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

1. LEGAL FRAMEWORK OF TUKIJA’S OPERATIONS

Medical Research Act (488/1999)
Government Decree on Medical Research (986/1999)
Government Decree on the Amendment of the 2 and 3 § of the Decree on Medical Research (313/2004, only in Finnish and Swedish)
Government Decree on the Amendment of the Decree on Medical Research (65/2016, only in Finnish and Swedish)
Government Decree on the National Committee on Medical Research Ethics (820/2010)
Government Decree on the Amendment of the 3 § of the Decree on the National Committee on Medical Research Ethics (788/2018, only in Finnish and Swedish)
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 (1287/2018, only in Finnish and Swedish)
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)

1.1 Members of TUKIJA (up to 11 October 2022), data including educational background and the expertise relevant to TUKIJA’s operations

<table>
<thead>
<tr>
<th>Members</th>
<th>Personal deputies</th>
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<tbody>
<tr>
<td>Erkki Palva, MD, PhD, pharmaceutical medicine, <strong>chairman</strong></td>
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<tr>
<td>Miia Turpeinen, MD, PhD, clinical pharmacology and pharmacotherapy, <strong>deputy chairman</strong></td>
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<tr>
<td>Heikki Tikkanen, MD, PhD, sports and exercise medicine, clinical physiology, <strong>deputy chairman</strong></td>
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<tr>
<td>Aleksi Tornio, MD, PhD, clinical pharmacology and pharmacotherapy</td>
<td>Petri Vainio, MD, PhD, clinical pharmacology and drug development</td>
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<tr>
<td>Kristian Lääksy, MD, PhD, psychiatry</td>
<td>Sami Räsänen, MD, PhD, psychiatry Soili Lehto, MD, psychiatry</td>
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<tr>
<td>Tero Tapiola, MD, PhD, neurology</td>
<td>Risto O. Roine, MD, PhD, neurology</td>
</tr>
<tr>
<td>Ville Kytö, MD, PhD, cardiology</td>
<td>Maija-Liisa Kalliomäki, MD, PhD, anaesthesiology</td>
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1.2 Meeting schedule

TUKIJA convenes regularly 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 (and research integrity);
- Issuing national opinions on clinical trials on medicinal products, or delegating the duty to regional ethics committees;
- Issuing opinions on research proposals previously rejected by regional ethics committees when these are resubmitted unchanged;
- Issuing opinions on the conditions for establishing a biobank;
- Supporting and coordinating the activities of the regional ethics committees by providing opinions and trainings in ethical principles and related issues;
- Participating in international cooperation on research ethics (and research integrity) between authorities;
- Gathering and conveying information on research ethics issues and providing 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 and biomedical research.

In other words, TUKIJA is responsible for carrying out ethics reviews on clinical trials on medicinal product, but it can delegate the duty to a regional ethics committee, which will then issue a national opinion. Applications for other medical research projects and clinical trials are reviewed by the regional ethics committee located in the region where the researcher in charge of the proposed clinical trial is operating or where 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 a manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a specific therapeutic strategy is not decided in advance by a trial protocol but falls within the current medical 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 then reconsider the cases. Any proposal that has 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 Finnish Medicines Agency (Fimea) to be included in the national biobank register.

2.2 Responsibilities of regional ethics committees

The responsibilities of regional ethics committees include
• Issuing opinions on proposals transferred to them by TUKIJA;
• Issuing opinions on other medical studies that fall within their jurisdiction;
• Issuing opinions on the transfer of 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. APPLICATION FOR ETHICS REVIEW ON CLINICAL TRIAL 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
the regional ethics committees (jurisdiction issue). Sponsors can apply for a ruling on jurisdiction as soon as it becomes probable that the trial in question will be run in Finland, even if the actual application is not yet complete. Depending on the jurisdiction ruling, the sponsor then sends an application 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 issued an application form to be used in connection with the rulings on jurisdiction. The same form is used both by the applicants and by TUKIJA (when answering). Applicants are also requested to submit their applications to TUKIJA’s secretary in electronic format (as word or rtf files) by e-mail to 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 regularly, once a fortnight.

