Medizinische Universität Graz

Dr.sci.med. / PhD - Programme

Scientific Basics

Ethics Committee

Peter H. Rehak
Department of Surgery
Research Unit for Biomedical Engineering and Computing
and
Ethics Committee of the Medical University of Graz

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 Ethical Standards
  - Declaration of Helsinki, CIOMS-Guidelines
- Ethics Committee
  - Composition, duties and responsibilities, elements of the assessment, development of Ethics Committees in Austria
  - Application to the Ethics Committee

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

Medical Research – Subjects

- **Hospital Act – Discretionary provisions for**
  - Applied medical research in human subjects
  - Nursing research projects
  - Application of new nursing or treatment concepts
  - Application of new nursing or treatment methods

An Ethics Committee may be involved with these projects.

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)

2001/20/EG – Guidance Documents

- **CT 1**: Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (2010/C 82/01)
  - Bundesamt für Sicherheit im Gesundheitswesen (BASG)
- **CT 2**: Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use, Rev. 1, February 2006
  - Ethikkommission
- **CT 3**: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, Rev. 2, April 2006
  - BASG und Ethikkommission

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

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.

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 14155:2009 12 01 – Draft

2. ENTWURF

2nd Draft

ÖNORM
EN ISO 14155
Ausgabe: 2009-12-01

Klinische Prüfung von Medizinprodukten an Menschen — Gute klinische Praxis

(ISO/DIS 14155:2009)

Clinical investigation of medical devices for human subjects — Good clinical practice
(ISO/DIS 14155:2009)

Investigation clinique des dispositifs médicaux pour sujets humains — Bonnes pratiques cliniques
(ISO/DIS 14155:2009)

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 Verkehrsauffassung dazu dienen oder nach Art und Form des In-Verkehr-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 ("Anwendungsbeobachtung") 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.

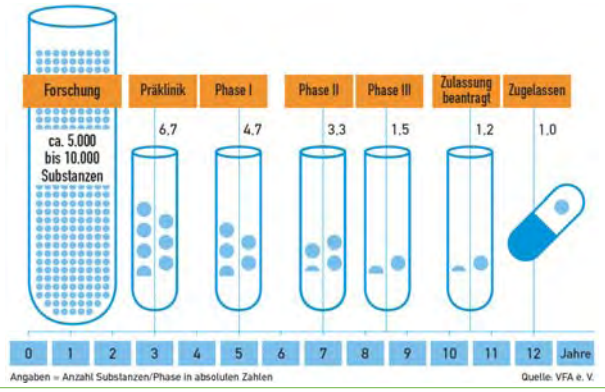
Definition – Clinical trial (§ 2a AMG) org.

- (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.

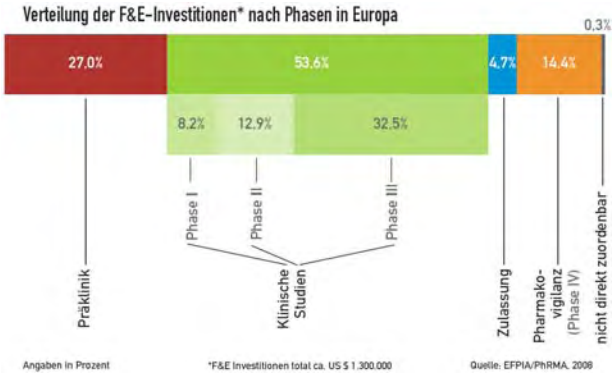
Research on medicinal products - Phases

- **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

Drug Development



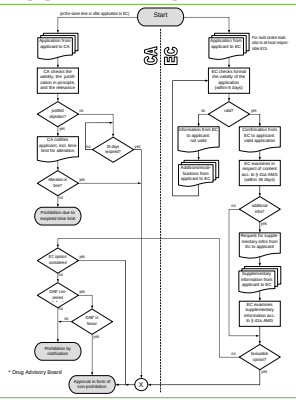
Distribution of Costs



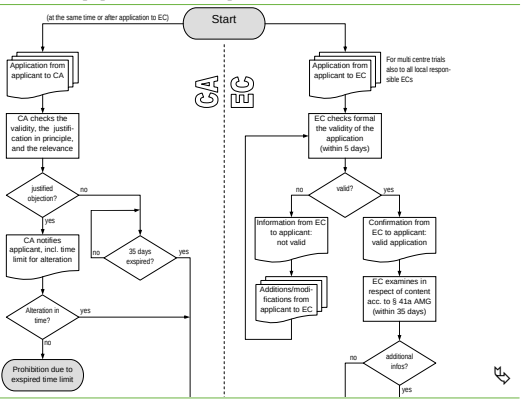
Research on medicinal products

- **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 approval
- **Non-interventional trial ("Anwendungsbeobachtung")**
  - Notification requirement to competent authority
  - An Ethics Committee may be involved

