Heidi Wasastjerna

# COMMON NORDIC PRACTICES IN THE ETHICAL EVALUATION OF CLINICAL TRIALS OF MEDICINAL PRODUCTS

Advanced Studies, Thesis
Autumn 2018

Heidi Wasastjerna

# COMMON NORDIC PRACTICES IN THE ETHICAL EVALUATION OF CLINICAL TRIALS OF MEDICINAL PRODUCTS

Institute of Biomedicine
Autumn 2018
Supervisor: Mika Scheinin

The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

UNIVERSITY OF TURKU
Institute of Biomedicine

WASASTJERNA HEIDI: Common Nordic Practices in the Ethical Evaluation of Clinical Trials of Medicinal Products

Advanced Studies, Thesis, 46 pages
Institute of Biomedicine / Pharmacology
December 2018

---

The European Parliament and the Council of the European Union approved in 2014 a new Regulation on clinical trials on medicinal products for human use (536/2014) and repealed the previous Clinical Trial Directive 2001/20/EC. The Regulation is supposed to be adopted by all member states by the end of the year 2019. The Nordic Trial Alliance (NTA), an initiative funded by the Nordic Council of Ministers, hosted a project on the harmonization of the ethical evaluation of clinical trials in the Nordic countries in 2013–2016. NTA's "Report on the Ethical Review Process for Clinical Trials in the Nordic Countries" described the influence of the EU Regulation on the Nordic countries and made suggestions for harmonization of their ethical review processes. In this thesis, the aim is to make a more detailed analysis of the current evaluation processes in the Nordic countries.

This study focuses on items K.-Q. of Annex 1 of the Regulation 536/2014, which are left for member state to regulate. These seven items are: subject recruitment arrangements, subject information leaflet and informed consent procedure, suitability of the investigator, suitability of the facilities, proof of insurance coverage or indemnification, financial and other arrangements and proof of payment of the handling fee (Regulation (EU) 536/2014). In this thesis, there is a summary of the current evaluation processes of the ethics committees in the Nordic countries and of the similarities and differences between the countries. The second part of the study describes in more detail the items K.-Q. and what should be regulated nationally according to the EU Regulation, as well as how the Declaration of Helsinki (WMA 2013) and the Good Clinical Practice guidelines (EMA 2016) deals with these items. It is also described how these issues may possibly be regulated in the current Finnish Draft for a Government Proposal for the Law on Clinical Drug Trials (14.7.2017 http://stm.fi/hanke?tunnus=STM077:00/2017).

As a result, it is noted that after the implementation of the Regulation, there will still remain differences in ethical evaluation processes between the Nordic countries, and that there would be a need for harmonizing these processes in the Nordic countries. Common procedures would make it easier to conduct clinical trials in the Nordic countries and foster their international competitiveness.

Keywords: clinical trial, ethical review process, Nordic countries

TURUN YLIOPISTO
Biolääketieteen laitos

WASASTJERNA HEIDI: Common Nordic Practices in the Ethical Evaluation of Clinical Trials of Medicinal Products (Kliinisten lääketutkimusten eettisen ennakkoarvioinnin yhtenäistäminen Pohjoismaissa)

Syventävien opintojen kirjallinen työ, 46 s.
Biolääketieteen laitos / Farmakologia
Joulukuu 2018

---

Euroopan parlamentti ja Euroopan unionin neuvosto hyväksyivät v. 2014 uuden asetuksen ihmisille tarkoitettujen lääkkeiden kliinisistä lääketutkimuksista (536/2014) ja ns. lääketutkimusdirektiivin 2001/20/EY kumoamisesta. Asetuksen mukainen lääketutkimusten lupa- ja valvontamenettely käynnistynee vuonna 2019. Pohjoismaiden Ministerineuvosto käynnisti v. 2013 kolmivuotisen Nordic Trial Alliance (NTA) -hankkeen, joka tarkasteli lääketutkimusten eettisen ennakkoarvioinnin yhtenäistämistä Pohjoismaissa. Projektiin liittyen NTA julkaisi v. 2016 raportin ”Report on the Ethical Review Process for Clinical Trials in the Nordic Countries”, jossa käsitellään EU-asetuksen vaikutuksia kliinisen lääketutkimuksen eettiseen arviointiin Pohjoismaissa ja hahmotellaan mahdollisuuksia yhtenäistää ennakkoarvioinnin prosesseja. Tässä katsauksessa pyritään luomaan tarkempi kuva kliinisen lääketutkimuksen nykyisistä arviointikäytännöistä Pohjoismaissa.