The ruling on jurisdiction is given by the working group comprising of two members of TUKIJA, a secretary, and variably a number of deputies. The members of the working group notify the secretary of their decisions by the deadine 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. The secretary draws up weekly minutes of the working group’s decisions.

If the working group is unable to reach agreement unanimously on the secretary’s proposal, the jurisdiction ruling for the ethics review will be redirected to TUKIJA’s meeting.

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 application form issued by the Finnish Ministry of Social Affairs and Health, and filling the form according to the instructions provided. The documents listed in the form must be included in the application. 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 (also admissible in English)
2. Summary of the trial protocol (in Finnish or Swedish)
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 regarding the appropriateness of the trial’s aims and planning and the evaluation of risks and benefits
5. Information for potential research subjects (in Finnish)
6. Informed consent form (in Finnish)
7. Information on the procedures to be used in order to seek informed consent (in Finnish)
8. Scientific rationale in cases where potential research subjects are unable to give informed consent to participating in the proposed trial
9. Information on detailed procedures to be used for the recruitment of subjects
10. Other materials to be made available to potential research subjects (CRFs, patient diaries, etc.) (in Finnish)
11. List of trial sites and investigators in Finland
12. Statement by the researcher in charge of the proposed trial regarding the quality of the trial facilities and the available equipment
13. Statement on the aptitude of the researcher in charge of the proposed trial and of the investigators located at other trial sites;
14. Report of the amounts used for rewarding or compensating investigators and trial subjects and of the relevant financial aspects of the sponsor and the site;
15. Report of the insurance coverage available for study subjects, potentially to be used in cases where patient insurance and pharmaceutical injuries insurance does not cover the trial

In case Swedish speaking patients are going to be recruited to the trial, all the information given (to these study subjects) should be in Swedish. Swedish translations can be sent to TUKIJA for notification after TUKIJA has evaluated the original research proposal and its attachments. If the text is a direct translation into Swedish in the patient information leaflets and informed consent forms, they do not need to be evaluated in TUKIJAs meetings, just by the secretaries.

Investigators’ Brochure may be replaced by SmPC in case the medicinal product has already 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 the 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 should 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 the necessary information and documents have been submitted. 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 either in Finnish or Swedish using plain language (comprehensible also to laypersons) and avoiding abbreviations or foreign expressions. The summary should be between 2 and 3 pages long and in any case not more than 5 pages.

The summary must cover the following:
• The title of the proposed trial and details of the sponsor and the researcher in charge of the trial, as well as details of any other possible trial sites and the investigators in charge of each research facility
• 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(s) 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 previously 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 processed during the trial and on data protection 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 Evaluation 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 the trial protocol to the meeting) is given all original copies.

The minutes of meetings include 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 ethically approved, whether additional information had to be requested, or whether the proposals were rejected, as well as the fees collected for the reviews.

TUKIJA’s ethical approval to a trial proposal can be conditional: certain conditions must be satisfied before the trial can be started. Unsuccessful applicants are given detailed explanations on why their applications were rejected.

Applicants can expect opinions from TUKIJA within 60 days after submitting admissible applications. Applications relating to trials that concern medicinal product(s) aimed at gene therapy or somatic cell treatments 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. TUKIJA has no deadline set for reviews or opinions relating to xenogeneic cell therapy.

TUKIJA will only make one request to investigators or sponsors for additional information. The time required for obtaining any necessary additional information is not included when counting TUKIJA’s deadline.
If additional information is required, TUKIJA defers reviewing 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 about trial protocols. In such cases, TUKIJA notifies in advance the sponsor and the researcher in charge of the trial in question about its plan to consult an external expert. Afterwards, TUKIJA asks the sponsor and the investigator to examine 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 located at other trial sites
- TUKIJA’s opinion on the trial
- Conditions and requests for amendments (when necessary)
- Signatures (chairman and secretary of the meeting)

The original TUKIJA’s opinion is sent to the applicant and a copy to the researcher in charge. The opinion is accompanied by minutes of the meeting during which the case in question was reviewed, and it also includes the fee to be paid for the opinion. TUKIJA’s fees are based on a Decree issued by the Finnish Ministry of Social Affairs and Health.

