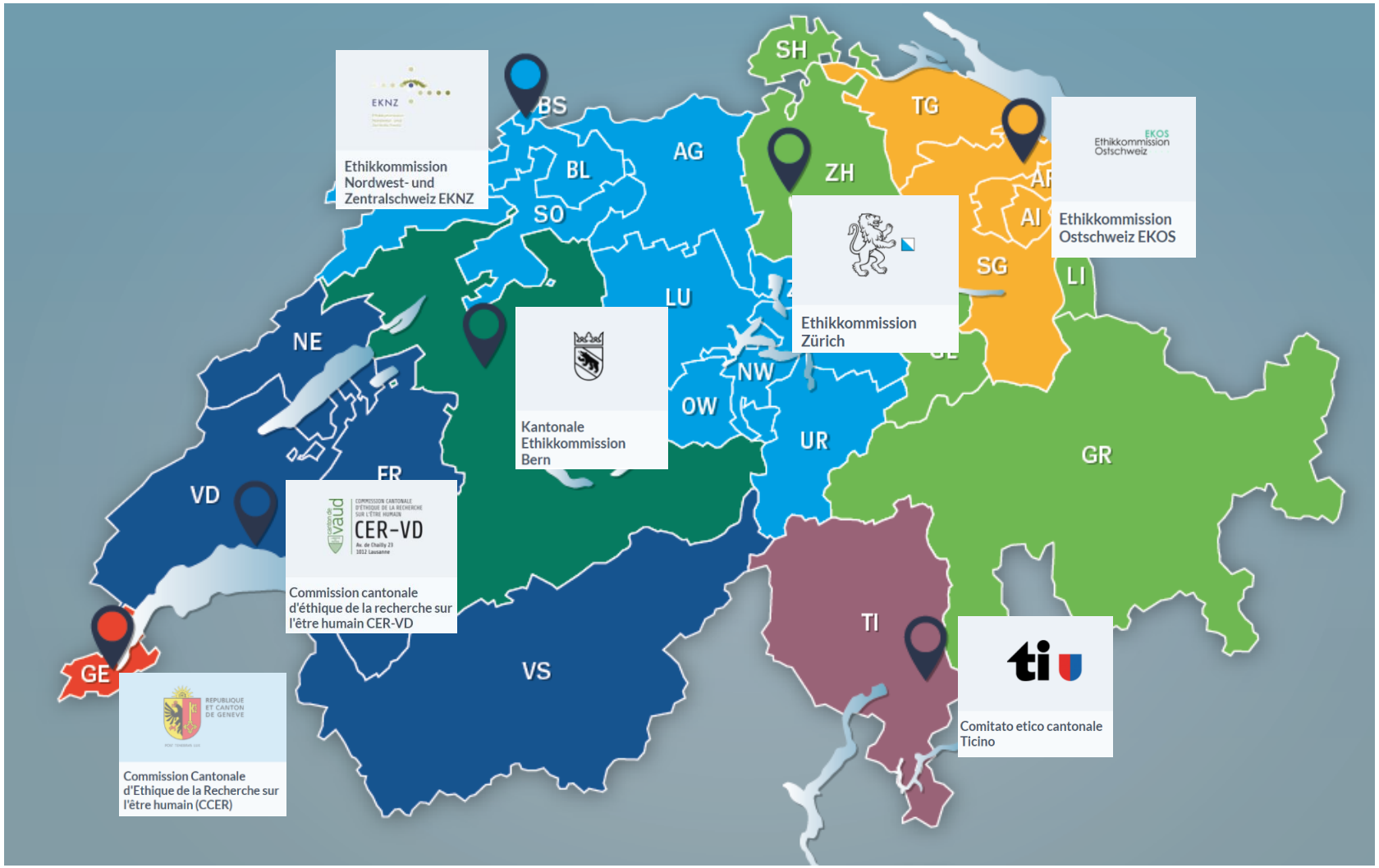
Lay Summaries of Clinical Trial Results: Ethical Considerations

