deklaration of Helsinki

If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have **ethical obligations** with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.

Deklaration of Helsinki

They should adhere to accepted guidelines for ethical reporting.

Negative and **inconclusive** as well as **positive** results should be published or otherwise made publicly available.

Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication.

Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

Deklaration of Helsinki

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

Deklaration of Helsinki

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research.

    The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

Deklaration of Helsinki

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering.

    Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy.

    In all cases, new information should be recorded and, where appropriate, made publicly available.

International Guidelines - CIOMS

Council for International Organizations of Medical Sciences (CIOMS)

International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

International Guidelines for Ethical Review of Epidemiological Studies (1991)

(in revision, draft text 02/2008)

CIOMS – Ethical Guidelines

Research involving human subjects includes:

- studies of a physiological, biochemical or pathological process, or of the response to a specific intervention – whether physical, chemical or psychological – in healthy subjects or patients;
- controlled trials of diagnostic, preventive or therapeutic measures in larger groups of persons, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;
- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures;

  and
- studies concerning human health-related behaviour in a variety of circumstances and environments.

CIOMS – Ethical Guidelines

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees.

The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.

The investigator must obtain their approval or clearance before undertaking the research.

The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

CIOMS – Ethical Guidelines

Epidemiological Studies - Guideline 33

The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals - academic, governmental, health-care, commercial, or other.

Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees.

Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data.

...

WHO – Guidelines for Ethics Committees

Operational Guidelines for Ethics Committees that Review Biomedical Research, WHO, Geneva, 2000

Recommendation of the World Health Organisation (WHO), comprehensive regulations for the composition and the modes of operation of Ethics Committees

Surveying and Evaluating Ethical Review Practices, WHO, Geneva, 2002

Recommendation of the WHO on Inspections of Ethics Committees

Biomedicine Convention – Council of Europe

- Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine – "Biomedicine Convention"
  - SEV-No.: 164
  - Oviedo, April 4, 1997
  - In force since December 1, 1999
  - Not signed yet by Austria and Germany
- Additional protocol to the convention on human rights and biomedicine, concerning biomedical research
  - SEV-No.: 195
  - Strasbourg, January 25, 2005
  - In force since September 1, 2007
  - Not signed yet by Austria and Germany

Ethics Committee Composition (KAKuG)

- **The Ethics Committee shall be composed of men and women and shall comprise at least:**
  - a physician, who is authorised to autonomous professionalism in Austria, and who is neither medical director of the hospital nor clinical investigator,
  - a medical specialist in the discipline of the particular clinical trial, or, if applicable, a dentist, who are not investigators,
  - a member of the nursing service,
  - a jurist,
  - a pharmacist,
  - a patient's advocate,
  - a person with biometric expertise,
  - a representative of an organisation of handicapped people

Ethics Committee Composition (KAKuG)

- another person, who deals with pastoral affairs in the hospital, or who otherwise holds equivalent ethical competence.
- Deputies with equal qualifications shall be appointed for each member.
- In case of the evaluation of a medical device a technical security officer has to be consulted at all means.
- If the Ethics Committee is concerned with a multi centre trial on a medicinal product, a medical specialist in pharmacology and toxicology shall be a member of the committee.
- If necessary, additional experts shall be consulted.
- Moreover, the legislation of the Federal States shall assure that the members of the Ethics Committee are not subject to any orders.

Ethics Committee Composition (KAKuG) org.

- **Die Ethikkommission hat sich aus Frauen und Männern zusammenzusetzen und mindestens zu bestehen aus:**
  - einem Arzt, der im Inland zur selbständigen Berufsausübung berechtigt ist und weder ärztlicher Leiter der Krankenanstalt noch Prüfer bzw. Klinischer Prüfer ist,
  - einem Facharzt, in dessen Sonderfach die jeweilige klinische Prüfung fällt, oder gegebenenfalls einem Zahnarzt, und die nicht Prüfer sind,
  - einem Angehörigen des gehobenen Dienstes für Gesundheits- und Krankenpflege,
  - einem Juristen,
  - einem Pharmazeuten,
  - einem Patientenvertreter,
  - einer Person, die über biometrische Expertise verfügt,
  - einem Vertreter einer repräsentativen Behindertenorganisation

Ethics Committee Composition (KAKuG) org.