Käsiteltävänä ovat eettisen ennakkoarvioinnin asiakokonaisuudet K.-Q., jotka EU:n lääketutkimusasetus jättää kunkin jäsenmaan itsenäisesti päätettäväksi. Asiakokonaisuudet ovat seuraavat: rekrytointijärjestelyt, tutkittavalle annettavat tiedot, tietoon perustuvaa suostumusta koskeva lomake ja suostumusmenettely, tutkijan pätevyys, tilojen soveltuvuus, todistus vakuutuksen kattavuudesta tai vahingonkorvauksesta, rahoitusjärjestelyt ja muut järjestelyt ja todistus käsittelymaksun suorittamisesta (Asetus (EU) 536/2014). Tässä katsauksessa esitetään yhteenveto kohtien K.-Q. nykyisestä arviointimenettelystä Pohjoismaiden eettisissä toimikunnissa ja tarkastellaan menettelyjen yhtäläisyyksiä ja eroavaisuuksia maiden välillä. Toinen osa kuvaa asiakohdat K.-Q. tarkemmin ja selostaa, mitä EU-asetus edellyttää jäsenmaiden säätävän omassa lainsäädännössään, ja mitä asiakohdista säädetään Helsingin julistuksessa (WMA 2013) ja GCP:ssä (EMA 2016). Lisäksi on kuvattu, miten näiden asiakokonaisuuksien arviointi on Suomessa uuden kliinisiä lääketutkimuksia koskevan lain luonnoksen (14.7.2017 http://stm.fi/hanke?tunnus=STM077:00/2017) mukaan mahdollisesti toteutettavissa.

Tarkastelun tuloksena todetaan, että arviointimenettelyissä on vielä EU-asetuksen voimaantulon jälkeenkin odotettavissa maakohtaisia eroavaisuuksia, ja että tarvetta menettelyjen yhtenäistämiseksi Pohjoismaissa olisi. Yhteiset menettelytavat eettiselle ennakkoarvioinnille helpottaisivat lääketutkimusten tekemistä Pohjoismaissa ja lisäisivät Pohjoismaiden kansainvälistä kilpailukykyä alalla.

Asiasanat: kliininen lääketutkimus, eettinen ennakkoarviointi, Pohjoismaat

# CONTENTS

# 1 INTRODUCTION

## 1.1 Regulation (EU) 536/2014

On 16 April 2014, the European Parliament and the Council of the European Union approved the new EU Regulation No 536/2014 on clinical trials on medicinal products for human use and repealed the previous Clinical Trials Directive (Directive 2001/20/EC). This Clinical Trial Regulation is expected to be fully implemented, and national legislation adapted to it by the end of the year 2019. Because of the Regulation, all Nordic countries must update their current legislation and systems in the field of clinical trials. Norway and Iceland are not members of the European Union, but they belong to the European Economic Area (EAA) and because of that they are also implementing the EU Regulation.

In Annex 1 of the Regulation 536/2014 there are requirements for the ethical review process of clinical trials. The ethical review process is considered to be an issue to be handled by national ethics committees, and its practical arrangements are therefore left to the individual member (and associated) states to define in their national legislation. Annex 1 contains rules for the Clinical Trial Application (CTA) and what information the CTA documents must contain and what materials should be included in the CTA. There are altogether 18 sections, A.-R., describing what information should be included in the CTA.

## 1.2 Ethical committees of the Nordic countries and the ethical review process

Until the implementation of the Regulation 536/2014, all five Nordic countries have followed quite similar but not identical, internationally accepted principles in the ethical review of clinical trials. The review processes have originally been derived from common source documents such as the World Medical Association's (WMA) Declaration of Helsinki, OECD's Good Clinical Practice (GCP) guidelines and the EU Clinical Trials Directive. In practice, the ethical review systems have evolved independently of each other in each country and show significant divergence in their structure and format. In the following, the ethical review

processes in place in each of the Nordic countries before the implementation of the Regulation 536/2014 are reviewed.

