



National Advisory Board on Health Care Ethics
(ETENE)

**Sub-Committee on Medical Research Ethics
(TUKIJA)**

**7.2.2001
effective from 1.6.2005
updated 20.6.2005,
translation 13.7.2005**

OPERATING PROCEDURES FOR THE SUB-COMMITTEE ON MEDICAL RESEARCH ETHICS

1. TUKIJA's operation is based on

Medical Research Act (488/1999)

Act Amending the Medical Research Act (295/2004)

Government Decree Amending the Medical Research Decree (313/2004)

Government Decree Amending the Decree on National Advisory Board on Health Care Ethics (791/2002)

Ministry of Social Affairs and Health Decree on the fees of charged for statements of the National Advisory Board on Health Care Ethics and the Sub-Committee an Medical Ethics and on remunerations payable to research subjects (1396/2004)

Ministry of Social Affairs and Health Decree on Clinical Trials (316/2005)

1.1 Members of TUKIJA (until 30.9.2006), the degrees of the members and areas of expertise relevant with regard to TUKIJA's operation

Chairman: Raimo Pekkanen, LLD, Justice of the Supreme Administrative Court
Vice Chairman: Professor Helena Kääriäinen, MD, docent, specialist in medical genetics

Members:

Professor Pauli Ylitalo	MD, docent, specialist in clinical pharmacology
Docent Tapani Keränen	MD, specialist in neurology and clinical pharmacology
Researchprofessor Elina Hemminki	MD, docent, epidemiology
Docent Katriina Aalto-Setälä	MD, specialist in internal medicine and cardiology
Professor Erkki Väisänen	MD, psychiatry
Docent Maija Pohjavuori	MD, specialist in paediatrics and neonatology
Ministerial Secretary Mervi Kattelus	LLM, legality questions
Docent Veikko Launis	PhD, docent, ethics
Executive Director Anneli Juutinen	public health nurse, patient association

Personal deputies:

Professor Kirsi Vähäkangas	MD, docent, toxicology and pharmacology
Professor Matti Vapalahti	MD, docent, specialist in neurosurgery
Professor Arpo Aromaa	MD, docent, epidemiology
Docent Kristiina Aittomäki	MD, specialist in medical genetics and gynaecology and obstetrics
Professor Pirkko Räsänen	MD, docent, specialist, psychiatry and forensic psychology
Docent Marjo Renko	MD, specialist, paediatrics
Secretary General Salla Lötjönen	LLD, MA, legality questions
Professor Juha Räikkä	PhD, docent, ethics
Chairman Karl-Gustav Södergård	patient association

Executive Secretary:

Outi Kontinen MSS

ETENE's Secretary General, MD Ritva Halila also works as a rapporteur for TUKIJA.

1.2 Meeting schedule

TUKIJA generally convenes once a month, the schedule is agreed upon approximately every six months. The meeting schedule is reported to the ethics committees of the hospital districts and the pharmaceutical industry association, and it can also be found under the "News"-heading on TUKIJA's Internet pages on www.etene.org.

2. Responsibilities of TUKIJA and other ethics committees

2.1 Responsibilities of TUKIJA

The responsibilities of TUKIJA are as follows:

- to review and give a national opinion of international multi-centre clinical trials on medicinal products, unless TUKIJA has transferred the review to an ethics committee of a hospital district;
- to give an opinion of resubmitted unchanged trial to ethics committees of hospital districts in cases where a prior negative opinion has been given;
- to support the ethics committees of the hospital districts in questions of principle, especially related to research ethics, and in training.

TUKIJA is responsible for the ethics review of international multi-centre clinical trials, but it can also transfer the review of the trial to an ethics committee of a hospital district, in which case the corresponding ethics committee gives a national opinion. Other medical research and clinical trials on medicinal products to be conducted only in Finland are reviewed by the ethics committee of the hospital district within which the person in charge of the investigation is operating or within which the trial is mainly to be carried out.

