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OPERATING PROCEDURES OF THE NATIONAL COMMITTEE ON MEDICAL RESEARCH ETHICS (TUKIJA)

1. LEGAL FRAMEWORK OF TUKIJA'S OPERATIONS

Medical Research Act (488/1999, amended 295/2004, 780/2009, 794/2010 and 143/2015)

Government Decree on Medical Research (986/1999, amended 313/2004)

Government Decree on the Amendment of the Decree on Medical Research (65/2016, *only in Finnish*)

Government Decree on the National Committee on Medical Research Ethics (820/2010)

Decree of the Ministry of Social Affairs and Health on the Fees Charged for Opinions of the National Committee on Medical Research Ethics and Regional Ethics Committees (1417/2016)

Decree of the Ministry of Social Affairs and Health on Clinical Trials on Medicinal Product (841/2010)

Decree of the Ministry of Social Affairs and Health on the Compensation for Research Participation (82/2011)

Biobank Act (688/2012)

Government Decree on Consent for Biobank (643/2013)

Decree of Ministry of Social Affairs and Health on Notification of Biobank (649/2013)

Act of the Medical Use of Human Organs and Tissues (101/2001, amended 547/2007, 778/2009, 653/2010, 336/2011, 689/2012, 277/2013)

1.1 Members of TUKIJA (up to 30 September 2018), including educational background and expertise relevant to TUKIJA's operations

Chairman

Docent Tapani Keränen MD, clinical pharmacology and neurology

Deputy Chairman

Medical Specialist Miia Turpeinen MD, docent, clinical pharmacology and pharmacotherapy

Members

Professor Janne Backman MD, clinical pharmacology

Medical Specialist Sirkku Jyrkkiö MD, docent, oncologist

Professor Markku Koskenvuo MD, epidemiology

Professor Kjell Nikus MD, cardiology

Advisory Medical Officer Kristian Läksy MD, psychiatry

Medical Specialist Kristiina Aalto MD, docent, paediatrics

Professor Timo Paavonen MD, pathology

Senior legal adviser Sirpa Soini LL.M, medical and bio law

University Lecturer Liisa Nieminen LL.D, M.Pol.Sc, docent, medical and bio law

Research Scientist Helena Siipi PhD (Politics), docent, MA (Educ.), ethics, lay member

Graphic designer Tiina Aaltonen Lay member

Professor Sanna Salanterä PhD (Health Sciences), clinical nursing science

Professor Heikki Tikkanen MD, sports and exercise medicine, clinical physiology

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Personal deputies

Medical Specialist Aleksi Tornio	MD, clinical pharmacology
Chief Nurse Executive Marjo Saarenmaa	MHSC, MBA, B.Sc. (Admin), MA (Educ.), midwife
University Lecturer Jari Haukka	PhD, docent, epidemiology
Research Manager Arto Palmu	MD, docent, public health medicine
Medical Specialist Sami Räsänen	MD, psychiatry
Professor Satu Lahti	DDS, social dentistry
Research Scientist Johanna Seppänen	PhD, biometrics
Company Lawyer Jari-Pekka Tuominen	LLM, legality issues
Lawyer Tuula Stark	LLM, PhD (biochemistry)
Professor Jaana Hallamaa	D.Th, social ethics, lay member
Researcher Ville Jalovaara	D.Th, docent, lay member
Professor Helvi Kyngäs	PhD in Health Sciences, nursing science
Medical Specialist Päivi Piirilä	MD, docent, clinical physiology and occupational pulmonary diseases

Secretariat

General Secretary Outi Konttinen	MSc (Soc.Sc.)
Assistant Nina Lindqvist	Nurse, BBA

1.2 Meeting schedule

TUKIJA generally convenes once a month. New schedules are drawn up at approximately six-month intervals. Meeting schedules are posted on TUKIJA's website.