Finland is following its Medical Research Act (Medical Research Act 488/1999) and has established a central national ethics committee for clinical drug trials, called TUKIJA, and a system of nine regional ethics committees in the five university hospital districts (National information: Finland http://www.eurecnet.org/information/finland.html). Each clinical trial should be submitted to TUKIJA for preliminary consideration; in this phase, TUKIJA decides whether it wants to handle the application itself or whether the application is to be submitted to a regional committee. There is an application form and guidance for the application on the website of TUKIJA (tukija.fi). Applications should be prepared in Finnish or Swedish; only those documents that are not meant to be evaluated by all (lay) members of the committee may also be submitted in English (such as the full clinical study protocol and the investigators brochure). The documents that should be submitted together with the application form are listed in Appendix 1. (Valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan toimintaohje 2017.)

Sweden is following its Act concerning the Ethical Review of Research Involving Humans (2003/460) and the Statute concerning the ethical vetting of research involving humans (2003/615). There is a Central Ethical Review Board, which is the national committee of ethics. There are also six regional committees, which are located in the main universities of Sweden. They have their own administration and finances. The Central Ethical Review board is the main body when there are controversial issues, and the decisions of the regional committees can be appealed to the Central Ethical Review Board. The language of the application should be Swedish. (National information: Sweden http://www.eurecnet.org/information/sweden.html.) An application form can be found from the website of the Central Ethical Review Board (epn.se).

In Denmark, the regulation followed is the Act on Research Ethics Review of Health Research Project (2013). There is a National Committee on Health Research Ethics which is the national committee. There are also 12 regional committees. Approval should be sought from the regional ethics committee of the region where the investigator is operating. (The System of Health Research Ethics Committees http://www.nvk.dk/english/the-system-of-health-research-ethics-committees.) The application process is electronic. There is an electronic

notification form and guidance documents on the website of The National Committee in Health Research Ethics. The application should be in Danish. (dnvk.dk.)

Norway has a National Committee for Medicinal and Health Research Ethics called NEM and nine regional committees called REKs (National information: Norway http://www.eurecnet.org/information/norway.html). There is an electronic application system. There was not much guidance available on the website of the REKs (ettikom.no), probably because the guidance might be located in the closed electronic portal, into which the investigator should create an account in order to submit an application. REKs are the main bodies to perform the ethical evaluation and each of the nine REKs has somewhat different systems and evaluation processes (National information: Norway http://www.eurecnet.org/information/norway.html). This may be the reason why there was rather little publicly available material about ethical review in Norway. The language of the application may be either Norwegian or English (when the research is conducted solely in another country) (Electronic communications and Language Requirements https://helseforskning.etikkom.no). The Health Research Act (2/18/2016) gives the legal basis for the national application process.

In Iceland, the Act of Law on Scientific Research in the Health Sector (No.44/2014) is the regulation followed nationally in scientific research. The national ethics committee is called The National Bioethics Committee (NBC). It includes seven members nominated by the Minister of Health. There are also two institutional ethics committees, the Health Research Committee of Landspitali University and The Health Research Ethics Committee of Akureyri Hospital. Both of these grant approvals for biomedical research carried out at their hospitals. The NBC is the body that grants approval for multinational and collaborative projects. All decisions of the institutional ethics committees can be appealed to the NBC if needed. An application form and information on the structure of Icelandic ethics committees is found on the website of NBC (vsn.is). Applications can be made in Icelandic or English. (The Bioethics Committee System http://www.vsn.is/en/content/bioethics-committee-system.)

## 1.3 Nordic Trial Alliance

The Nordic Trial Alliance (NTA) was established in 2013 by the Nordic Council of Ministers, initially as a three-year project. Its main purpose was to foster Nordic collaboration as well as to promote the competitiveness of the Nordic countries in the field of clinical trials. A report on the ethical review process of clinical trials in the Nordic countries was published in 2016 (Report on the Ethical Review Process for Clinical Trials in the Nordic Countries, The Challenges and Opportunities of the New Clinical Trials Regulation 2016). There was a need to update the current practises because of the Regulation 536/2014. The report described the current ethical review process in each of the Nordic countries and made suggestions on how the current legislation and practises should be changed to comply with the Regulation 536/2014. There were also proposals to achieve Nordic harmonization of the ethical review process of CTAs. The current study is a more detailed analysis of the parts of the CTA process that concern the ethical review process of clinical drug trials left to each member and associated state to organize in compliance with Regulation 536/2014.