- einer weiteren, nicht unter die Z 1 bis 8 fallenden Person, die mit der Wahrnehmung seelsorgerischer Angelegenheiten in der Krankenanstalt betraut ist oder sonst über die entsprechende ethische Kompetenz verfügt.
- Für jedes Mitglied ist ein in gleicher Weise qualifizierter Vertreter zu bestellen.
- Bei der Beurteilung eines Medizinproduktes ist jedenfalls ein Technischer Sicherheitsbeauftragter beizuziehen.
- Wird die Ethikkommission im Rahmen einer multizentrischen klinischen Prüfung eines Arzneimittels befasst, so haben ihr weiters ein Facharzt für Pharmakologie und Toxikologie anzugehören.
- Erforderlichenfalls sind weitere Experten beizuziehen.
- Weiters hat die Landesgesetzgebung sicherzustellen, dass die Mitglieder der Ethikkommissionen keinen Weisungen unterliegen.

Duties of Ethics Committees (§ 41a AMG)

The Ethics Committees which are established in execution of § 8c of the Federal Law on Hospitals according to the regulations of the law of the Federal States, according to the regulations of the University Act, and according to § 41 shall observe the rules on the procedures laid down in section 2 to 7, and in preparing its opinion, the Ethics Committee shall consider, in particular:

1. the relevance of the clinical trial and the trial design,
2. the appropriateness of the in § 29 stipulated evaluation of the anticipated benefit and the anticipated risks,
3. the study protocol,
4. the suitability of the investigator and supporting staff,
5. the investigator's brochure,
6. the appropriateness of the facilities,

Duties of Ethics Committees (§ 41a AMG)

7. 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 as regards the specific restrictions laid down in §§ 29, 38, 39, 42, 43, and 43a,
8. the personal injury insurance taken out according to § 32, section 1, number 11, as well as any insurance or indemnity to cover the liability of the investigator and the sponsor,
9. 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, and
10. the arrangements for the recruitment of subjects.

Duties of Ethics Committees (§ 41a AMG) org.

Die in Ausführung des § 8c des Bundesgesetzes über Krankenanstalten und Kuranstalten nach landesrechtlichen Bestimmungen, die nach universitätsrechtlichen Bestimmungen und die gemäß § 41 eingerichteten Ethikkommissionen haben die in den Abs. 2 bis 7 enthaltenen Regelungen über das Verfahren einzuhalten und in ihrer Stellungnahme insbesondere zu berücksichtigen:

1. die Relevanz der klinischen Prüfung und ihre Planung,
2. die Angemessenheit der durch § 29 vorgeschriebenen Bewertung des erwarteten Nutzens und der erwarteten Risken,
3. den Prüfplan,
4. die Eignung des Prüfers und seiner Mitarbeiter,
5. die Prüferinformation,
6. die Angemessenheit der Einrichtungen,

Duties of Ethics Committees (§ 41a AMG) org.

7. die Angemessenheit und Vollständigkeit der zu erteilenden schriftlichen Auskünfte sowie das Verfahren im Hinblick auf die Einwilligung nach Aufklärung und die Rechtfertigung für die Forschung an Personen, die zur Einwilligung nach Aufklärung nicht in der Lage sind, was die spezifischen Einschränkungen gemäß den §§ 29, 38, 39, 42, 43 und 43a anbelangt,
8. die gemäß § 32 Abs. 1 Z 11 abgeschlossene Personenschadenversicherung, sowie jede Art von Versicherung oder Schadenersatz zur Deckung der Haftung des Prüfers und des Sponsors,
9. die Beträge und die Modalitäten für die etwaige Vergütung oder Entschädigung für Prüfer und Prüfungsteilnehmer und die einschlägigen Elemente jedes zwischen dem Sponsor und dem Prüfzentrum vorgesehenen Vertrages, und
10. die Modalitäten für die Auswahl der Prüfungsteilnehmer.

Tasks of the Ethics Committee

The **main business** is the evaluation of clinical research projects (clinical trials, clinical investigations) in patients or in healthy volunteers.

Such projects may concern:

- **Medicinal products**
- **Medical devices**
- **New medical methods** (e.g. surgical techniques)
- **Applied medical research in human beings**

The evaluation is done considering

- **ethical,**
- **legal,** and
- **methodical-scientific**

aspects.

Application to the EC necessary?