2. RESPONSIBILITIES OF TUKIJA AND REGIONAL ETHICS COMMITTEES

2.1 Responsibilities of TUKIJA

TUKIJA's responsibilities include

- Serving as an expert on research ethics;
- Monitoring, steering and coordinating the processing of issues related to research ethics;
- Issuing national opinions on clinical trials on medicinal products, unless the duties are delegated to regional ethics committees;
- Issuing opinions on previously rejected trial proposals to regional ethics committees where these are resubmitted unchanged;
- Issuing opinions on the conditions for establishing a biobank;
- Supporting and coordinating the activities of regional ethics committees regarding the procedures for requesting opinions and matters of ethical principle including provision of related training;
- Participating in international cooperation on research ethics between authorities;
- Gathering and conveying information on research ethics issues and provide information on the international debate on research ethics in the form of publications, training sessions and other such activities; and
- Promoting the public debate on medical biomedical research.

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In other words, TUKIJA is responsible for carrying out ethics reviews on clinical trials on medicinal product, but it can delegate the duties to regional ethics committees, which will then issue any necessary national opinions. Applications for other medical research projects and clinical trials are reviewed by the regional ethics committee of the region in which the researcher in charge of the proposed trial is based or in which the trial is to be primarily carried out.

Clinical trials on medicinal products are interventional studies carried out on human subjects for the purpose of finding out the effects of drugs in humans and compiling information on the absorption, distribution, metabolism, and excretion of drugs in the human body. (Finnish Medical Research Act, Section 2 (6))

Non-interventional trials are studies where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data. (Directive 2001/20/EC, Article 2 (c))

Opinions issued by TUKIJA cannot be appealed. However, TUKIJA can request amendments to be introduced to applications and they reconsider cases. Any proposal that has been previously been given a negative opinion by a regional ethics committee can be resubmitted unchanged, in which case the regional ethics committee in question is obligated to refer the case to TUKIJA. Previously rejected proposals can also be resubmitted to the ethics committee that initially reviewed the case after any amendments requested by said ethics committee have been introduced.

TUKIJA is also responsible for carrying out ethics reviews on the conditions for establishing a new biobank. This evaluation is to be done before the biobank makes a notification to the National Supervisory Authority for Welfare and Health for the purposes of the national biobank register.

2.2 Responsibilities of regional ethics committees

The responsibilities of regional ethics committees include

- Issuing opinions on proposals referred to them by TUKIJA;
- Issuing opinions on other medical studies that fall within their jurisdiction;
- Issuing opinions on the transfer of the old biological samples to a biobank;
- Issuing opinions on the change of purpose for which biological samples will be used if the consent for such use cannot be received by the donor himself/herself.
- Monitoring and steering the processing of research ethics issues in its region;

3. APPLYING FOR ETHICS REVIEWS ON CLINICAL TRIALS ON MEDICINAL PRODUCT(S)

3.1 Rulings on jurisdiction for clinical trials on medicinal product(s)

The first step in all clinical trials on medicinal product(s) is for the sponsor to apply for a ruling from TUKIJA on whether the ethical admissibility of the proposal is to be reviewed by TUKIJA or by one of

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the regional ethics committees. Sponsors can apply for a ruling on jurisdiction as soon as it becomes likely that the trial in question will be run in Finland, even if the actual application is not yet complete. Depending on the ruling, the sponsor then applies for an ethics review to be carried out either by TUKIJA or by the relevant regional ethics committee.

The Finnish Ministry of Social Affairs and Health has produced a form to be used in connection with rulings on jurisdiction. The same form is used both by the applicants and by TUKIJA. Applicants are also requested to submit their applications to TUKIJA's secretary in electronic format (as word or rft files) by e-mail to [tukija\(at\)valvira.fi](mailto:tukija(at)valvira.fi).

Applications must be submitted to TUKIJA by the end of office hours on the Monday of the week during which rulings are required at the latest. TUKIJA's secretary reviews the applications and issues proposals on their admissibility via e-mail. Deadlines for submitting applications for rulings on jurisdiction are posted on TUKIJA's website at www.tukija.fi. Jurisdiction issues are referred to a special working group which convenes, as a rule, once a fortnight.