Dr. Pietro Gervasoni

swissethics

Ethics Committees Human Research Switzerland



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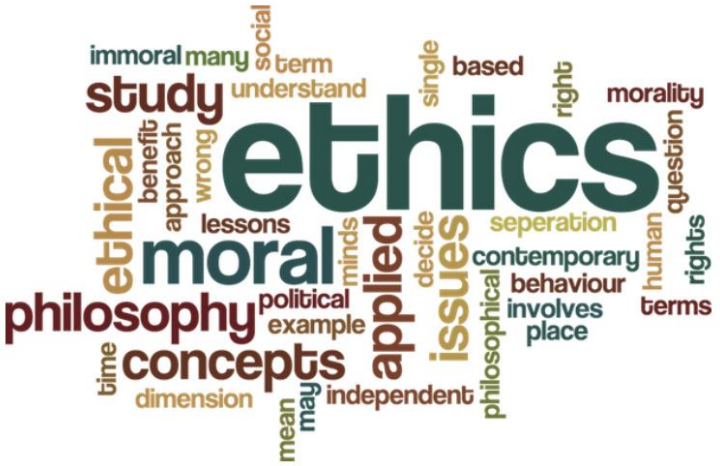
Quelle: Humanforschungsgesetz und Koordinationsstelle Forschung am Mensch, BAG, Mai 2016

The legal requirements for the publication of lay summaries of clinical trial results will come into force in the EU at the beginning of 2022 for trials involving medicinal products (EU-CTR 536/2014).

For clinical trials with medical devices, the legal basis already applies in Switzerland and the EU from May 26, 2021 (EU-MDR 2017/745, ClinO-MD 810.306).

Lay summaries of clinical trials results are not just a regulatory requirement



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Moral Norm	Ethical Standards	Legislation
Based on moral judgement with the claim of truth	Based on agreement or decision → Rules (without claim of truth)	System of legal norms with the claim of appropriateness
	E.g., Declaration of Helsinki	E.g., National Law
	Soft Law	**Hard Law**
	Factual validity = Level of adherence; Normative validity = Level of engagement	Legality = Duly enactment = Legal validity; Possibility of sanctions!

Examples:

«We must always say the truth!»

«You must not harm!»

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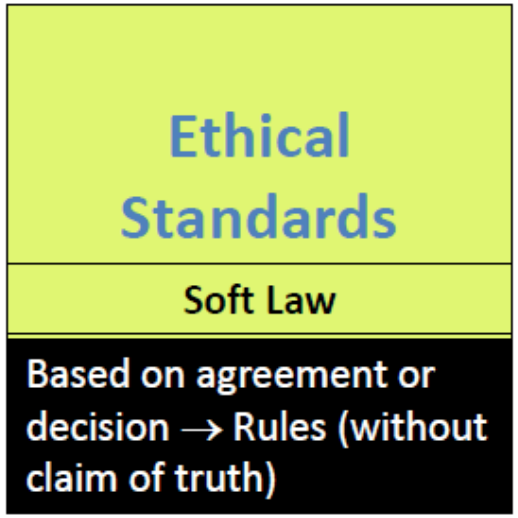
Dr. Peter Kleist
Managing Director, EC Zürich



Ethical principles

e.g. Declaration of Helsinki

Technical rules, standards, good practices

e.g. Good Clinical Practice Guidelines, ISO14155, guidance docs

Legislation

e.g. HRA, EU-CTR, EU-MDR

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modified from Dr. Peter Kleist
Managing Director, EC Zürich

Principles of Biomedical Ethics

autonomy («Autonomie») voluntas aegroti suprema lex	**beneficence («Fürsorge»)** salus aegroti suprema lex
justice («Gerechtigkeit») suum cuique	**non maleficence («Nicht-Schaden»)** primum non nocere

T. L. Beauchamp/J. F. Childress, Principles of Biomedical Ethics, 7th Ed., OUP 2012.

Special Communication

May 24/31, 2000

What Makes Clinical Research Ethical?

