swissethics

Schweizerische Vereinigung der Forschungsethikkommissionen
Association suisse des Commissions d'éthique de la recherche
Associazione svizzera delle Commissioni etiche della ricerca
Swiss Association of Research Ethics Committees

Ethical & Legal Considerations For Clinical Trial Design

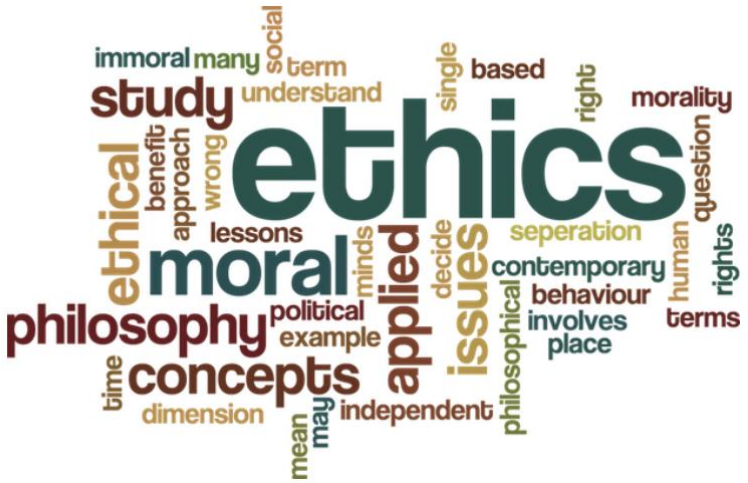
Future Leaders of Hematology & Oncology

Bern, 4th April 2025

Dr. Pietro Gervasoni
swissethics

Ethics

- is a normative discipline and not an exact science
- it mirrors the reflection of our reason in deciding whether a behavior is right or wrong / good or bad
- the interesting cases in ethical discussions are those in which people do not agree (Derek Parfit 1984, On What Matters)



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Ethics

Question of right and good action in a social context:

«ethos»: custom practice → inner reflection, values, norms, principles

«should ethics»: oriented towards the action, evaluation of the action

1. teleology - telos «goal»:

utilitarianism, oriented towards the goal,

consequentialist theory, sum calculation

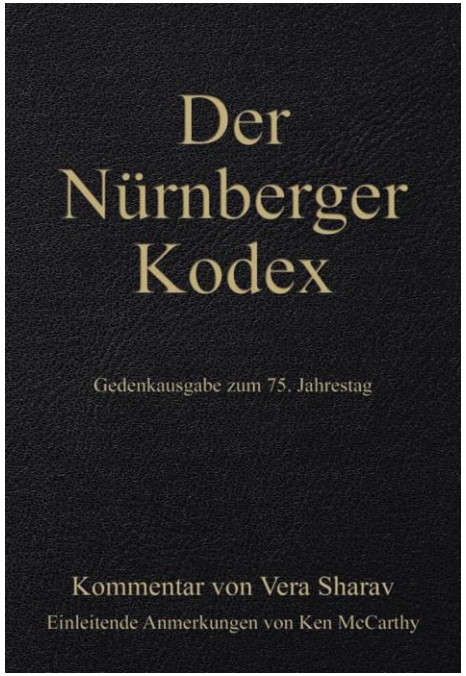
2. deontology – deon «duty»:

duty ethics, the «necessary», the desired, orientated towards morality

What makes clinical research ethical ?

Nuremberg Code (1947)

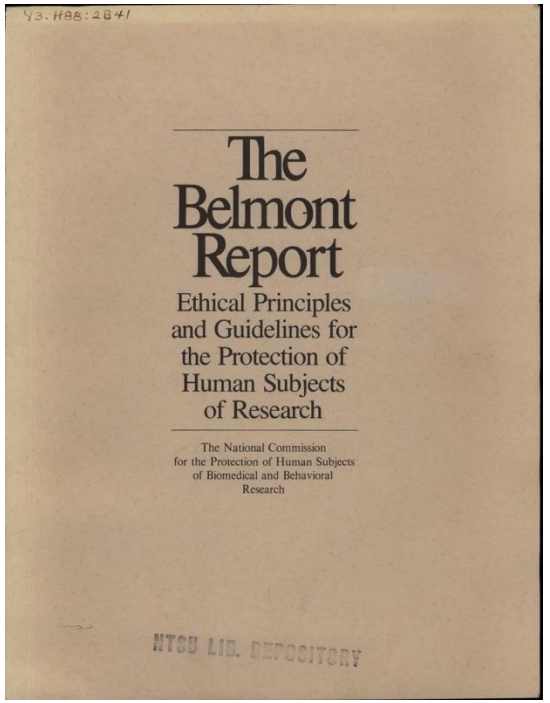
- **Why it matters:** First major international document on **human research ethics**, developed after the **Nazi medical experiments**.
- **Key principles:**
  - **Voluntary informed consent** is essential.
  - Research must **benefit society** and be **scientifically justified**.
  - Avoid **unnecessary physical and mental suffering**.
  - Participants can **withdraw at any time**.
  - Researchers must **terminate** studies if harm is detected



Declaration of Helsinki (1964, updated regularly)

- **Issued by: World Medical Association (WMA)**.
- **Why it matters:** The **foundation of modern medical research ethics**, widely used in clinical trials.
- **Key principles:**
  - Research must have a **favorable risk-benefit ratio**.
  - Participants must be **fully informed** and give **voluntary consent**.
  - **Vulnerable populations** (e.g., children, prisoners) need **extra protection**.
  - Use of **placebos is only ethical** when no proven treatment exists.
  - Results must be **publicly reported**, even if negative.