The ruling on jurisdiction is used by the working group comprising two members of TUKIJA, a secretary, and the required number of deputies. The members of the working group notify the secretary of their decisions by the deadline set by the secretary. As a rule, the secretary records the working group's rulings on the application forms and notifies the applicants of the decisions via e-mail on the Friday of the same week. Written rulings are posted to applicants at the earliest convenience. Schedules may vary during holiday seasons.

If the working group is unable to reach unanimous agreement on the secretary's proposal, the jurisdiction for the ethics review remains with TUKIJA. The secretary draws up weekly minutes of the working group's decisions.

The other members of TUKIJA are notified of all of the rulings of the working group, but they cannot overrule the working group's decisions. The other members of TUKIJA are nevertheless entitled to give instructions to the working group.

3.2 Applying for ethics reviews to be carried out by TUKIJA or by regional ethics committees

All applications for ethics reviews of clinical trials must be made using the form issued by the Finnish Ministry of Social Affairs and Health according to the instructions provided. The documents listed on the form must be included in all applications. All documents pertaining to trials must be submitted to TUKIJA no later than two weeks before the meeting during which the proposal in question is to be reviewed.

Applications submitted to TUKIJA must be accompanied by the following documents:

1. Trial protocol (admissible in English)
2. Summary of the trial protocol
3. Investigator's brochure (admissible in English)
4. Statement by the researcher in charge of the proposed trial regarding the conformity of the trial with research ethics and especially as regards the appropriateness of the trial's aims and planning and the evaluation of risks and benefits
5. Information for potential research subjects
6. Informed consent form

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7. Information on the procedures to be used to seek consent
8. Scientific rationale in cases where potential research subjects are unable to give informed consent to participating in the proposed trial
9. Information on the detailed procedures to be used for the recruitment of subjects
10. Other materials to be made available to potential subjects (CRFs, patient diaries, etc.)
11. Description of the personal data file required under Section 10 of the Finnish Personal Data Act (No 523/1999)
12. List of trial sites and investigators in Finland
13. Statement by the researcher in charge of the proposed trial regarding the quality of the trial facilities and the available equipment
14. Statement on the aptitude of the researcher in charge of the proposed trial and the investigators based at other trial sites;
15. The amounts for rewarding or compensating investigators and trial subjects and the relevant financial aspects of the sponsor and the site;
16. Insurance cover available for potential subjects in cases where patient insurance and pharmaceutical injuries insurance do not cover the trial

In case Swedish speaking patients are going to be recruited to the trial all the information given to them must be written in Swedish. Swedish translations can be sent to TUKIJA for notification after TUKIJA has evaluated the original research proposal and its attachments. Swedish translations of patient information leaflets and informed consent forms will not be evaluated in TUKIJAs meetings.

Investigators' Brochure may be replaced by SmPC in case the medicinal product has got a marketing authorization (MA) in Finland and it is used in compliance with the MA.

TUKIJA keeps a register of the diary numbers of trial protocols, codes provided by sponsors, EudraCT numbers, details of sponsors and contact persons, and the application dates. All documents associated with trials are time-stamped and marked as confidential. Any amendments, additions and supplementary documents introduced to trial protocols are recorded under the original diary number along with the dates on which they arrived and were processed. To avoid confusion, applicants are asked to quote the diary number provided by TUKIJA in any subsequent correspondence or enquiries.

Sponsors must have a contact person in Finland to facilitate communication during the application procedure.

Applicants are only issued confirmation of receipt once their applications are deemed admissible, i.e. once all of the necessary information and documents have been supplied. The review process begins once applications have been deemed admissible. More detailed information and instructions on the requirements relating to the admissibility of applications for ethics reviews can be found in the guidelines published by the European Commission.