Clinical trial is defined as an interventional study in human subjects intended to discover or verify the absorption, distribution, metabolism and excretion of medicinal product(s). (Act on Medical Research, § 2)

Non-interventional trial is defined as a study 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 shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data. (Directive 2001/20/EC, Article 2, c.)

Opinions given by TUKIJA cannot be appealed. However, TUKIJA may reconsider the application after requested changes. Where the ethics committee of a hospital district gives a negative opinion of a trial and the applicant resubmits an unchanged research proposal the ethics committee shall apply for an opinion from TUKIJA. A trial which has been given a negative opinion may be resubmitted when changes requested by the ethics committee have been made.

2.2 Responsibilities of hospital district ethics committees

The responsibilities of ethics committees of hospital districts are as follows:

- to give opinions of trials transferred to the ethics committee
- to give opinions of other medical studies relevant to its field of activities.

Where the ethics committee gives a negative opinion of a trial and the applicant resubmits an unchanged research proposal, the ethics committee shall apply for an opinion from TUKIJA. After appropriate corrections an opinion can be given without TUKIJA's opinion.

3. Application for ethics review

3.1 Preliminary announcement of the multi-centre clinical trials on medicinal products

For all international multi-centre clinical trials, the sponsor shall initially apply for a decision from TUKIJA on whether TUKIJA is to evaluate the trial or whether the review will be transferred to a relevant hospital district ethics committee. A decision to transfer the review can be applied for when it becomes probable that the trial will be conducted in Finland, even if the actual application should not yet be complete. In accordance with the decision, an ethics review of the trial shall then be applied for either from TUKIJA or the ethics committee of the hospital district.

A decision to transfer the review shall be applied for by using a form issued by the Ministry of Social Affairs and Health as an attachment to the Decree (316/2005), on which information given by the sponsor and the opinion given by TUKIJA shall be included. The announcement concerning a trial should also be forwarded to the secretary of TUKIJA as an e-mail attachment (etene@stm.fi).

The applications shall be submitted to TUKIJA within office hours on the Monday of the week when the application is to be reviewed, at the latest. The decision is based on a proposal made by the secretary on the e-mailed form. Deadlines for announcements can be found under the "News"-heading on the Internet pages www.etene.org. The sub-group deciding on transferral issues makes decisions at least every two weeks.

A sub-group consisting of TUKIJA members makes the transferring decisions assigned for a limited period of time. The sub-group consists of two TUKIJA members, a secretary and a adequate number of deputies. The members shall inform the secretary of their opinion on Thursday by 12:00, at the latest. The secretary shall register the decision of the sub-group on the form, sign it and inform the applicant by e-mail on the Friday of the same week, at the latest. A decision in writing shall be mailed at the earliest convenience. During vacation periods timelines may be subject to changes.

If the sub-group issuing transferral decisions does not unanimously agree on the secretary's proposal, TUKIJA shall give the ethics opinion of the trial protocol. The secretary shall draw up records on decisions made by the sub-group on a weekly basis.

TUKIJA shall be informed of the decisions issued by the sub-group, but the decision cannot be altered. TUKIJA may provide the sub-group with further instructions.

3.2. Application for ethics review from TUKIJA or a hospital district ethics committee

The application shall in all cases be made using the form issued by Ministry of Social Affairs and Health (Decree 316/2005) following the instructions on the form. Documents listed on the form must be included in the application.

The documents of the trial shall be submitted to TUKIJA at least two weeks prior to the meeting where the review is considered to take place.