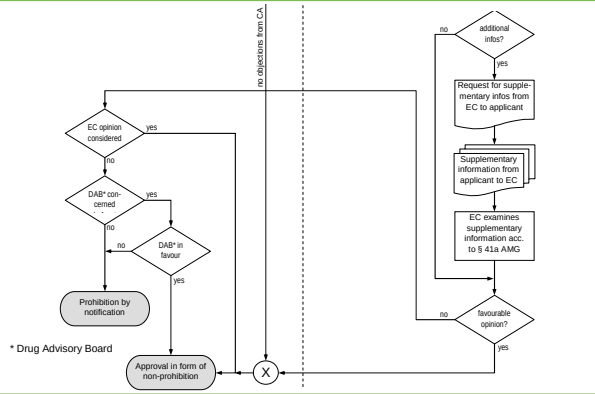
Drug Law: Application procedures CA - EC



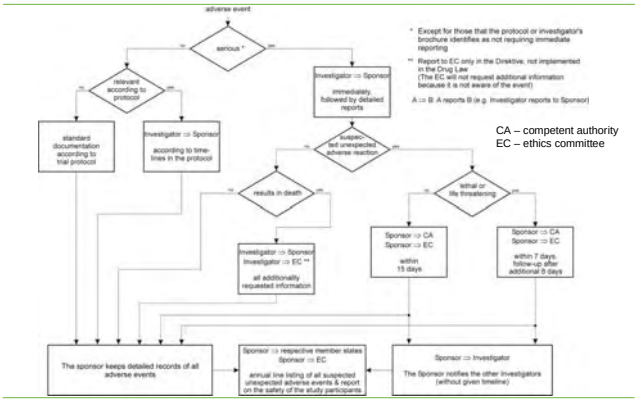
Drug Law: Application procedures CA - EC



Drug Law: Application procedures CA - EC

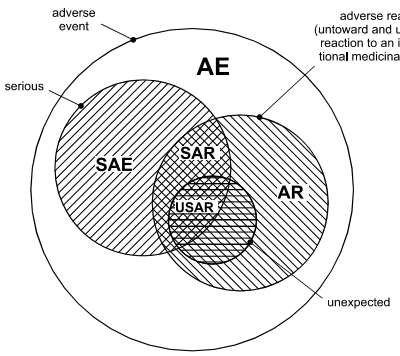


Trials on medicinal products – safety reporting



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**,

including software intended by the manufacturer to be used for **diagnostic** or **therapeutic** purposes and **software** necessary for a **proper application** of the medical device, **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**,

Definition – Medical device (§ 2 MPG)

- investigation, replacement or modification of the **anatomy** or of a **physiological process**, or
- **control** of **conception**

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**, **Software**,
- **Stoffe** oder andere **Gegenstände**,

einschließlich der vom Hersteller speziell zur Anwendung für **diagnostische** oder **therapeutische** Zwecke bestimmten und 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**,

Definition – Medical device (§ 2 MPG) org.

- Untersuchung, Veränderung oder zum Ersatz des **anatomischen Aufbaus** oder **physiologischer Vorgänge**, oder
- **Empfängnisregelung**.

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 evaluation (§ 3 MPG)

(1) **„Clinical Evaluation"** means the **medical evaluation** of a medical device as defined by

- Annex 7 No. 1.1 Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to **active implantable medical devices** (OJ L 189, 20.7.1990), **and**
- Annex X No. 1.1 Council Directive 93/42/EEC of 14 June 1993 concerning **medical devices** (OJ L 169, 12.7.1993).

Definition – Clinical evaluation (§ 3 MPG) org.

(1) **"Klinische Bewertung"** ist die **medizinische Bewertung** eines Medizinproduktes im Sinne des

- Anhanges 7 Nr. 1.1 der Richtlinie **90/385/EWG** des Rates vom 20. Juni 1990 zur Angleichung der Rechtsvorschriften der Mitgliedstaaten über **aktive implantierbare medizinische Geräte**, ABl. EG Nr. L 189 vom 20. Juli 1990, **und** des
- Anhanges X Nr. 1.1 der Richtlinie **93/42/EWG** des Rates vom 14. Juni 1993 über **Medizinprodukte**, ABl. EG Nr. L 169 vom 12. Juli 1993.

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 Prüfungsteilnehmern, 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 Nebenwirkungen** 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 Prüfungsteilnehmern, 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**.