3.3 Summaries of trial protocols (in Finnish or Swedish)

The trial protocol must be summarised in Finnish or Swedish using plain language (understandable to laypersons) and avoiding abbreviations or foreign expressions. The summary should be between 2 and 3 pages long and in any case no more than 5 pages.

The summary must cover the following:

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- The title of the proposed trial and details of the sponsor and the researcher in charge of the trial as well as any other trial sites and the investigators in charge of these facilities
- The objectives, purpose, and rationale of the trial (the aim of the trial, primary and secondary endpoints)
- Trial design and methods
- Basic information on the pharmacology of the medicinal product, such as its ATC group, mechanism of action, trial phase, etc.
- The efficacy and safety of the investigational product based on prior information (brief description of the results of animal tests and prior phases as well as adverse reactions) and information on the number of patients and the time that the current dosage of the drug has been investigated
- Sample size, main inclusion and exclusion criteria
- Any special groups involved
- Information on whether vulnerable subjects are to be included
- Treatments (especially invasive) to be carried out on subjects and foreseeable risks, benefits and disadvantages
- Alternative treatments
- Justifications for the use of a placebo
- Information on how personal data are to be treated during the trial and on information security measures (sources, data entry and storage, transfer and destruction)
- Information on any special features of the proposed trial, such as unusual trial design, first trial on humans (phase I), etc.

3.4 Reviews of trial protocols by TUKIJA

Meeting agendas, documents relating to the trial proposals that are to be reviewed, and other necessary documentation are sent to all members of TUKIJA (or their personal deputies where members are unable to attend) at least one week prior to each meeting. One member (the person responsible for presenting each trial protocol) is given all original copies.

The minutes of meetings generally specify the diary numbers of any trial proposals reviewed, the names of the persons responsible for presenting the protocols, any necessary trial codes, and information on whether the proposals discussed were approved, whether additional information had to be requested, or whether the proposals were rejected, as well as the fees collected for the reviews. TUKIJA can approve proposals subject to certain conditions that must be satisfied before the trial can commence. Unsuccessful applicants are given detailed explanations of why their applications were rejected.

Applicants can expect opinions from TUKIJA within 60 days of submitting admissible applications. Applications relating to trials that concern medicinal product(s) aimed at gene therapy or somatic cell treatment or drugs that include genetically modified organisms can take up to 90 days to process. TUKIJA can extend the deadline by a further 90 days if extensive additional investigations are deemed necessary. No deadline has been set for opinions relating to xenogeneic cell therapy.

TUKIJA can only make one request for additional information to investigators or sponsors. The time required for obtaining any necessary additional information does not count towards the deadline.

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If additional information is required, TUKIJA defers the application in question and issues a written request to the applicant. The case is then resumed at a later date. Requests for additional information specify the date by which the requested information must be submitted to TUKIJA's secretary in order for TUKIJA to be able to resume the case in its next meeting. Requests for additional information are addressed to the researcher in charge of the trial in question and to the sponsor and sent off as soon as possible and in any case no later than one week from the meeting during which TUKIJA began to review the case. E-mail and fax can be used to speed up communication.

TUKIJA can also consult external experts on trial protocols. In such cases, TUKIJA notifies the sponsor and the researcher in charge of the trial in question about its plan to consult an external expert in advance. Afterwards, TUKIJA asks the sponsor and the investigator to inspect the expert's opinion and to give comments.

Opinions issued by TUKIJA include the following information:

- Date
- Diary number, title and code of the trial
- Documents reviewed (including versions and dates)
- Trial sites and locations
- Details of the researcher in charge of the trial and the investigators based at other trial sites
- TUKIJA's opinion on the trial
- Conditions and requests for amendments (where necessary)
- Signatures (chairman and secretary of the meeting)

Originals of TUKIJA's opinions are sent to the applicant and copies to the researcher in charge. Opinions are accompanied by minutes of the meeting during which the case in question was reviewed, which indicate the fee payable for the opinion. TUKIJA's fees are based on a Decree of the Finnish Ministry of Social Affairs and Health.