The application to TUKIJA shall include the following documents:

1. trial protocol, *can be in English*
2. Finnish summary of the trial
3. investigator's brochure, *can be in English*
4. statement by the person in charge of the investigation on its conformity with research ethics; especially regarding appropriateness of aims and planning and evaluation of risks and benefits
5. subject information
6. informed consent form
7. information on how the consent will be obtained

8. rationale for the trial in cases where subjects who are not able to give their informed consent are included in the trial
9. information on detailed procedures for selection of subjects
10. other material to be given to the subject (CRFs, patient diaries etc.)
11. description of the personal data file (523/1999) in accordance with 10 § of the Personal Data Act
12. list of trial sites and investigators in Finland
13. statement by the person in charge of the investigation on the quality of trial facilities and equipment of the trial sites
14. statement on the suitability of the person in charge of the investigation and the responsible investigators at other trial sites
15. trial fees and compensations
16. insurance coverage for the subjects, unless patient insurance and medicines-related inquiries insurance cover the trial

The following will be registered in TUKIJA's register: the diary number of the research plan, the code provided by the sponsor, the EudraCT-number, the sponsor, the contact person and arrival date of the trial. The register of TUKIJA is a public register and, therefore, no confidential information will be entered. Trial documents will be provided with arrival date and a stamp, "confidential". The diary number issued to the original trial will be used for subsequent trial amendments, addendums and other information and their arrival dates will be correspondingly registered. To avoid any confusion, further handling or requests related to the trial shall be made using the TUKIJA diary number.

The sponsor of the trial shall have a contact person in Finland for communication related to the application procedure.

A notification on arrival of the trial will be sent to the applicant when the application has been judged appropriate, i.e. when it includes all required information and documents. The review time starts when the application has been judged appropriate. More detailed information on the requirements related to the appropriateness of the application can be found in guidelines published by the European Commission.

3.3 Finnish summary of the trial

The Finnish summary of the trial shall be explicit, avoiding abbreviations or foreign expressions (understandable to lay persons). The appropriate length of a summary is 2-3 pages, 5 pages at most.

The summary shall explicitly clarify the following:

- the title of the trial, the sponsor and the name of the person responsible for the trial as well as the trial sites and their responsible investigators, if known
- 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 substance, such as ATC-group, mechanism of action and trial phase etc.
- the efficacy and safety of the investigational product based on prior information (animal tests and results from prior phases and adverse reactions briefly) as well as information on the number of patients and the time the current dosage of the drug have been investigated
- sample size, main inclusion and exclusion criteria
- inclusion of vulnerable subjects
- treatment (especially invasive) of subjects and foreseeable risks, benefits and disadvantages
- alternative treatments
- justification of the use of placebo
- handling of personal information in the trial and data security measures (sources, data entry and storage, transfer and destruction)
- possible specific features of the trial, such as different trial design, first trial on humans (phase I) etc.

3.4 Handling of trials by TUKIJA

All members of TUKIJA (if a member is prevented, his/her personal deputy) will be provided with an agenda of the meeting, the related trial documents and other related documents at least one week prior to the TUKIJA meeting. One of the members (the member presenting the trial protocol) will be provided with all original documents.

The meeting minutes related to the trial generally include the diary number of the trial, the person preparing the matter, the trial code and a decision whether the trial or the amendment was given a favourable opinion, a request for additional information or a negative opinion as well as fees for the review. A positive opinion may include the request for additional activities which have to be dealt with prior to commencement of the trial. A negative opinion will be associated with detailed justifications.

TUKIJA shall give its opinion within 60 days of arrival of a valid application. If the trial concerns drugs aimed at gene therapy or somatic cell treatment or drugs including genetically modified organisms, the deadline for giving the opinion is 90 days, which by the committee can be prolonged by an additional 90 days if the evaluation requires extensive additional investigations. An opinion related to xenogenic cell therapy is not bound to any timelines.

The ethics committee may request additional information from an investigator or the sponsor of the trial only once. The review time is interrupted for the time needed for obtaining additional information.

In cases where TUKIJA requests additional information, the review of the trial is interrupted and a request for additional information will be provided in writing. The review will be continued in later TUKIJA meetings. The request for additional information will include a date by which the information shall be provided to TUKIJA's secretary, if the requested information is intended to be taken into consideration in the next meeting. The request for additional information will be forwarded to the person in charge of the investigation /the sponsor as soon as possible after the meeting, however, not later than within a week of the meeting of TUKIJA. In order to speed up the transmission of information and to allow speedy preparations of requested activities, e-mail and telecopy may be used, if needed.