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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.

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

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

clear research question

reliable methodology

adequate population

assesment by investigator and EC

EC

respect of autonomy

Throught the whole course of the trial

Declaration of Helsinki - Ethical principles for medical research involving human subjects

WORLD MEDICAL ASSOCIATION

(39) The sponsor should submit a summary of the results of the clinical trial together with a summary that is understandable to a layperson, and the clinical study report […]

(36) […] Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. […] Negative and inconclusive as well as positive results must be published or otherwise made publicly available. […]

Ethical obligation to enable reliable and comprehensive transparency by providing correct, comprehensive and objective trial result information

Recommendations, Good Practice, ….

- Guidance **Good Lay Summary Practice** adopted by the EU Clinical Trials Expert Group (v.1, Oct. 2021)
- Recommendations **Summaries of clinical trials results for lay persons** of the expert group on clinical trials for the implementation of the EU CTR (v2, 2018)
- **Summaries of Clinical Trials Results for Laypersons**. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 (v2. 2017)
- Multi-Regional Clinical Trials (MRCT) – **Return of Aggregate Results**; Tools and guidance for the clinical trial community (2013, 2017)
- Multi-Regional Clinical Trials (MRCT) and TransCelerate Inc.: **Draft FDA Guidance on Provisions of Plain Language Summaries** (2017)
- TransCelerate Inc.: **Layperson Summaries of Clinical Trials**: An Implementation Guide (2017)

Respect – Appreciation – Transparency – Reciprocity – Timely

- All participants' right to be informed of the results of the research to which they contributed
- All participants' right and public's right to receive that information in an objective, understandable way
- Acknowledge the participants contribution and expression of appreciation (not limited to the summary of study results!)
  - Study participants are not 'guinea pigs' of research
  - Good medical care
  - Appropriate risk management
- Open discussion/feedback to the participants (not solely direct the participants to the lay summaries on the web-portals ...)
- Within one year from the regular end of a clinical trial
- Recognise and protect the legitimate economic interests of sponsors

Development of the Lay Summary – Key points

- Ensure that the lay summary content and presentation of data is balanced and strictly non-promotional
- Language and design
- Consider development of lay summaries for children (ages 12 and up)

KOMMENTAR

Prof. Dr. med. Werner Golder, Radiologe, Avignon

TEILNAHME AN KLINISCHEN STUDIEN

Ein kostbares Geschenk

Die Teilnahme an der Studie verlangt viel Zeit und viel Geduld – bei den An- und Abfahrten, in den Warteräumen, bei den Gesprächen, bei den Untersuchungen. Manchmal wird aus Gründen des Studiendesigns der Verzicht auf die Fortsetzung der Einnahme bisher verwendeter Medikamente und/oder die Unterbrechung der bisherigen therapeutischen Maßnahmen gefordert. Nicht immer wird im Detail erläutert, ob die begleitenden körperlichen und instrumentellen Untersuchungen studienbedingt sind oder auch sonst sinnvoll und notwendig gewesen wären. Jeder einzelne Test erhöht aber die physische und psychische Belastung des Patienten.

...

Die Studienpatienten bleiben im Schatten des Kollektivs verborgen. Gerade dann, wenn die Teilnehmer im Anhang wieder einmal nicht dankend erwähnt werden, sollten sich nicht nur die Leser und Nutznießer jeder einzelnen Studie, sondern auch die Initiatoren laufender und geplanter klinischer Prüfungen deren Verdienste voll Bewunderung und Dankbarkeit vergegenwärtigen.

Deutsches Ärzteblatt | Jg. 110 | Heft 45 | 8. November 2013

Say THANK YOU!

- Thank you letter for participation
- Acknowledgements in publications (not only to researchers,…)
- Lay summary of study results

Ethics committee

ClinO-MD

Art. 37 Final report

[1] The sponsor shall submit to the Ethics Committee a final report in accordance with Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV to EU-MDR[28]:

a. within one year of the clinical trial being concluded;

b. within three months of the clinical trial being terminated or interrupted.