Belmont Report (1979)

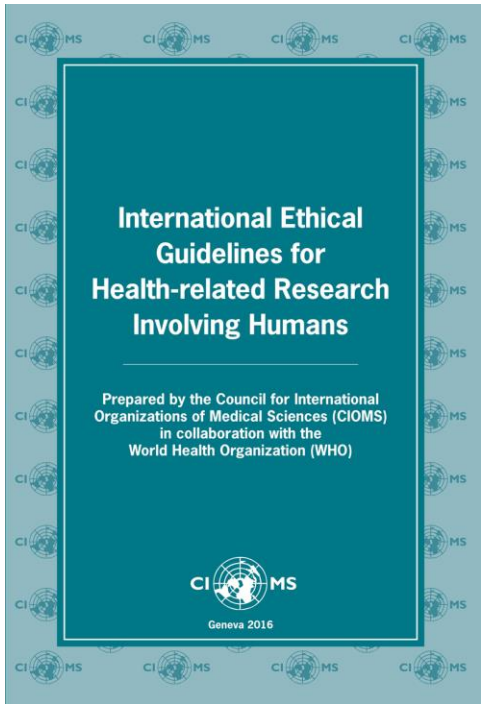


Issued by: U.S. National Commission for the Protection of Human Subjects.

- **Why it matters:** Established three fundamental **ethical principles** for human research.
- **Key principles:**
  - **Respect for persons** – Individuals must give informed consent.
  - **Beneficence** – Research must maximize benefits and minimize risks.
  - **Justice** – Fair distribution of risks and benefits (no exploitation of vulnerable groups)

CIOMS Guidelines (1982, updated 2016)

- **Issued by: Council for International Organizations of Medical Sciences (CIOMS)**, in collaboration with the **World Health Organization (WHO)**.
- **Why it matters:** Focuses on **research in low-resource countries**.
- **Key principles:**
  - Ethical guidelines must be **adapted for different cultures and economic settings**.
  - Strong protections for **vulnerable populations**.
  - Requires **post-trial access**—ensuring participants in developing countries can access treatments after trials.



Good Clinical Practice (GCP) (1996, updated 2013, 2016, 2025)

- **Issued by: International Council for Harmonisation (ICH).**
- **Why it matters:** Sets global **standards for clinical trials**, ensuring ethical and scientific quality.
- **Key principles:**
  - **Protection of human rights** and safety of participants.
  - Trials must be **scientifically and ethically justified**.
  - **Informed consent** is mandatory.
  - **Data integrity**—research findings must be accurate and transparent.


ICH

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R3)

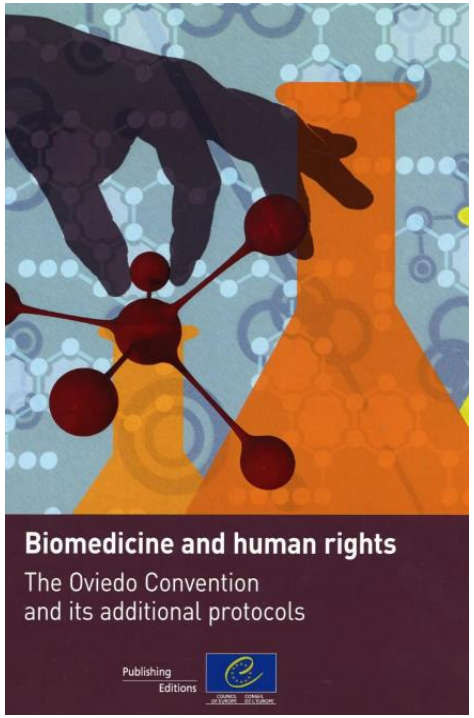
Final version

Adopted on 06 January 2025

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

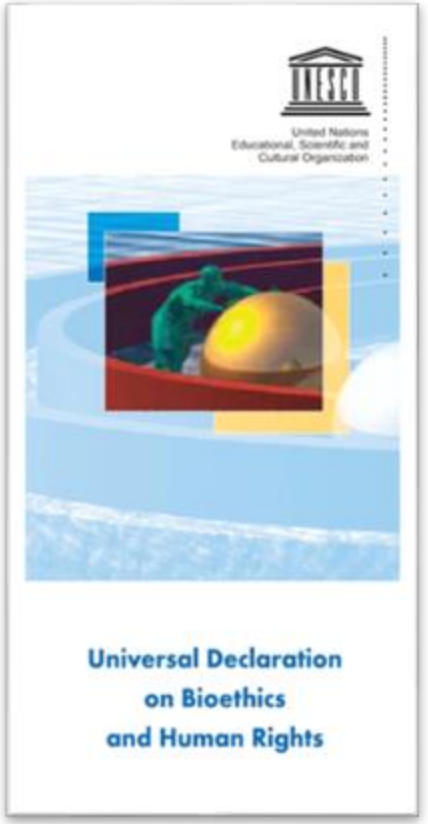
Convention on Human Rights and Biomedicine; Oviedo Convention (1997)

- **Issued by: European Council**
- **Why it matters:** Links **human rights with bioethics**, **Binding international law** for signatory countries.
- **Key principles:**
  - Human rights and dignity take precedence over scientific or societal interests.
  - Prohibition of Financial Gain in Organ Donation.
  - **Modifying the human genome** is prohibited unless done for **therapeutic** reasons. **Human cloning** is explicitly banned.
  - Protection of Vulnerable Persons.
  - Right to Privacy.