Opinions are issued as soon as possible and in any case no later than two weeks from the meeting during which the case in question was reviewed. Copies of the opinions are also forwarded to the Clinical Drug Trials Unit of the Finnish National Agency for Medicines (Fimea).

3.5 Amendments to trial protocols

TUKIJA only reviews substantial amendments that are likely to have a bearing on the ethical aspects of trial proposals. Substantial amendments include changes relating to the following, for example:

- The physical or mental integrity of subjects
- The scientific value and significance of trials
- The implementation of trial protocols
- The quality or safety of investigational products

More detailed instructions on substantial amendments can be found in guidelines published by the European Commission.

Applications for amendments must be accompanied by the form issued by the Finnish Ministry of Social Affairs and Health, a summary of the main contents of the updates/changes and the

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investigator's opinion on the impact that the proposed amendments are likely to have on the ethics of trials.

As regards amendments introduced to investigators' brochures, all that is required from applicants are brief summaries of the contents of the updates/changes in Finnish or Swedish, accompanied by the investigator's opinion on the effects of the proposed amendments. In case the medicinal product has received MA during the ongoing trial the updates of the investigators' brochure don't need to be submitted to TUKIJA. If the updates introduced to investigators' brochures call for amendments in other documents such as the information presented to potential research subjects, applicants must notify TUKIJA of the same in connection with providing summaries and the investigator's opinion on the effects of the proposed amendments.

Applicants can expect opinions on proposed amendments within 35 days of submitting admissible applications. The time required for obtaining any necessary additional information does not count towards the deadline.

As a rule and without infringement of the secrecy regulations the opinions of the amendments to trial protocols are recorded to the minutes of the meeting.

3.6 Annual list of serious adverse effects

Sponsors are responsible for compiling lists of suspected cases of serious adverse effects identified in connection with trials each year for the relevant ethics committee (Finnish Medical Research Act, Section 10 (g)). The lists must be accompanied by reports on the safety of subjects and the investigator's opinion on the impacts of the reported cases.

If an annual list of adverse effects gives rise to suspicions that the safety of subjects has been compromised, TUKIJA can refer the matter to the Finnish National Agency for Medicines.

3.7 Notifications of termination

Sponsors and investigators must inform the relevant ethics committee of the completion of clinical drug trials within 90 days. If a trial is discontinued prematurely, notification must be submitted within 15 days. The notification must specify the reasons for discontinuing the trial prematurely. Notifications of termination must be made using the form specified by the Ministry of Social Affairs and Health.

Summaries of the findings of clinical trials on medicinal product(s) must be submitted to the relevant ethics committee within one year of completing trials.

4. APPLYING FOR ETHICS REVIEWS ON THE CONDITIONS FOR ESTABLISHING A BIOBANK

4.1 Establishing a biobank

A favourable opinion by the TUKIJA is a precondition of the establishment of the biobank. TUKIJA must issue its statement within 60 days of receiving the valid request for statement. For its statement,

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TUKIJA must determine whether the activities of the biobank meet the conditions concerning the protection of privacy and self-determination laid down in this act and elsewhere in law and present a justifiable view on the ethicality of the activities.

Applications submitted to TUKIJA must be accompanied by the following documents:

1. Application form published by TUKIJA
2. Name or other identifier of the biobank;
3. Owner of the biobank, business name of the owner and main financiers of the biobank;
4. Location and method of storing the samples and information associated with them and an account of arranging the management of information in the registers;
5. Description of the biobank's area(s) of research and an account of the principles and terms to be applied in the collection, granting of access to for the purposes of biobank research and other processing of samples and information associated with them and restrictions concerning the use of samples;
6. The consent form used and a model for a written report to be submitted when requesting consent or information on the content of the report and a description of submitting the report;
7. An account of whether samples and related information other than those based on consent will be stored in the biobank;
8. An account of whether samples and related information other than those owned by the biobank will be stored in the biobank and, if necessary, information on the owner of the samples;
9. An action plan that outlines the planned scale of the biobanking activities, the organisation of the activities and the division of responsibilities;
10. Statement on the ethicality of the activities of the biobank, especially the objectives and the planning of the biobank, as well as the pre-evaluation of the risks and benefits of the biobank;
11. Statement on the realization of conditions concerning the protection of privacy and self-determination of the individual donors.