## 1.4 Aims of the study

This study focuses on items K.-Q., of Annex 1 of the Regulation, i.e. the issues that are left for each member and associated state to regulate in the CTA ethical review process. These seven issues are:

K. Study subject recruitment arrangements

L. The subject information leaflet, the informed consent form and information on the informed consent procedure

M. evaluation of the suitability of the investigator

N. evaluation of the suitability of the facilities

O. proof of insurance cover or indemnification

P. information on financial and other arrangements for the study

Q. proof of payment of the handling fee (Regulation (EU) 536/2014)

The aim of this study is to make a more detailed analysis of these seven issues left to each individual member and associated state to decide, from the perspective of the five Nordic countries. In order to foster Nordic collaboration in clinical trials, it should be an aim to harmonize the ethical evaluation processes of clinical trials. The requirements, procedures and application processes should be similar in each country. This would make it possible to use only one application in all five countries and would make it easier to conduct joint clinical trials in the Nordic countries. This would enhance the competitiveness of the Nordic countries in the field of clinical trials and unite the Nordic countries into one large Nordic clinical research area.

First, there is an outline of the current practices in place before the implementation of the Regulation and the new national legislation and practises to be followed, in the ethical evaluation concerning these seven sections, K.-Q., in each of the five Nordic countries; Finland, Sweden, Denmark, Norway and Iceland. Next, the application and review processes of the ethical committees are compared between the countries, and an attempt is made to identify similarities and differences between the national processes and applications. Based on the identified information, the second part outlines what requirements the sections K.-Q. of Regulation No 536/2014 as well as the Guidelines for Good Clinical Practice (EMA 2016) and the Declaration of Helsinki (WMA 2013) place on the evaluation of these sections. Then it is outlined how the implementation process has been started in Finland presenting the Draft for the Government Proposal for the Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017). Also, some comments from the first public consultation round concerning these seven issues are presented. It is also outlined why a concerted effort for harmonization of these seven topics would make it easier to carry out joint research projects in the Nordic countries.

## 1.5 Methods

The information for this study was collected from the websites of each of the five national ethical committees (TUKIJA, NBC, The Central Ethical Review Board, The National Committee on Health Research Ethics and NEM). The materials of the first part concerning the situation before implementation of the EU Regulation and the planned new national legislation are

derived from the national application instructions and codes of conduct in each of the five countries, found on the national committees' websites in January 2017 before each of the countries started to change their applications and processes to implement the Regulation 536/2014. Detailed information was not always found because there are for example electronic application processes in Denmark and Norway and much of the information was not available without access to these protected electronic systems. The legislation on which the procedures are based was left outside of the current study. The main material for the second part consists of the Finnish Draft for the Government Proposal for the Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017) and the international ruling concerning these seven sections K.-Q. The focus is on the Regulation No 536/2014, OECD's Good Clinical Practice guidelines and WMA's Declaration of Helsinki.

# 2 CURRENT MATERIALS

## 2.1 Study subject recruitment arrangements

The first topic left to each member state, as detailed in Annex 1 of the Regulation 536/2014 is its section K., recruitment arrangements. A separate document shall describe in detail the planned procedures for inclusion of subjects and shall provide a clear indication what the first act of recruitment is (Regulation (EU) No 536/2014). According to the Regulation, all advertising materials, including website addresses, audio, any printed material etc. should be included as an attachment to the CTA.

There was not much information about recruitment arrangements to be found on the websites of the ethical committees of the Nordic countries. In Finland, recruitment arrangement plans and materials should be attached to the application (Tutkittavien rekrytoinnin yleisiä periaatteita 2012). In Sweden, section 3:1 of the application form should explain the methods how the participants in research are chosen (Application for Ethical Vetting www.epn.se). In Denmark, recruitment arrangements should be described in the clinical trial protocol section k. (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011). There is a guide for preparation of advertising materials for participants on the NBC website.

Participation in a clinical trial is always voluntary and this also needs to be stated when recruiting participants. In Finland, Sweden and Denmark, the application should explain where and how the participants are recruited (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Tutkittavien rekrytoinnin yleisiä periaatteita 2012, Application for Ethical Vetting www.epn.se). Also, the selection criteria should be stated in Finnish and Swedish applications, including inclusion and exclusion criteria (Tutkittavien rekrytoinnin yleisiä periaatteita 2012, Application for Ethical Vetting www.epn.se). In Finland, it should also be evaluated before start of recruitment what kind of participants are suitable for the study (Tutkittavien rekrytoinnin yleisiä periaatteita 2012). It is common for the applications, except in Norway, where such information was not found, that all advertising materials should be enclosed as an annex to the application

(Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Tutkittavien rekrytoinnin yleisiä periaatteita 2012, Application for Ethical Vetting www.epn.se, Advertising Recruit Participants, www.vsn.is).