Universal Declaration on Bioethics and Human Rights (2005)

- **Issued by: United Nations Educational, Scientific and Cultural Organization (UNESCO)**.
- **Why it matters:** Links **human rights with bioethics**, emphasizing global responsibility.
- **Key principles:**
  - Research must **respect human dignity**.
  - Protection of **future generations** (e.g., genetic research).
  - **Equal access** to scientific benefits, regardless of wealth.



What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

JAMA. 2000;283:2701-2711 www.jama.com

WHAT MAKES RESEARCH INvolving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children [25-29] raise questions not of informed

JAMA. 2000;283(20):2701-2711. doi:10.1001/jama.283.20.2701

7 ethical requirements

1. Social and scientific value
2. Scientific validity
3. Fair participants selection
4. Favourable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for potential and enrolled participants

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

Art. 1 Purpose

[1] The purpose of this Act is to protect the dignity, privacy and health of human beings involved in research.

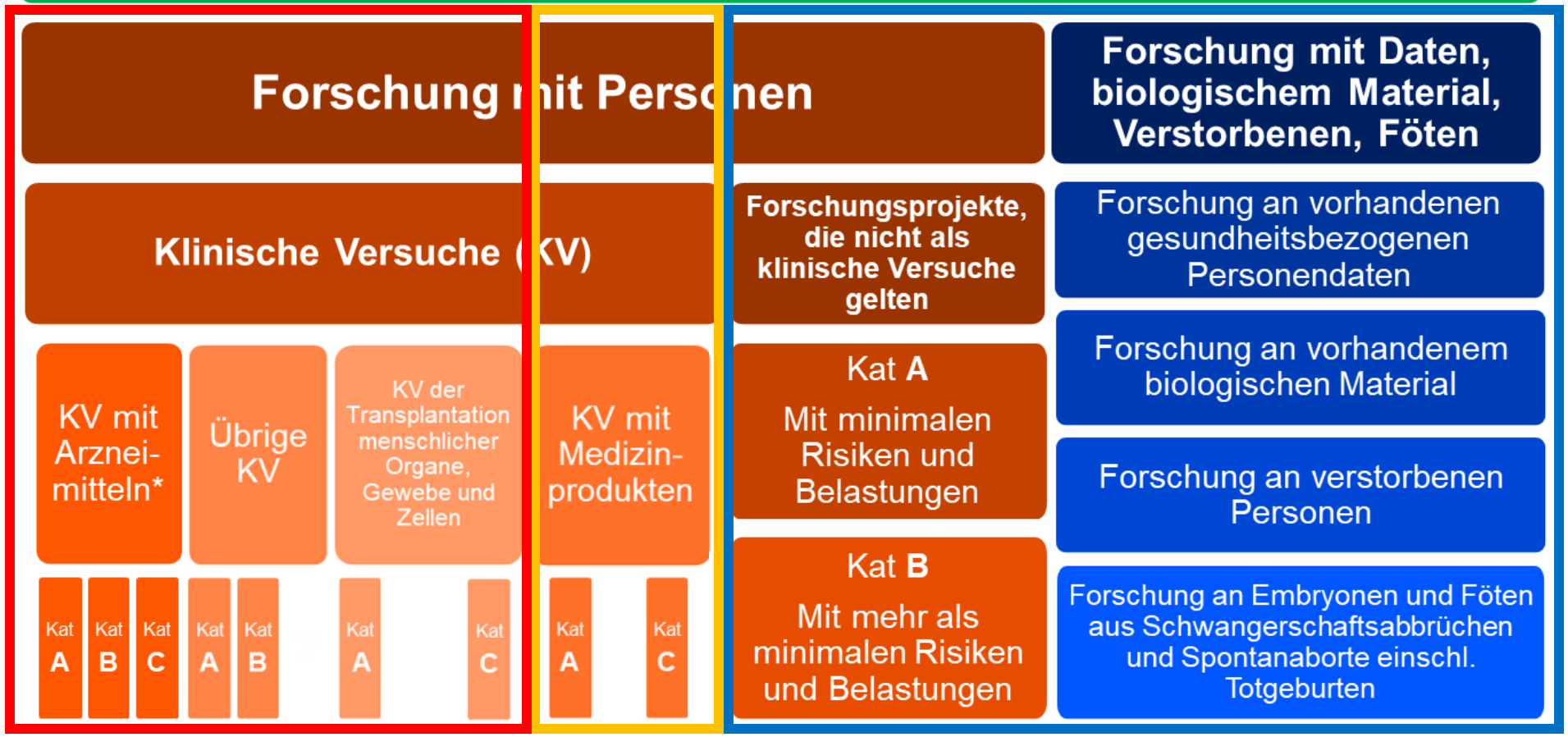
[2] It is also designed to:

a. create favourable conditions for research involving human beings;

b. help to ensure the quality of research involving human beings;

c. ensure the transparency of research involving human beings.