The undersigned application with its attachments shall be posted to TUKIJA.

4.2 Changes in the information provided to the biobank register

Any substantial changes in the information provided to the national biobank register must be submitted to TUKIJA for an ethical evaluation. National Supervisory Authority for Welfare and Health shall estimate the need for ethical evaluation. As a rule changes must be submitted to TUKIJA in case the changes relate to the information referred to in section 6 of the Biobank Act.

5. FEES

Fees are imposed on the basis of the Decree of the Finnish Ministry of Social Affairs and Health on the Fees Charged for Opinions of the National Advisory Board on Health Care Ethics and Regional Ethics Committees. The decree governs all cases that require an ethics review and an opinion to be issued by TUKIJA.

If applicant/sponsor and investigator want TUKIJA to issue opinions on matters that TUKIJA would otherwise file as notifications, the subsequent fees can be based on the fees payable for amending trial protocols. No fees are charged for filing notifications.

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Applicants/sponsors are requested to notify the invoicing address and Business Identity Code in its' application.

6. CONTACT DETAILS

Outi Konttinen, General Secretary
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Mannerheimintie 103b
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PL 210, 00281 Helsinki
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Tel. +358 (0)295 209 111
E-mail: firstname.lastname@valvira.fi

TUKIJAs email: [tukija\(at\)valvira.fi](mailto:tukija(at)valvira.fi)

7. REFERENCES

National legislation:

Finnish Medical Research Act (488/1999, amended 295/2004, 794/2010, 143/2015)
Finnish Medical Research Decree (986/1999, amended 313/2004)
Finnish Government Decree on the National Advisory Board on Health Care Ethics (No 820/2010)
Decree of the Finnish Ministry of Social Affairs and Health on the Fees Charged for Opinions of the National Advisory Board on Health Care Ethics and Regional Ethics Committees (No 1417/2016)
Decree of the Finnish Ministry of Social Affairs and Health on Clinical Trials on Medicinal Products (No 841/2010)
Decree of the Ministry of Social Affairs and Health on the Compensation for Research Participation (82/2011)
Biobank Act (688/2012)
Government Decree on Consent for Biobank (643/2013)
Decree of Ministry of Social Affairs and Health on Notification of Biobank (649/2013)
Finnish Act on the Medical Use of Human Organs and Tissues (No 101/2001)
Finnish Act on the Status and Rights of Patients (No 785/1992)

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Finnish Personal Data Act (No 523/1999)
Finnish Act on the Openness of Government Activities (No 621/1999)
Finnish Administrative Procedure Act (434/2003)

EU legislation and guidelines:

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

Guidelines relating to the Clinical Trials Directive 2001/20/EC and Commission Directive 2005/28/EC as well as other additional information can be found at
http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

International regulations and recommendations:

Convention of the Council of Europe 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 (ETS No 164)

Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (CETS No 195)
<http://conventions.coe.int>

Recommendation No R (90) 3 of the Council of Europe Committee of Ministers
<https://wcm.coe.int>

Recommendation No (2006) 4 of Council of Europe on Research on Biological Materials of Human Origin
<https://wcm.coe.int>

CIOMS: International Ethical Guidelines for Biomedical Research Involving Human Subjects
www.cioms.ch

WMA: Declaration of Helsinki 1964 and later amendments
www.laakariliitto.fi

WHO: Operational Guidelines for Ethics Committees That Review Biomedical Research (2000)
<http://www.who.int/tdr/publications/publications/ethics.htm>

CPMP: Guideline for Good Clinical Practice (CPMP/ICH/135/95)