OPERATING PROCEDURES OF THE NATIONAL COMMITTEE ON MEDICAL RESEARCH ETHICS (clinical trials on medicinal products in accordance with the Directive 2001/20/EC)

1. Legal framework of Tukija's operations

Act on Clinical Trials on Medicinal Products (983/2021)
Medical Research Act (488/1999, with changes 295/2004, 794/2010, 143/2015 and 984/2021, version before 31st January 2022)
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)
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 (1171/2020, only in Finnish and Swedish)
Decree of the 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 the Ministry of Social Affairs and Health on Notification of Biobank (649/2013)
Act of the Medical Use of Human Organs and Tissues (101/2001)
Medical Devices Act (719/2021)
Act on Certain Medical Devices Specified in EU Directives (629/2010)
Finnish Medicines Agency Fimea's Administrative Regulation (1/2022): Clinical Studies on Medical Devices

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 (Clinical Trials Regulation)

The formation of Tukija and the expertise of its members are stated in the Government Decision of appointment (27 January 2022, STM/2022/21).

National Committee on
Medical Research Ethics (Tukija)
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1.1 Meeting schedule

The Committee shall meet regularly, at least every other week. The meeting timetable shall be published on the Tukija website.

2. Duties of Tukija during the transition period

Tukija's duties are prescribed in the law.

Tukija is responsible for the ethical assessment of clinical trials on medicinal products. Between 31st January 2022 and 31st January 2023, sponsors of clinical trials may choose whether to submit their clinical trial applications in accordance with the procedure for submitting national applications under the Clinical Trials Directive (2001/20/EC) or through the EU portal and database (Clinical Trials Information System, CTIS) under the Clinical Trials Regulation (536/2014).

The present Operating Procedures are valid to clinical trial applications submitted via process described in the Directive 2001/20/EC which are send to Tukija between 31st January 2022 and 31st January 2023. They also apply to applications regarding substantial amendments for clinical trials which are submitted to Tukija or to a Regional Committee on Medical Research Ethics, whoever has reviewed the first application of the clinical trial.

Other on medical studies (i.e. medical studies other than clinical trials on medicinal products) are reviewed by Regional Committees on Medical Research Ethics.

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 authorization. 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).)

In the Directive-based process, opinions issued by Tukija cannot be appealed. However, Tukija can reconsider an application (as a new application) when changes introduced in the negative opinion have been made. This applies only to applications submitted before 31st January 2023 and amendment applications submitted before 31st January 2025.

An application for Substantial Amendments (under the Directive-based process) that has previously been given a negative opinion by a Regional Committee on Medical Research Ethics (/Regional Ethics Committee) can be resubmitted unchanged, in which case the Regional Committee in question, when requested, is obligated to refer the case to Tukija and request its opinion.

3. Application for ethics review on clinical trial on medicinal product(s)

3.1 Procedure under the Directive 2001/20/EC (until 31.1.2023)

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. The form should be filled according to the instructions provided.

The documents listed in the form must be enclosed to 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. An application should be submitted via electronic form that is available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish). This form allows submitting the attachments as well. Documents should preferably be in PDF/A form, but they can also be received in PDF form. Zipped files cannot be attached to electric form and the combined size of all the files cannot be more than 45 MB. If the total size of the attachments is more than 45 MB, then application can be divided into two submissions (each attachment should be submitted only once). If necessary, the application form as a PDF document (also found on Tukija's website) can be filled and sent by e-mail to hakemukset(at)tukija.fi.

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

1. Signed cover letter
2. Trial protocol (also admissible in English)
3. Summary of the trial protocol (in Finnish or Swedish)
4. Investigator's brochure (admissible in English)

5. Statement by the principal investigator (i.e. 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
6. Information for potential research subjects (in Finnish)
7. Informed consent form (in Finnish)
8. Information on the procedures to be used in order to seek informed consent (in Finnish)
9. Scientific rationale in cases where potential research subjects are unable to give informed consent to participating in the proposed trial
10. Information on detailed procedures to be used for the recruitment of subjects
11. Other materials to be made available to potential research subjects (CRFs, patient diaries, etc.) (in Finnish)
12. List of trial sites and investigators in Finland
13. Statement by the principal investigator of the proposed trial regarding the quality of the trial facilities and the available equipment
14. Statement on the aptitude of the principal investigator of the proposed trial and of the main investigators located at other trial sites
15. 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
16. 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
17. Data protection notice or other corresponding document

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 need not to be evaluated in Tukija's meetings.

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

Tukija keeps a register of all the application documents received and the relevant processing-related metadata. 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. Documents are confidential on the basis of the Finnish Act on the Openness of Government Activities 621/1999 24.1§ (20 and 21).

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

Once all the necessary information and documents have been submitted and an application have been deemed complete, processing time starts and the review process begins. More detailed information and instructions on the requirements relating to the completeness of applications for ethics reviews can be found in the guidelines published by the European Commission.

3.2 Summaries of trial protocols (in Finnish or Swedish)

The trial protocol must be summarized 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 principal investigator (i.e. person 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.

3.3 Evaluation of applications by Tukija

A meeting agenda, documents relating to the trial proposals that are to be reviewed, and other meeting documentation are sent to all members of Tukija at least one week prior to each meeting.