Humanforschung



Clinical Trial Ordinance, ClinO

Ordinance on Clinical Trials on Medical Devices, ClinO-MD

Human Research Ordinance, HRO
Chapter 2: with Persons
Chapter 3: Further Use of Biological Material and Health-related Personal Data

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Wording in the Ordinances ClinO, ClinO-MD, HRO

Scientific relevance
Suitability of methodology
ICH E6 conformity
Vulnerable persons
Benefit / Risk
Independent review
Ethics committee, Swissmedic
Informed consent
Scientific integrity
Transparency
Compensation
…

Essential questions I

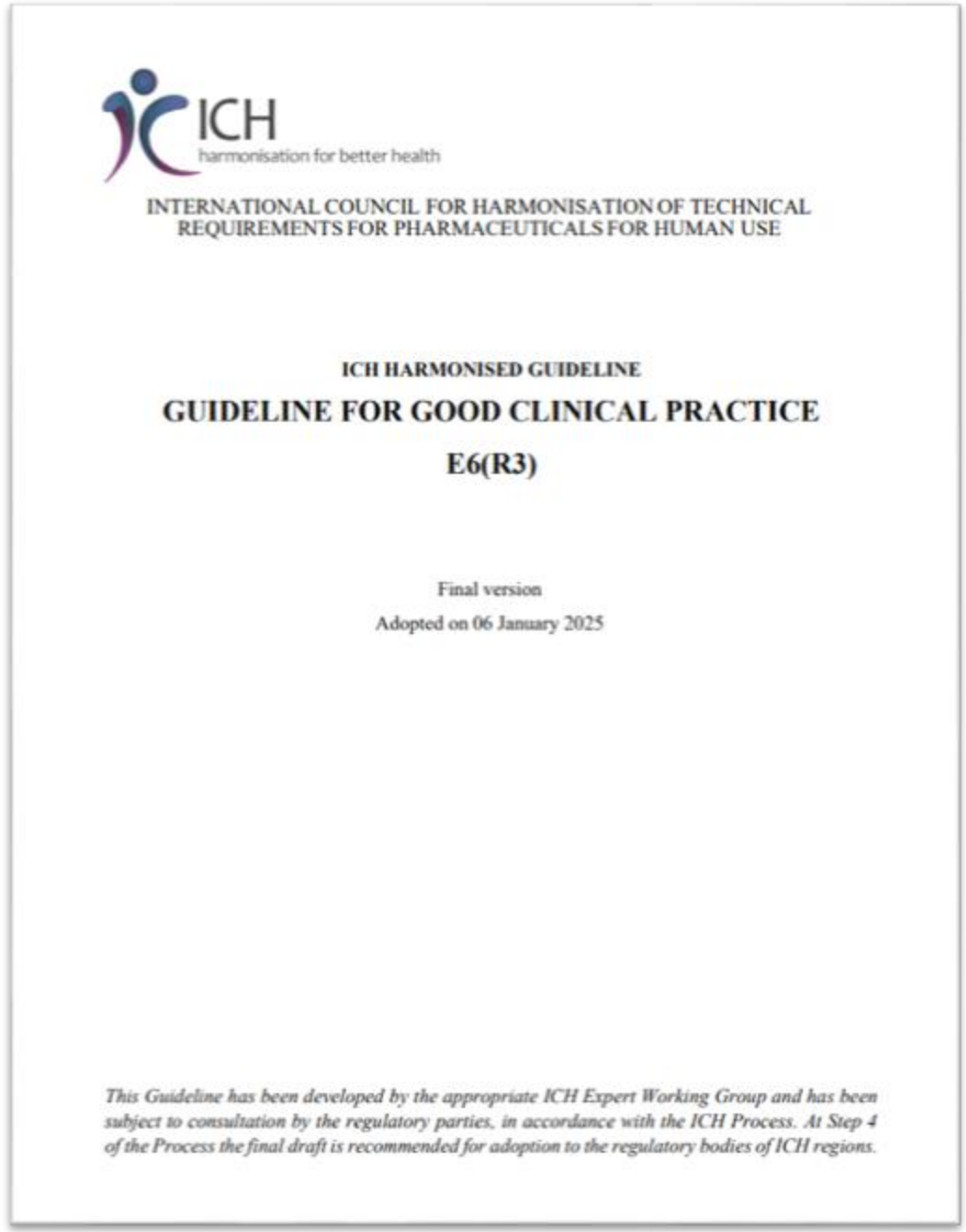
Science / Methodology / Risk:

- Is this an appropriate study for a relevant question with expected knowledge gain?
- Is the design appropriate to answer the study question?
  Are scientific integrity and quality considered?
- Are individual risks adequately addressed?
  The scientific value must «outweigh» the personal risks and burdens to the individual.

Essential questions II

Other ethical considerations:

- Are patients selected «fairly»?
- Are patients adequately informed so that they understand what will happen when they sign the informed consent?
- Are patients treated with dignity and respect and has an overall attempt been made to minimize conflicts and risks?



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ICH HARMONISED GUIDELINE

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Appendix B. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S) 58

1. Social and scientific value
2. Scientific validity
3. Fair participants selection
4. Favourable risk-benefit ratio
5. Independent review
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Study protocols
Patient information and Declaration of consent
Contracts
Insurance
Notifications
Research on and with children
Research in an emergency situation
Various
BASEC
Topics
Training
Ethics Committees
Links

Study protocols

Templates and documents that were updated in the last 2 months are marked with green color.