TUKIJA may also approach external experts for opinions of the trial. In case of such requests, the sponsor and person responsible for the trial will be informed and they will eventually be requested to comment on the opinions.

The opinion of a trial given by TUKIJA includes the following:

- date of the opinion
- the diary number, name and code of the trial
- arrived documents (including versions and dates)
- trial sites and locations
- person responsible for the trial and responsible investigators
- opinion
- possible additional activities and requests for corrections
- signatures (chairman and secretary of the meeting)

The original opinion will be sent to the sponsor and a copy of the opinion will be sent to the person in charge of the investigation. As an attachment to the opinion there will be an extract from the record concerning the evaluated case including information on the fees related to the evaluation. The fees for trial and the amendments will be charged in accordance with the Ministry of Social Affairs and Health Decree (1396/2004). An invoice will be sent with the opinion.

The opinion will be sent as soon as possible after the meeting, however, not later than two weeks after the meeting of TUKIJA. Copy will also be sent to the Clinical Trials Unit of the NAM.

3.5 Amendments to trial

TUKIJA will only review amendments to trials which may be of significance with regard to the ethics review. Such amendments significantly influence e.g. the following aspects of the trial:

- the safety or physical or mental integrity of the subjects
- the scientific value and significance of the trial
- the conduct of the management of the trial
- the quality or safety of any investigational medicinal product used in the trial

If an originally national trial later becomes an international trial, according to this procedure, TUKIJA will transfer the evaluation of the amendment to the ethics committee which originally reviewed the trial.

More detailed instructions on *substantial changes* can be found in EU Commission guidelines.

The application for review of an amendment shall include a summary of the main changes and a statement by the person in charge of the investigation concerning the impact of the amendment on the ethics of the trial. The application may include the same form as the one used to inform the National Agency for Medicine; for more information see EU Commission guidelines.

The ethics committee shall give its opinion within 35 days of receipt of a valid application for an opinion of the amendment. The review time is interrupted for the time needed for obtaining additional information.

When the trial has been given favourable opinion before the Act on Medical Research (488/1999) became effective the provisions should be followed as applicable.

4. Informing TUKIJA of adverse reactions

4.1 Serious unexpected adverse drug reactions, Medical Research Act 10 §

In accordance with the Medical Research Act 10 §, the investigator shall report all serious adverse events to the sponsor. The person in charge of the investigation shall discontinue the trial immediately if the safety of the subject so requires (Medical Research Act 5 §).

Primarily the responsibility for follow-up of unexpected serious adverse drug reactions in Finland and undertaking of appropriate actions lies with the investigator, the person in charge of the investigation and the sponsor.

The National Agency for Medicines' possibilities of retrospective control are substantially better than those of the ethics committees. The National Agency for Medicines as an office works daily and it possesses information which is unavailable to ethics committees. The National Agency for Medicines can also request additional information, discontinue trials and, notwithstanding confidentiality provisions, inspect both the trial and patient files.

TUKIJA and the ethics committees, in fact, cannot estimate the overall impact of an adverse reaction on the entire trial. They have neither the safety data required nor the staff to analyze safety data and they cannot discontinue trials, when needed. Therefore, with a few exceptions, the reports can only be registered as notifications. If TUKIJA expresses a concern for the safety of the subjects, it will inform the National Agency for Medicines.

TUKIJA shall be informed only of unexpected serious adverse reactions occurring in trials in Finland which have been reviewed by TUKIJA. A statement on the adverse reaction made by the person in charge of the investigation is not needed. If the drug administration is blinded, the code needs not be broken for the report to TUKIJA. No reports on unexpected serious adverse reactions occurred in trial centres abroad, also unexpected serious adverse reactions occurred in other trials, also periodic reports on serious adverse reactions in all trials or serious unexpected spontaneous reports or reports based on literature, need not to be reported to TUKIJA.