TUKIJA’S 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 the trial proposal. Substantial amendments include changes related, for example to the following issues:

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

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

Applications for amendments are sent to TUKIJA by using the application form issued by STM (STM= Finnish Ministry of Social Affairs and Health), and the application should be accompanied by a summary of the main contents of the updates/changes, as well as the investigator’s opinion on the
ethics of the trial, especially evaluation of the impacts of the changes/amendments on the ethics of the trial.

Regarding the amendments introduced to investigators’ brochures, all that is required from the investigator, is a brief summary of the updates/changes, written 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 do not need to be submitted to TUKIJA. However, if the updates introduced to investigators’ brochures call for amendments in other trial documents, such as the information presented to potential research subjects, the investigators must notify TUKIJA of the amendments according to the procedure mentioned above.

Applicants can expect opinions on proposed amendments within 35 days of submitting admissible applications. The time required for obtaining any necessary additional information is not included when counting TUKIJA’s deadline.

In general, the opinions on the amendments to trial protocols are recorded to the minutes of the meeting, taking into account the secrecy regulations.

3.6 Annual lists 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 safety of the trial subjects.

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 the clinical drug trial 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 application form issued 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 after completion of the trial.

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

4.1 Establishing a biobank

A favourable opinion by TUKIJA is a precondition on the establishment of a biobank. TUKIJA must issue its opinion within 60 days of receiving the valid request for ethical evaluation. For its opinion, TUKIJA must determine whether the activities of the biobank meet the conditions concerning the
protection of privacy and self-determination laid down in the Biobank act and in other regulations and present a justifiable view on the ethics of the activities.

Applications submitted to TUKIJA must also include the following documents:

1. Application form issued by TUKIJA
2. Name or another identifier of the biobank;
3. Owner of the biobank, business name of the owner and main financiers of the biobank;
4. Locations and methods 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 of samples, in granting access to the samples for the purposes of biobank research, and in processing of samples, and an account of the information associated with the samples, and of the restrictions concerning the use of the samples;
6. The informed consent form used, and an example of the written document to be presented when requesting consent, or information on the contents of the written document and a description on how this document will be presented;
7. An account of, whether the biobank stores samples and related information other than those based on consent;
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 operational plan that outlines the scale planned for the biobanking activities, the plan for organising the activities and for the division of responsibilities;
10. Statement on the ethics of the activities of the biobank, especially the objectives and the planning of the biobank, as well as on the pre-evaluation of the risks and benefits of the biobank;
11. Statement on the realization of the protection of privacy and self-determination of the donors.

The signed 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. Finnish Medicines Agency (Fimea) 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 imposed are based on the Decree of the Finnish Ministry of Social Affairs and Health on the Fees Charged for Opinions of the National Committee on Medical Research Ethics (TUKIJA) 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/or 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.
Applicants/sponsors are requested to notify the invoicing address and Business Identity Code in applications.

6. CONTACT DETAILS

National Committee on Medical Research Ethics TUKIJA
National Supervision Authority for Welfare and Health Valvira
Ratapihantie 9
FI-00520 Helsinki
Mailing address:
PO Box 43, FI-00521 Helsinki
Tel. +358 (0)295 209 111
TUKIJA's email: tukija(at)valvira.fi

7. REFERENCES

National legislation:

Finnish Medical Research Act (488/1999)
Finnish Medical Research Decree (986/1999)
Government Decree on the Amendment of the 2 and 3 § of the Decree on Medical Research (313/2004, only in Finnish and Swedish)
Government Decree on the Amendment of the Decree on Medical Research (65/2016, only in Finnish and Swedish)
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Decree of the Finnish Ministry of Social Affairs and Health on Clinical Trials on Medicinal Products (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 (101/2001)
Finnish Act on the Status and Rights of Patients (785/1992)
Finnish Act on the Openness of Government Activities (621/1999)
Finnish Administrative Procedure Act (434/2003)
Data Protection Act (1050/2018)

EU legislation and guidelines:

Commission Directive 2005/28/EC of 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 (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

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
Recommendations of the Council of Europe https://www.coe.int/en/web/bioethics/treaties-recommendations
WHO's recommendations and guidelines http://www.who.int/ethics/research/en/
WMA: Declaration of Helsinki 1964 and later amendments www.laakariliitto.fi
CPMP: Guideline for Good Clinical Practice (CPMP/ICH/135/95)