Requirements for study protocols according to the Human Research Act (HRA)

Requirements for study protocols according to the Human Research Act (HRA), the ordinance on clinical trials in human research (ClinO), the ordinance on clinical trials of medical devices (ClinO-MD) and the ordinance on human research with the exception of clinical trials (HRO)

English 8.0 updated: 15.10.2024

"Swiss specific addendum" for clinical trials according to ClinO

This Swiss specific addendum, or other document but with equivalent purpose and content, must be submitted to the ethics committee, for applications submitted before November 1, 2024, but which can only be approved after November 1 under the new law.

If the trial protocol is prepared under the old law and submitted after November 1, 2024, the Swiss specific addendum must be submitted at the same time.

In any case, the addendum must be submitted before the first participant is included in the clinical trial.

English 1.0 updated: 17.10.2024

Clinical trials according to ClinO

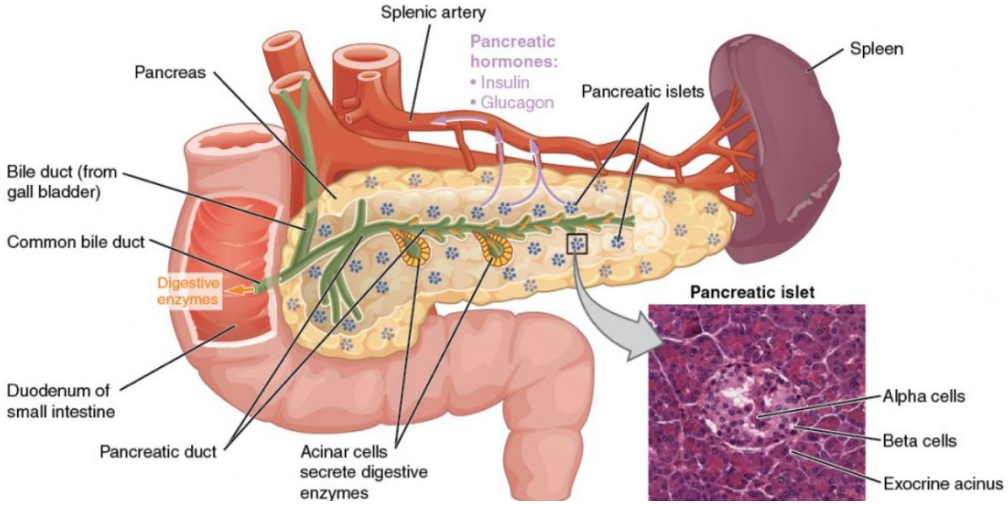
Protocol template according to ClinO, for clinical trials

English 2.0 updated: 16.09.2024

Clinical trials according to ClinO chapter 4

- The swissethics templates for writing protocols and patient information and consent forms comply with Swiss legislation, international guidelines and ethical principles.
- However, the templates should always be adapted to the specific requirements of the project.
- Article 3.3.3, ICH E8(R1), General considerations for clinical studies.

Case study I
5. Independent Review



The islet case

Islets of Langerhans produce insulin and can be isolated from the pancreas. Their transplantation allows to improve the treatment of the worst cases of diabetes. However, it may happen that after isolation, these islets prove to be unsuitable for transplantation. In these cases, the transplantation laboratory has made them available to the researchers. The Ethics Committee approved this practice years ago, and this approval has been tacitly renewed since. However, voices were raised recently questioning the legality of the procedure. In fact, the donors or their relatives had consented to the transplantation but not to the research.

The use of samples (taken for the purpose of transplantation) for research is provided for in the Human Research Act (HRA) without consent, under certain conditions.

Art. 38 Research in connection with an autopsy or transplantation

Small quantities of bodily substances removed in the course of an autopsy or transplantation may be anonymised for research purposes without consent, in the absence of a documented refusal of the deceased person.

What does “small quantities" mean? Islets weigh less than a gram, but their isolation requires the destruction of an entire organ.

Is article 38 HRA applicable?

A) Yes
B) No
C) Maybe

Would you / should the ethics committee authorize the project?

A) Yes
B) No
C) Maybe

case study I

good - bad

right - wrong

Ethics ≠ Enforcement of the law

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Case study II
2. Scientific validity, 6. Informed consent

The support trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 27, 2010 VOL. 362 NO. 21

Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

The SUPPORT trial

Background:

Preterm infants receive oxygen because they have problems with breathing. - too much oxygen: risk of blindness (retinopathy)

- too little oxygen: increased mortality

Question:

Which oxygen saturation in the blood is optimal?

Methods:

Randomization into 2 study arms: Oxygen saturation

85-89% vs. 91-95%

Informed consent process

Information to the parents on the project

- Both oxygen saturations are **within the range of clinical practi**ce (standard of care).
- The project wants to assess which oxygen saturation is associated with the best risk profile.

What is missing? where is the problem?

What is missing?

- The information is deficient.
- Explicit reference should have been made to the potentially higher risk of mortality with low O_2-saturation and the potentially higher risk of retinopathy with a higher O_2 saturation should have been pointed out.

Where is the problem?

PERSPECTIVE

INFORMED CONSENT FOR STUDIES WITHIN STANDARD OF CARE

Foreseeable Risks? Informed Consent for Studies within the Standard of Care

Chana A. Sacks, M.D., and Celestine E. Warren, A.B.