The minutes of meetings include the diary number of a trial proposal reviewed, the name of the persons responsible for presenting the application (rapporteur), a trial code, and information on whether the proposal discussed were issued a positive opinion (ethically approved), whether additional information had to be requested, or whether the proposal was issued a negative opinion (rejected), as well as the fees collected for the reviews. Tukija's favourable opinion (i.e. ethical approval) of a trial proposal can be conditional: certain conditions must be satisfied before the trial can be started. When a negative opinion is issued, the applicant is given detailed explanations on why their application were rejected.

Tukija should issue its opinion within 60 days from receiving an admissible application. 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 may 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 meeting. Requests for additional information specify the date by which the requested information must be submitted to Tukija's secretariat in order for Tukija to be able to resume the case in its meeting. Request for additional information is addressed to the principal investigator (i.e. person in charge of the trial in question and to the sponsor, and it will be sent to them by email as soon as possible and in any case

no later than one week from the meeting during which Tukija began to review the case. The principal investigator should answer to the request for additional information. The response should be submitted via electronic form that is available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish). If necessary, the response can also be sent by e-mail to hakemukset(at)tukija.fi.

Tukija can also consult external experts about trial proposals. In such cases, Tukija notifies in advance the sponsor and the principal investigator of the trial in question about its plan to consult an external expert. Afterwards, Tukija may ask 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 principal investigator (i.e. person in charge) of the trial and the main 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 in electronic form to the sponsor and to the principal investigator. The opinion is accompanied by minutes of the meeting during which the case in question was reviewed, and the fee to be paid for the opinion is also documented in the minutes. Tukija's fees are based on a decree (1171/2020) issued by the Finnish Ministry of Social Affairs and Health.

Tukija's opinions are issued as soon as possible after the meeting where the applications is discussed, and in any case no later than two weeks from the meeting. Opinions are also forwarded to the Clinical Drug Trials Unit of the Finnish Medicines Agency Fimea.

3.4 Amendments to a clinical trial under the Directive 2001/20/EC (until 30.1.2025)

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 trial
- The implementation of trial protocol
- The quality or safety of investigational product

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

Applications for amendments are submitted to Tukija by using the application form issued by the Finnish Ministry of Social Affairs and Health completely filled. The application should be accompanied by a signed cover letter, a summary of the main contents of the updates/changes in Finnish, as well as the principal investigator's opinion on the ethicality of the trial, especially evaluation of the impacts of the changes/amendments on the ethics of the trial. An application should be submitted via electronic form that is available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish). If necessary, the application form as a PDF document (also found on Tukija's website) can be filled and sent by e-mail to hakemukset(at)tukija.fi.

Regarding the amendments introduced to the investigators' brochure, what is required from the investigator is a brief summary of the updates/changes, written in Finnish or Swedish, accompanied by the principal 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' brochure call for amendments in other trial documents, such as the information presented to potential research subjects, then the application form must be submitted. The application needs to be accompanied by a signed cover letter, a summary of the main contents of the updates/changes in Finnish, as well as the principal investigator's opinion on the ethicality of the trial, especially evaluation of the impacts of the changes/amendments on the ethics of the trial.

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.

3.5 Transition of a clinical trial authorised under the Directive

If the sponsor considers that substantial modifications need to be done to the clinical trial to make it compliant with the Regulation and/or if the protocols of a clinical study employed in different

countries are being harmonised to one protocol, these changes shall be made in the procedure specified in the Directive to Tukija. This is not dependent on which committee (TUKIJA/Tukija or a local ethics committee) has given favourable opinion for the clinical trial. After receiving a favourable opinion on the modification, the clinical trial shall be entered in the EU portal as a new clinical trial, using the simplified authorisation procedure. (Please see Commission Questions and Answers Document – Regulation (EU) 536/2014, Chapter 11 and CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014.)

A fee is charged for modification applications (Decree 1171/2020).

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. The lists must be accompanied by reports on safety of the trial subjects. The lists to Tukija together with a signed cover letter should be submitted via electronic form that is available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish). If necessary, the application form as a PDF document (also found on Tukija's website) can be filled and sent by e-mail to hakemukset(at)tukija.fi.

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 Medicines Agency Fimea.

3.7 Notifications of termination

Sponsors or 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.

The above-mentioned notifications and summaries to Tukija together with a signed cover letter should be submitted via electronic form that is available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish). If necessary, the application form as a PDF document (also found on Tukija's website) can be filled and sent by e-mail to hakemukset(at)tukija.fi.

4. 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 (1171/2020).

If an applicant, a sponsor and/or an investigator wants 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.

5. Contact details

National Committee on Medical Research Ethics (Tukija)
National Supervisory Authority for Welfare and Health Valvira

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More information: info(at)tukija.fi

Applications and notifications, as well as responses to requests for additional information and for corrections (based on conditional positive opinions issued) should be submitted via electronic forms that are available on Tukija's website (www.tukija.fi the forms are available in Finnish and Swedish).

Version history

Date	Modification
11.2.2022	First version in Finnish
5.4.2022	Ch. 3.4, Tukija's meeting frequency changed

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