The NBC has made a list of what information an advertisement calling for participants should include: the nature of the research project and the scope of the trial, which type or group of subjects might be included, the investigator clinically or scientifically responsible for the trial, the person responsible for the project to contact for more information, that sensitive information about those responding might become part of registers made up for the trial, the procedures followed to contact those interested to participate, any compensation for expenses, and that a response on the part of a potential subject only signifies an interest to obtain further information (Advertising Recruit Participants www.vsn.is).

Table 1 Requirements for the recruitment arrangements in the Nordic countries

| K. | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| Where are the participants recruited | X | X | X | | |
| How are the participants recruited | X | X | X | | |
| The selection criteria | X | X | | | |
| Evaluation of what kind of participants are suitable to the study | X | | | | |
| All advertising materials should be included (any printed material, audio, website address etc.) | X | X | X | | X |
| Participation is voluntary | X | X | X | X | X |
| The purpose and the aims of the study should be kept in mind while recruiting | X | | | | |
| The schedule and scope of the study should be kept in mind while recruiting | X | | | | |

(Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Tutkittavien rekrytoimisen yleisiä periaatteita 2012, Clinical trial information leaflet and consent, Template 1 2016, Advertising Recruit Participants www.vsn.is, Application for ethical vetting www.epn.se/en)

## 2.2 The information leaflet, the informed consent form and information on the informed consent procedure

Section L. of Annex 1 of the EU Regulation 536/2014 is about the subject information leaflet and all information given to participants before they give their informed consent and about the informed consent procedure.

In Finland, Sweden and Denmark, the written information leaflet should be attached to the application as an attachment (Clinical trial information leaflet and consent 2016, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Information for research participants www.epn.se). In Finland, the leaflet text should not exceed five A4 sheets (Clinical trial information leaflet and consent 2016) and in Sweden it should be fitted into 3-4 A4 pages (Information for research participants www.epn.se).

In all five countries, there should be written information, but additional verbal information should be provided as needed, as well (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Information for research participants www.epn.se, Informed Consent www.vsn.is, Request for Participation in a clinical trial https://helseforskningen.ettikom.no). In Finland and Sweden, there should be a possibility to ask questions (Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guide to the application www.epn.se). It is also considered important that the information leaflet should use layman's terms and avoid terms that may come across as forceful, patronising or persuasive (Clinical trial information leaflet and consent 2016). If there is more information to be given than can fit into the 5 pages of the main leaflet, in Finland it is possible to also prepare a separate document that may include more detailed information on e.g. the study procedures and visit details (Clinical trial information leaflet and consent 2016).

Table 2 below contains more detailed information about the issues that the information leaflet for participants should at least include in each of the countries.

Table 2 Requirements for subject information leaflet in the Nordic countries

| L. Information leaflet | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| Title of the study | X | X | X | | |
| Request to participate | X | | X | | |
| Enquiry concerning participation | | X | | | |
| Participation is voluntary | X | X | X | X | X |
| Details of the organization and individuals responsible for the clinical trial / Responsibility | X | X | X | | |
| Background and purpose of the trial | X | X | | X | |
| Trial methodology and procedures | X | X | X | X | |
| Application of approved and non-approved medicines | | | X | | |
| Potential benefits of participation | X | X | X | X | |
| Circumstances which may result in the involuntary exclusion | | | X | | |
| Information about alternative research methods | | | X | | |
| Risks of participation, adverse effects | X | X | X | X | |
| Confidentiality and data protection | X | X | | X | |
| Expenses and statements of financial interests | X | | X | | |
| Insurance policy | X | X | | | |
| Name of sponsors | | | X | | |
| Authorisation to get access to patient records and their content | | | X | | |
| The conclusion of the clinical trial | X | | | | |
| Biobank samples | X | X | X | X | X |
| Further information | X | X | X | | |

(Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Clinical trial information leaflet and consent, Template 1 2016, Application for ethical vetting www.epn.se/en, Guidelines for Applicants www.vsn.is/en/content/guidelines-applicants, Informed Consent www.vsn.is, Information for research participants www.epn.se, Request for Participation in a clinical trial https://helseforskningen.ettikom.no)

The description of the informed consent procedure should indicate how the informed consent is to be obtained and by whom and when. In every country, consent should be provided in writing (Clinical trial information leaflet and consent 2016, Application for ethical vetting www.epn.se, Informed Consent www.vsn.is, Request for Participation in a clinical trial https://helseforskningen.ettikom.no), but in Denmark electronic consent forms are used as well (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011). Table 3 below lists what should be stated in the written consent form.