[2] If scientific reasons prevent compliance with the reporting deadline specified in paragraph 1 letter a, the sponsor must submit the report as soon as it is available. The protocol must specify when the final report will be submitted and provide reasons.

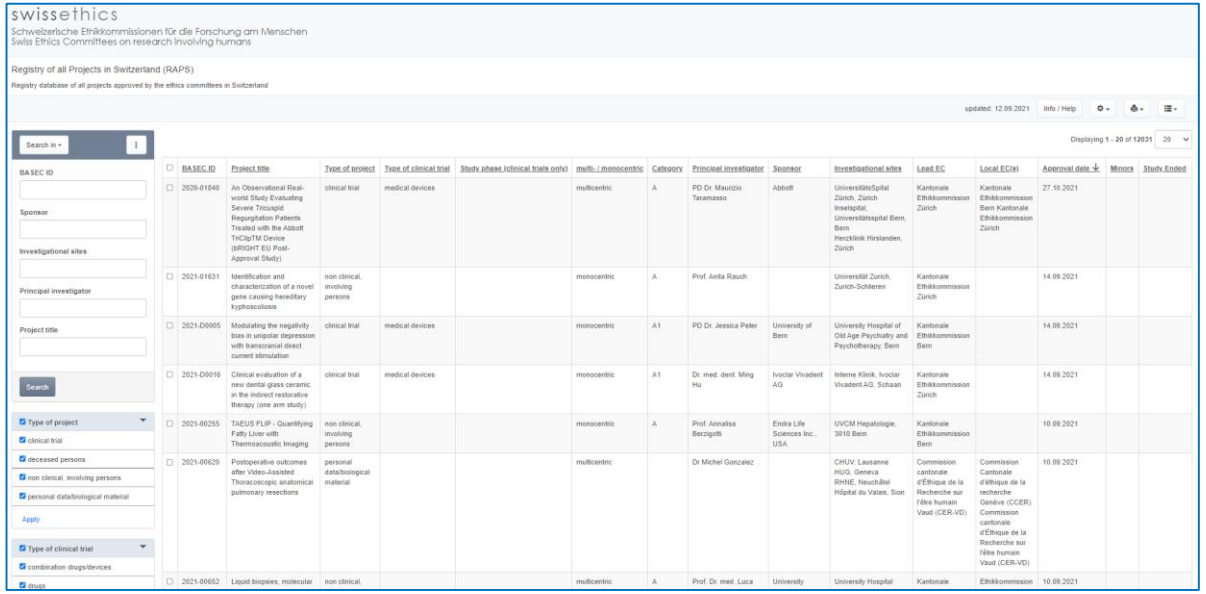
[3] A summary in lay language must be included with the final report.

Ethics committee

EU and Swiss legislation do not foresee ethics committee review of communication to patients after the notification of the end of trial.

However, the Good Lay Summary Practice recommends that sponsors generally mention their planned Lay Summary dissemination approach in the patient informed consent form.

Publication and Dissemination



- EU-CTR in CTIS, EU-MDR in EUDAMED
- ClinO-MD does not foresee the publication of the Lay Summaries outside EUDAMED (provision *on hold*)
- RAPS (Registry of <u>All</u> Projects in Switzerland) is a public registry of all projects that were approved by the ethics committees (since January 2016).
- swissethics launched it in Mai 2018 to promote transparency in research on humans for the general public, researchers and institutions.
- ClinO, HRO

Thank you!

Back-up

Annex V EU-CTR Content of the summary of the results of the clinical trial for laypersons

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

- 1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);
- 2. Name and contact details of the sponsor;
- 3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);
- 4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
- 5. Investigational medicinal products used;
- 6. Description of adverse reactions and their frequency;
- 7. Overall results of the clinical trial;
- 8. Comments on the outcome of the clinical trial;
- 9. Indication if follow up clinical trials are foreseen;
- 10. Indication where additional information could be found.