More than 1400 babies were born prematurely in the United States every day in 2005, according to the Centers for Disease Control and Prevention, and neonatologists still weren't process was inadequate — that increased mortality, though it hadn't been recognized previously, was a reasonably foreseeable risk of lower oxygen saturation and should have been included ric cancer in which participants are randomly assigned to either a higher or a lower radiation dose. The study's purpose is "to compare the effectiveness of the two treatments in curing the current

- The issue with the randomization !

In contrast to the treatment available off project the choice of treatment is denied to the parents in the study !

Case study III
1. Social value, 2. Scientific validity

COVID-19 Vaccine Trials (2020-2021)

Many vaccine trials (e.g., Pfizer, Moderna) used placebo groups to compare effectiveness. After vaccines were proven highly effective, debates arose over whether placebo participants should be offered the real vaccine.

What is the ethical issue?

- Continuing the placebo group meant withholding a life-saving vaccine during a pandemic.
- Public health vs. scientific rigor – removing the placebo group too soon could weaken long-term data.

Outcome:

- Some participants were offered the vaccine after a certain point.

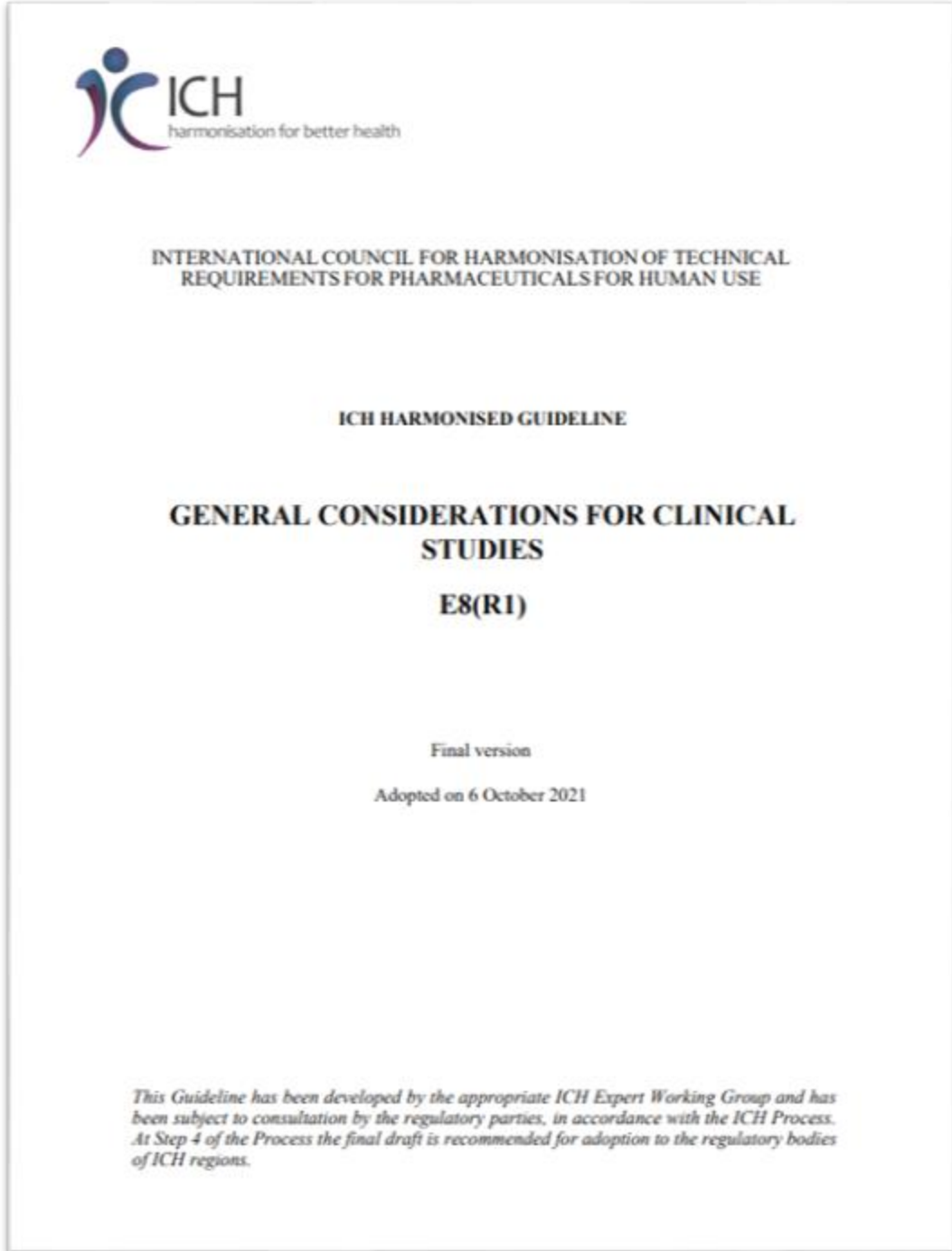
Declaration of Helsinki

Use of Placebo

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- If no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- If for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and the participants who receive any intervention other than the best proven one(s), placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

  Extreme care must be taken to avoid abuse of this option.



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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

E8(R1)

Final version

Adopted on 6 October 2021

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3.3.3 Engaging Stakeholders in Study Design

Clinical study design is best informed by input from a broad range of stakeholders, including patients and healthcare providers. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation.