Definition – Clinical data (§ 3 MPG)

(2b) '**Clinical data**' means the **safety** and/or **performance information** that is generated from the use of a device. Clinical data are **sourced from**:

1. clinical **investigation(s)** of the device concerned; or
2. clinical **investigation(s)** or **other studies** reported in the **scientific literature**, of **a similar device** for which **equivalence** to the device in question **can be demonstrated**; or
3. published and/or unpublished **reports** on **other clinical experience** of either **the device** in question **or a similar device** for which **equivalence** to the device in question **can be demonstrated**.

Comment: Clinical data are essential for the clinical evaluation.

Definition – Clinical data (§ 3 MPG) org.

(2b) **„Klinische Daten"** sind **Sicherheits-** oder **Leistungs-angaben**, die aus der Verwendung eines Medizinprodukts hervorgehen und aus **folgenden Quellen** stammen:

1. klinischen **Prüfung/en** des betreffenden Medizinprodukts, oder
2. klinischen **Prüfung/en** oder **sonstigen** in der wissenschaftlichen **Fachliteratur wiedergegebenen Studien** über ein **ähnliches Medizinprodukt**, dessen **Gleichartigkeit** mit dem betreffenden Medizinprodukt **nachgewiesen** werden **kann**, oder
3. veröffentlichten oder unveröffentlichten **Berichten** über **sonstige klinische Erfahrungen** entweder mit dem **betreffenden Medizinprodukt** oder einem **ähnlichen Medizinprodukt**, dessen **Gleichartigkeit** mit dem betreffenden Medizinprodukt **nachgewiesen** werden **kann**.

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
- **Hospital Act and University Act**
  - Applied medical research in human beings
  - Nursing studies, concepts, methods
  - Non-interventional trials
- **Data Protection Act ("Datenschutzgesetz 2000")**
- **Principles of ICH-GCP**

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**.
2. **Medical progress** is based on **research** that ultimately must include **studies involving human subjects** …
5. In medical research involving human subjects, **the well-being of the individual** research subject **must take precedence over all other interests**.
6. 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).

Deklaration of Helsinki

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 …
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** ...
14. The **design** and **performance** of each **research study** involving human subjects must be **clearly described** in a **research protocol** …

    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 ...

Deklaration of Helsinki

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.
    …
    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

22. **Participation** by **competent individuals** as subjects in medical research must be **voluntary** ...
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**.
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.

Deklaration of Helsinki

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** ...
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.

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

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.
    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.

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.

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 (2009)

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**;
- 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 – Guidelines 1 and 2

The **ethical justification** of epidemiological research involving human subjects is the **prospect** of **discovering new ways** of **improving** the **health** of individuals, groups and populations.

Such research can be **ethically justifiable only** if it is carried out in ways that **respect** and **protect**, and are **fair to**, **research subjects** and that are **morally acceptable** within the communities in which the research is carried out …

All proposals to conduct epidemiological 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**.

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

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"
- **2009: KAKuG** – Federal Hospital Act (Amendment)
  - EC also responsible for nursing studies (concepts, methods), for non-interventional trials and applied medical research

Ethics Committee Composition (KAKuG)

- **The Ethics Committee shall be composed of men and women in a balanced ratio 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.
- In case of the evaluation of a nursing research project or the application of new nursing or treatment concepts or methods a person with expertise in qualitative research shall be a member of the committee.
- 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 in einem ausgewogenen Verhältnis aus Frauen und Männern zusammenzusetzen und mindestens zu bestehen aus:
  1. einem Arzt, der im Inland zur selbständigen Berufsausübung berechtigt ist und weder ärztlicher Leiter der Krankenanstalt noch Prüfer bzw. Klinischer Prüfer ist,
  2. einem Facharzt, in dessen Sonderfach die jeweilige klinische Prüfung fällt, oder gegebenenfalls einem Zahnarzt, und die nicht Prüfer sind, oder gegebenenfalls einem sonstigen entsprechenden Angehörigen eines Gesundheitsberufes,
  3. einem Angehörigen des gehobenen Dienstes für Gesundheits- und Krankenpflege,
  4. einem Juristen,
  5. einem Pharmazeuten,

Ethics Committee Composition (KAKuG) org.

6. einem Patientenvertreter,
7. einer Person, die über biometrische Expertise verfügt,
8. einem Vertreter einer repräsentativen Behindertenorganisation
9. 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 ent-sprechende ethische Kompetenz verfügt.

- Bei der Beurteilung von Pflegeforschungsprojekten und der Anwendung neuer Pflege- und Behandlungskonzepte und -methoden hat der Ethikkommission überdies eine Person anzugehören, die über Expertise hinsichtlich Methoden der qualitativen Forschung verfügt.

Ethics Committee Composition (KAKuG) org.

- 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.
- die Mitglieder der Ethikkommissionen dürfen in ihrer Funktion keinerlei Weisungen unterliegen (Verfassungsbestimmung)

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**
- **Nursing research and new nursing or treatment concepts and methods**

The evaluation is done considering

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

aspects.