- **In Austria legally binding**
  - All clinical trials on medicinal products (AMG) except non-interventional trials* and all investigations on medical devices (MPG). Applicant: the **investigator** (leader of the trial), or the **sponsor,** or an **authorised representative** of the sponsor.

    * "Anwendungsbeobachtung": only routine medical care, no comparisons, no measures beyond the routine treatment
  - The application of a new medical method (= a method which is not applied in Austria yet (KAKuG). Applicant: the **head of the** respective **organisation unit**
  - In the university setting, and in Vorarlberg additional (§ 30 UG 2002, Hospital Act Vorarlberg):
    Applied clinical research in human beings.

Application to the EC necessary?

- **International**
  - Every research project in humans which comprises measures in addition to routine patient care (e.g. questionnaires, but also usage of tissue or blood samples, etc.)

    Advice: Most ***Journals*** request a vote of the responsible Ethics Committee, or a declaration that the Ethics Committee has been involved, prior to the acceptance of study results for publication!

    In case of doubt it is recommended to ask the Ethics Committee **prior** to the start of the project whether an application is necessary!
- **When?**
  - In any case **prior** to the commencement of the project / the trial / the application of the new method (and **prior** to potential screening investigations, too)

Substantial elements of the ethical evaluation

- **Central element: benefit/risk-balance**
  - Potential benefits for the participants
  - Risks for the participants
  - Potential benefits for the society
  - Risks for the society
- **Form and extent of the information/elucidation**
  - Measures for advertising
  - Recruiting
  - informed consent form, informed consent process
- **Protection measures and precautions**
  - Measures to minimise risks
  - Insurance for the case of an injury
  - Protection of the personal sphere (data protection)

Potential benefits

- **Individual benefits**
  - Better control/observation
  - Potential benefits of the »new« treatment (diagnostic/ prophylactic measures)
  - Monetary compensation
  - ...
- **Common (societal) benefit**
  - Increase in medical knowledge
  - Better possibilities for diagnosis / treatment / prophylaxis for future patients
  - Savings of treatments costs (drug trials)
  - ...

Risks

- **Individual risks**
  - Undesired / unexpected effects
  - Inferiority of the »new« treatment (diagnostic/ prophylactic measures)
  - Withholding of effective therapies
  - Additional burdens
    - Blood drawing
    - Radiation
    - Other study specific measures
  - **...**

Risks

- **Common (societal) Risks**
  - Faulty/spurious results / wrong conclusions from the results

    ⇒ **wrong medical *»knowledge«***

    - Insufficient basis for additional (unnecessary) studies
    - Unjustified modification or retention, respectively, of therapeutic or diagnostic regimens

Ethical relevance of the benefit/risk-ratio

A research project is in general as ethical unobjectionable if

1. the potential **benefits overbalance** the potential **risks** (benefit/risk-ratio > 1)

and

2. the **sum of the individual risks** does not exceed an acceptable maximum

A sole judgement of the benefit/risk-ratio could lead to the acceptance of projects where a high potential benefit for the society faces very high potential risks for the participating individuals.

Scientific quality

The scientific quality is addressed in the ICH-GCP-Guideline under ***»Principles of ICH GCP«***: Clinical trials have to be ***»scientifically sound«***!

- Inadequate planning,
- insufficient realisation,
- improper analysis, and/or
- poor presentation of the results

derogate or even nullify the potential benefit of the study.

Under such circumstances even a small risk or a small burden for the participants, respectively appear to be unacceptable:

Studies of poor scientific quality are *ipso facto* unethical!

ICH-GCP – Informed Consent (1)

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 that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

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.

ICH-GCP – Informed Consent (2)

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability or negligence.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

ICH-GCP – Informed Consent (3)

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research.

b) The purpose of the trial.

c) The trial treatment(s) and the probability for random assignment to each treatment.

d) The trial procedures to be followed, including all invasive procedures.

e) The subject's responsibilities.

f) Those aspects of the trial that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.

ICH-GCP – Informed Consent (4)

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of trial-related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

l) The anticipated expenses, if any, to the subject for participating in the trial.

ICH-GCP – Informed Consent (5)

m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.

ICH-GCP – Informed Consent (6)

o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

ICH-GCP – Informed Consent (7)

s) The expected duration of the subject's participation in the trial.

t) The approximate number of subjects involved in the 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..