The process of building quality into the study may be informed by participation of those directly involved in successful completion of the study such as clinical investigators, study coordinators and other site staff, and patients/patient organisations. Clinical investigators and potential study participants have valuable insights into the feasibility of enrolling participants who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints and study settings to the targeted patient population. They may also provide insight into the value of a treatment in the context of ethical issues, culture, region, demographics, and other characteristics of subgroups within a targeted patient population.

Early engagement with regulatory authorities is encouraged, particularly when a study has novel elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints).

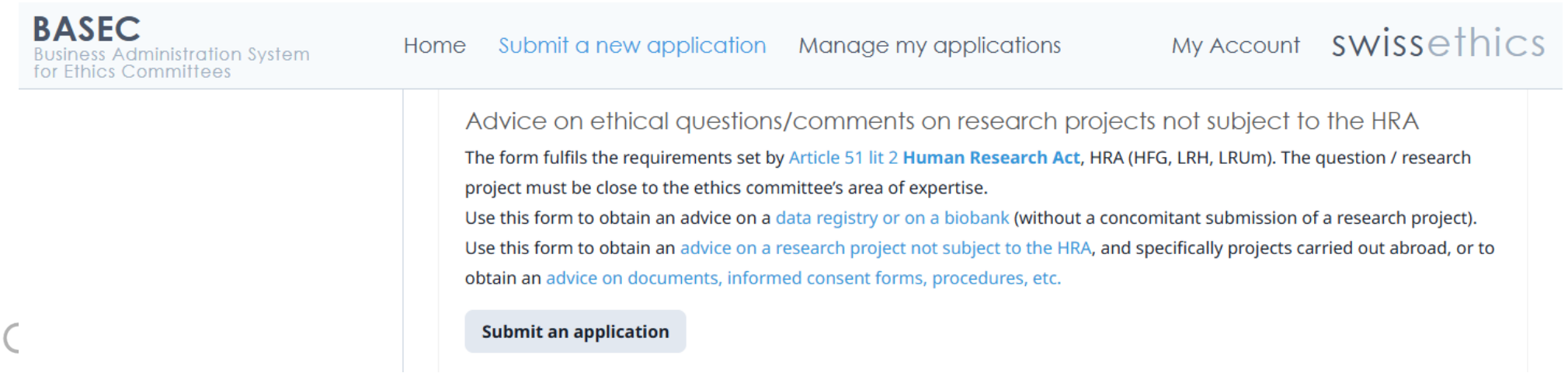
Advice on ethical questions

Human Research Act

Art. 51 Duties

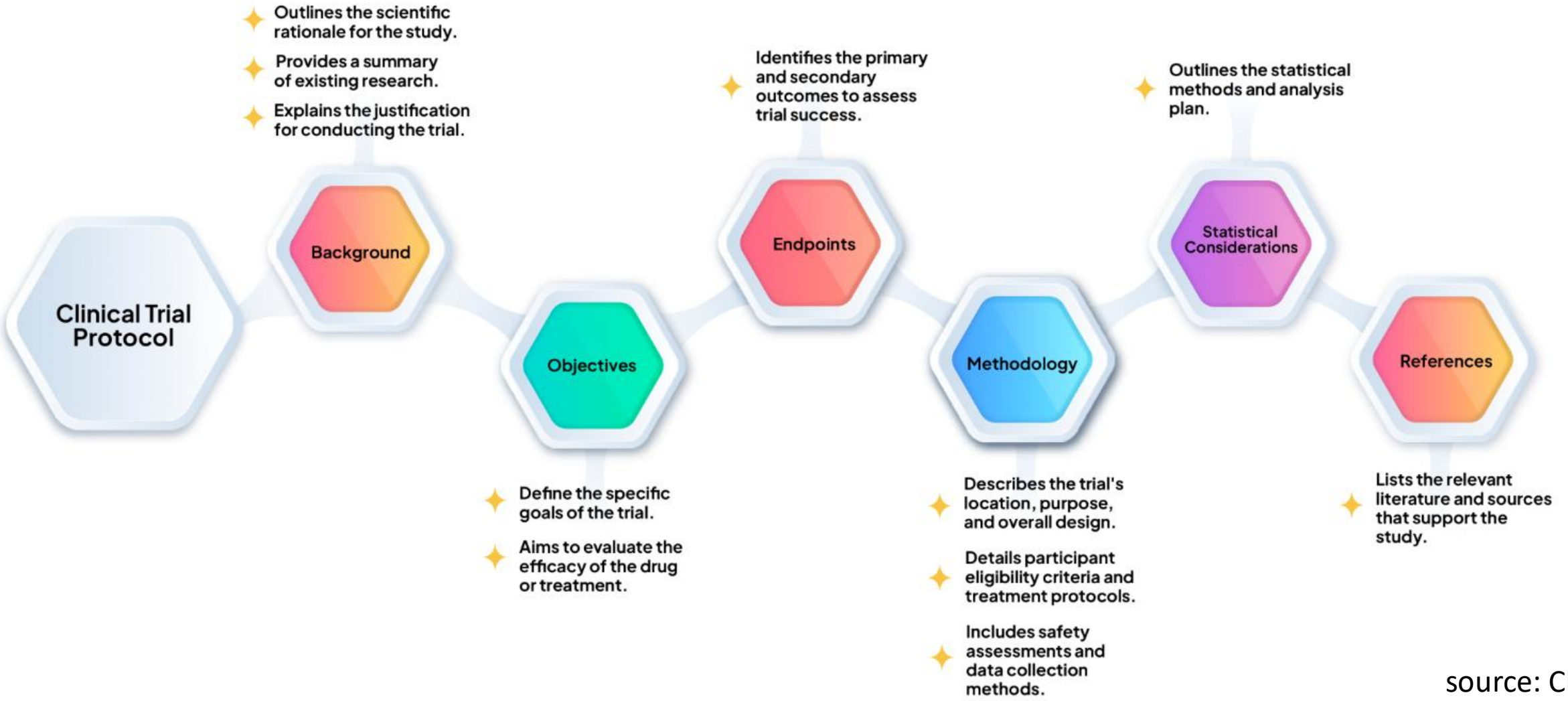
[1] Within the framework of their responsibilities under Chapter 8, ethics committees shall assess whether research projects and the conduct thereof comply with the ethical, legal and scientific requirements of this Act. In particular, they shall assess whether the protection of the persons concerned is guaranteed.