Application to the EC necessary?

- **Legally binding in Austria**
  - Clinical trials on medicinal products (AMG, KAKuG, UG)
  - Clinical trials on medical devices (MPG, KAKuG, UG)
  - Application of a new medical method (KAKuG, UG)
  - Applied medical research in human beings (UG)
- **Discretionary provision in "KAKuG"**
  - Applied medical research in human beings
  - Nursing research
  - Application of new nursing or treatment concepts
  - Application of new nursing or treatment methods

Application to the EC necessary?

- **International**
  - Each 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

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 small risks or small burdens for the participants, respectively appear to be unacceptable:

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

ICH-GCP – Informed Consent (1)

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 (2)

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 (3)

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 (4)

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 (5)

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**

Documents to submit

General (number of copies as required by the respective EC, follow possible requirements of an electronic application)

- **Application form**
  - of the *Forum of Austrian Ethics Committees* – one copy signed by applicant and investigator(s)
- **Study protocol** (including amendments, if applicable)
  - one copy signed by investigator(s)
- **Informed consent form**
- **Case Report Form (CRF)**
- **Proof of qualification of the investigator(s)**
  - actual CV(s)
- **Conflict of interests**
  - if applicable

Documents to submit

- **Financial arrangements**
  - if applicable
- **Votes of other ECs**
  - if available
- **Advertising material** (insertion-text including layout, etc.)
  - if applicable
- **Patient card, patient diary, questionnaires, etc.**
  - if applicable
- **Insurance certificate(s)**
  - if necessary
- **Proof of payment of the fee**
  - or application for remission of the fee (informal, with justification)

Documents to submit

Additional for trials on medicinal products

- **EudraCT-number**
- **Form ENTR/CT 1, Annex 1**
  - "Request for opinion of the ethics committee"
  - via "EudraCT"
- **List of centres and list of the local responsible ECs for** multicentre trials
- **Agreement between sponsor and centres**
  - as well as list of the amounts and modalities for the allowance or compensation of investigators and trial subjects, if applicable
- **Investigator's Brochure**

Documents to submit

Additional for trials on medical devices

- **Declaration of conformity** (CE-certificate)

  or – if not CE-earmarked or used in new indication –
- **Risk analysis**

  and
- **Proof of compliance with the "essential requirements"**

  as well as
- **User manual**
- **Preclinical documentation**

Recommendations for the application

- **First Step: Planning ⇨ Study protocol**
  - look about chapter 6 of the ICH-GCP-Guidelines
  - ideally the protocol is written so that an appropriately qualified person not involved in the study planning could carry out the study according to the protocol
- **Clinical trials on medicinal products**
  - obtain EudraCT-number (webpage)
  - obtain information about the medicinal product
  - fill in the EudraCT-form online
  - store PDF-files for the competent authority (CA) and the ethics committee as well as the XML-file (for CA) locally
  - print PDF-files
- **Clinical trials on medical devices**
  - obtain product information, declaration of conformity, etc.

"Failing to plan is planning to fail."

Alan Lakein

"To call in the statistician after the experiment is done may be no more than asking him to perform a post-mortem examination:
he may be able to say what the experiment died of."

Sir Ronald Aylmer Fisher
(1890 - 1962)

Recommendations for the application

- **Not till then: fill in the EC application form**
  - Hint: The information given in the application form represents a synopsis of the study protocol. Thus, the form could not contain any information that is not – more comprehensive – given in the study protocol!
  - The application form is standard for all study applications in Austria. For certain projects not all points may apply ⇨ "n.a."
  - When relevant points can not be taken from the protocol ⇨ amend the protocol
- **Generate additional documents**
  - Informed consent form
  - CRF
  - Questionnaites, diaries, etc.
  - Advertising material, etc.
  - …

Links – EC (EU)

- General: Document search
  (Official Journal, Directives, etc.)
  http://eur-lex.europa.eu/en/index.htm
- Everything about medicinal products
  http://ec.europa.eu/health/human-use/index_en.htm
- EMA, inter alia Guidelines – Medicinal products
  http://www.ema.europa.eu/ema/index.jsp
- EudraCT Database
  https://eudract.ema.europa.eu/
- Everything about medical devices
  http://ec.europa.eu/enterprise/medical_devices/index_en.htm
- Guidelines – Medical devices
  http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/

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 quite bad.

Further Links

- ICH – International Conference on Harmonization
  http://www.ich.org/
- WMA – World Medical Association
  Declaration of Helsinki
  http://www.wma.net/en/30publications/10policies/b3/index.html
- WHO – World Health Organization
  http://www.who.int/en/
- CIOMS – Guidelines
  http://www.cioms.ch/publications/guidelines/frame_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