Additional requirements (1)

A - Formal

Medical and scientific terms – if unavoidable, e.g. if they are part of the study title – shall be explained.

Examples:

randomised	"... which of these therapies you will receive will be decided by chance"
double-blind	"... neither you nor your doctors know, which of the medication you will receive"
Placebo	"dummy drug without any active component"
multi centre	"... carried out in more than one hospital"

The version of the informed consent form shell be clearly indicated by a date and a version number in the head or foot line of the document.

Furthermore, a paging including the total number of pages is required (e.g. "page 2 of 5").

Additional requirements (2)

- **B - Content**
  1. **Title of the study**
     according to the protocol, translated into German if applicable
  2. **Salutary address and explanation about the disease**
     "Dear patient, you suffer from ... / we diagnosed you with ... " / etc.
  3. **Ask for participation in the study**
  4. **Information about the study subject**
     - Statement whether and where the subject has a marketing authorisation (in Austria, in the EC, in other countries)
     - Information about the number of patients, in which previous experience with the study subject exist
     - Total number of planned participants, number of centres, total duration of the study

Additional requirements (3)

5. **Risks and burdens**
   - Information about potentially occurring non-foreseeable undesired effects/risks
   - Information about the necessary pregnancy test (in drug trials)
6. **Insurance**
   - Notice of the insurance institution and police number
   - Warranty of the liability regardless of negligence or fault
   - Information that the patient may enforce her/his claims directly to the insurance institution
   - Information about obligations, if any, which – if violated – may compromise the insurance coverage (e.g. other medical treatments, intake of medications, etc.)
7. **Withdrawal of the consent**
   - Information about the potential risks which might be associated with a premature termination of the study participation
8. **Integrated declaration of consent with paging throughout**

Development in Austria

- **Late 70s / early 80ies**
  - Establishment of Ethics Committees in the three Medical Faculties according to international developments, "unsolicited"
- **1988: KAG –** Federal Hospital Act (Amendment)
  - "Committees" – term "Ethics Committee" not until **1992**
- **1994: AMG** – Drug Law – Amendment
- **1996: MPG** – Law on Medical Devices
- **1997: UOG 93 –** University Organisation Act – Amendment
  - Special provisions for the Medical Faculties
- **2002: UG 2002 –** University Act
  - Special provisions for the clinical divisions of the Medical Universities, Reference to the Federal Hospital Act
- **2004: Directive 2001/20/EC** → AMG – Amendment 2004
  - One vote for Austria in drug trials – "Leading Ethics Committees"

Links – EC

- General: Document search
  (Official Journal, Directives, etc.)
  http://europa.eu.int/eur-lex/de/search/index.html
- Everything about medicinal products
  http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
- EMEA: Guidelines – Medicinal products
  http://www.emea.europa.eu/htms/human/humanguidelines/background.htm
- EudraCT Database
  http://eudract.emea.europa.eu
- Everything about medical devices
  http://ec.europa.eu/enterprise/medical_devices/index_en.htm
- Guidelines – Medical devices
  http://ec.europa.eu/enterprise/medical_devices/meddev/index.htm

Links – Council of Europe

- Convention on Human Rights and Biomedicine

  http://conventions.coe.int/Default.asp

  Select <Treaties>, then < You know the CETS number or the abridged title of the treaty>
  CETS Number: 164
- Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research

  http://conventions.coe.int/Default.asp

  Select <Treaties>, then < You know the CETS number or the abridged title of the treaty>
  CETS Number: 195

  Hint: The documents are also available in German. Do not use the German version, the translation is not exact.

Further Links

- ICH – International Conference on Harmonization
  http://www.ich.org/
- WMA – World Medical Association
  Declaration of Helsinki
  http://www.wma.net/e/policy/b3.htm
- WHO – World Health Organization
  http://www.who.int or http://www.who.int/tdr/ (good starting place)
- CIOMS – Guidelines
  http://www.cioms.ch/frame_menu_texts_of_guidelines.htm
- Relevant Laws (KAKuG, AMG, MPG, etc.)
  http://ethikkommissionen.at – select <Formulare>, then <Gesetze>
  or: http://www.ris.bka.gv.at – select <geltendes Recht>
- US study registry (DHHS, FDA, NIH)
  http://www.clinicaltrials.gov – view registry
  http://register.clinicaltrials.gov – register studies