4.2. Annual list on serious adverse reactions, Medical Research Act 10 §

The sponsor shall annually provide the appropriate ethics committee with a list of suspected serious adverse drug reactions from the trial including a statement on the safety of the subjects. The person in charge of the investigation shall include his/her evaluation of the sponsors' statement.

If TUKIJA expresses a concern for the safety of the subjects, it will inform the National Agency for Medicines.

5. Information on completion of the trial

The sponsor or the person in charge of the investigation shall inform the ethics committee of the completion of clinical trials within 90 days of completion. If the trial has been discontinued earlier, the report shall be made within 15 days of discontinuation. The report shall include the reason for premature discontinuation. The report shall be made using the same form as the one used to inform the National Agency for Medicine; for more information see EU Commission guidelines.

A summary of the clinical trial report shall be provided to the ethics committee within a year of trial completion.

6. Fees

Opinions are subject to a fee in accordance with the Decree of the Ministry of Social Affairs and Health on the fees of charged for statements of the National Advisory Board on Health Care Ethics and the Sub-Committee an Medical Ethics and on remunerations payable to research subjects (1396/2004). The Decree is applicable to all decisions that require review and opinion by TUKIJA. If the applicant wishes an opinion on issues that TUKIJA would otherwise regard as notifications, a fee equivalent to the fee for an amendment can be charged. No fee is charged for entry of notification issues into the minutes of a meeting.

7. TUKIJA's contact information

Executive Secretary	ETENE's Secretary General
Outi Konttinen	Ritva Halila
Ministry of Social Affairs and Health	Ministry of Social Affairs and Health
POB 33 (Kirkkokatu 14)	POB 33 (Kirkkokatu 14)
FIN-00023 Valtioneuvosto	FIN-00023 Valtioneuvosto
Finland	Finland
Telephone: +358-9-160 73147	+358-9-160 73834
Telefax: +358-9-160 74312	+358-9-160 74312
E-mail: firstname.lastname@stm.fi	firstname.lastname@stm.fi

8. References:

National legislation:

Medical Research Act (488/1999)

Decree issued by the Council of state on Medical Research Decree (986/1999)

Act Amending the Medical Research Act (295/2004)

Decree issued by the Council of State on Decree Amending the Medical Research Decree (313/2004)

Ministry of Social Affairs and Health Decree on the fees of charged for statements of the National Advisory Board on Health Care Ethics and the Sub-Committee an Medical Ethics and on remunerations payable to research subjects (1396/2004)

Ministry of Social Affairs and Health Decree on Clinical Trials (316/2005)

Ministry of Social Affairs and Health Decree on the National Advisory Board on Health Care Ethics (494/1998)

Government Decree Amending the Decree on National Advisory Board on Health Care Ethics (309/2000)

Government Decree Amending the Decree on National Advisory Board on Health Care Ethics (791/2002)
 Personal Data Act (523/1999)
 Administrative Procedure Act (434/2003)
 Act on the States and Rights of Patients (785/1992)
 Act on the Openness of Governmental Activities (621/1999)
 Act of the Medical Use of Human Organs and Tissues (101/2001)
 Regulation issued by the National Agency of Medicines on clinical trials on medicinal products in human subjects 2/2004

EU Commission directives and guidelines:

Detailed guidance on the request format and documentation to be submitted in an request for a Ethics Committee opinion on the clinical trial on medicinal products for human use
 Detailed guidance for the request for authorisation of a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial
 Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
 Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (– Clinical Trial Module)
<http://pharmacos.eudra.org>

International Guidelines:

Council of Europe’s Convention on Human Rights and Biomedicine (ETS 164) <http://conventions.coe.int>
 Recommendation R (90) 3 by the Council of Europe <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
 WHO: Operational Guidelines for Ethics Committees That Review Biomedical Research (2000)
<http://www.who.int/tdr/publications/publications/ethics.htm>
 CPMP:n Guide for Good Clinical Gractice (CPMP/ICH/135/95)

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TUKIJAs’ guidelines: <http://www.etene.org/tukija/index.shtml>
 TUKIJAs’ instructions on patient information concerning DNA tests