[2] They may advise researchers in particular on ethical questions and, if so requested by the researchers, comment on research projects not subject to this Act, and specifically projects carried out abroad.



swissethic

What about using AI to design the clinical trial and write the trial protocols ?



source: Clinion

Yes, …

- Training on Real-World Protocols
  - Data collection and analysis
- Standardized Templates and Frameworks
  - Template utilization
- Automated Document Generation
  - Initial draft creation, text generation, formatting and structuring
- Collaboration and version control
- Customization

high-quality protocols
enhance efficiency
reduce errors

…, but, …

Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension

*Samantha Cruz Rivera, Xiaoxuan Liu, An-Wen Chan, Alastair K Denniston, Melanie J Calvert, and The SPIRIT-AI and CONSORT-AI Working Group**

The SPIRIT 2013 statement aims to improve the completeness of clinical trial protocol reporting by providing evidence-based recommendations for the minimum set of items to be addressed. This guidance has been instrumental in promoting transparent evaluation of new interventions. More recently, there has been a growing recognition that interventions involving artificial intelligence (AI) need to undergo rigorous, prospective evaluation to demonstrate their impact on health outcomes. The SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence) extension is a new reporting guideline for clinical trial protocols evaluating interventions with an AI component. It was developed in parallel with its companion statement for trial reports: CONSORT-AI (Consolidated Standards of Reporting Trials-Artificial Intelligence). Both guidelines were developed through a staged consensus process involving literature review and expert consultation to generate 26 candidate items, which were consulted upon by an international multi-stakeholder group in a two-stage Delphi survey (103 stakeholders), agreed upon in a consensus meeting (31 stakeholders) and refined through a checklist pilot (34 participants). The SPIRIT-AI extension includes 15 new items that were considered sufficiently important for clinical trial protocols of AI interventions. These new items should be routinely reported in addition to the core SPIRIT 2013 items. SPIRIT-AI recommends that investigators provide clear descriptions of the AI intervention, including instructions and skills required for use, the setting in which the AI intervention will be integrated, considerations for the handling of input and output data, the human–AI interaction and analysis of error cases. SPIRIT-AI will help promote transparency and completeness for clinical trial protocols for AI interventions. Its use will assist editors and peer reviewers, as well as the general readership, to understand, interpret, and critically appraise the design and risk of bias for a planned clinical trial.

Lancet Digital Health 2020; 2: e549–560

Published Online September 9, 2020 https://doi.org/10.1016/S2589-7500(20)30219-3

See Review page e537

*Members listed at the end of the paper

Centre for Patient Reported Outcome Research, Institute of Applied Health Research (S Cruz Rivera PhD, Prof A K Denniston PhD, Prof M J Calvert PhD), **Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences** (X Liu MBChB, Prof A K Denniston), **and Birmingham Health Partners Centre for Regulatory Science and Innovation** (X Liu

JAMA Network Open

Original Investigation | Ethics

Ethical Considerations in the Design and Conduct of Clinical Trials of Artificial Intelligence

Alaa Youssef, PhD; Ariadne A. Nichol, BA; Nicole Martinez-Martin, JD, PhD; David B. Larson, MD, MBA; Michael Abramoff, MD, PhD; Risa M. Wolf, MD; Danton Char, MD, MS

JAMA Network Open. 2024;7(9):e2432482. doi:10.1001/jamanetworkopen.2024.32482

How generalizable are the 7 ethical requirements for conduct of clinical trials of AI, and what unique ethical considerations arise in trials of AI?

Challenges unique to clinical trials of AI

Difficulties

- in measuring social value and establishing scientific validity,
- ensuring fair participant selection,
- evaluating risk-benefit ratios across various patient subgroups,
- and addressing the complexities inherent in the data use terms in the informed consent.

Conclusion

- Ethics is fundamental in clinical research, ensuring human dignity, safety, and scientific integrity.
- Emerging challenges – scientific and technological advancements, artificial intelligence, data privacy, and evolving regulations demand continuous ethical reflection.
- Ultimately, balancing scientific progress with ethical responsibility is key to building trust in clinical research.
- "Ethics is not about enforcing laws – it is about making the right decisions."

Thank You

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