Table 3 Requirements for informed consent in the Nordic countries

| L. Informed consent | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| What is being consented to | X | | | | X |
| Name of study and the parties of the research | X | | | | |
| Statement of the fact that the person is consenting / Request to participate | X | | | | X |
| Clause to access to personal data, also from other registers if needed | X | | | | X |
| Consent to the collection and storage of coded information | X | | | | X |
| Data protection | X | | | | |
| Insurance coverage | X | | | | |
| Right to withdraw the consent | X | | | | |
| Consent for collecting of biological materials and their storage in a research biobank | X | | X | | |
| Signature of the study subject | X | X | X | X | X |
| Date and location | X | X | X | X | X |

(Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Infoskriv generell biobank 2015, Clinical trial information leaflet and consent, Template 1 2016, Application for ethical vetting www.epn.se/en, Biobanks www.vsn.is/en/content/biobanks, Guidelines for Applicants www.vsn.is/en/content/guidelines-applicants, Informed Consent www.vsn.is, Request for Participation in a clinical trial https://helseforskningen.ettikom.no)

In Finland, Sweden and Iceland, there are specific rules for withdrawal of consent. It should be possible to revoke the consent at any time during the research, and no explanation or reason for that needs to be provided. Withdrawal of consent to participate in the research should not affect the future treatment of the participant. (Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Information for research participants www.epn.se , Withdrawal of consent www.vsn.is.) According to Finnish law, amended in 2016 to comply with GCP requirements, the information and results that have already been generated prior to withdrawal of consent cannot be destroyed (Clinical trial information leaflet and consent 2016). In Sweden and Iceland, a withdrawn subject's samples should be destroyed or marked so that they cannot be traced if consent for sample storage and use is also withdrawn (Information for research participants www.epn.se, Withdrawal of consent www.vsn.is).

Children are defined in Finland as being either under 15 or 18 years of age, and in Sweden, Denmark and Iceland, under 18 years of age (Lepola etc. 2016). Norway has two different documents of informed consent in research with children as participants. One is for children under 12 years of age and another for children aged 12-16 (Infoskriv barn under 12 år 2015, Infoskriv ungdom 12-16 år 2015).

The main rule in Norway is that both parents should sign the consent form if they have parental responsibility for the child. In Denmark, consent should be asked from both parents unless the child is aged 15-17 and the study is non-interventional and non-risky; then, the child's own consent is enough. Also Sweden has rules for both parents signing the consent form. In Finland, consent from one parent is usually sufficient, but both parents should be informed. Also in Iceland, consent from one parent is sufficient. The child's level of development should be considered. It is common to all five countries that consent should be asked from the custodial parents / legally authorised representative. (Lepola etc. 2016.) If the child reaches adulthood during the research project, informed consent should be asked again before the research can continue (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011). The information leaflet for children should be tailored for them (Clinical trial information leaflet and consent 2016).

Consent of legally incompetent adults is to some extent similar to consent of minors. Consent can be surrogate consent, i.e. consent by a legally authorised representative. In Denmark, surrogate consent can be provided by a next of kin and the general practitioner of the subject

(or the medical officer of the health care provider) together, when the subject is not under legal guardianship. A legal guardian may give consent if a person is under legal guardianship (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011).

Only Danish ethical committees have documents about consent in emergency situations. Surrogate consent is possible, as is also subsequent consent. If subsequent consent is used, informed consent from the participant or surrogate consent should be asked as soon as possible, and if the participant regains his or her legal capacity, consent should be asked before continuing the research. (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011.)

## 2.3 Evaluation of the suitability of the investigator

Annex 1, section M. of the Regulation 536/2014 leaves the evaluation of the suitability of the investigator for each concerned member state to perform. The name and position of the principal investigator and qualifications of the investigator, for example in the form of a CV, belong to this section. Any economic interests and institutional affiliations that might have an influence on the neutrality of the investigator should be also mentioned.

In Finland, the application documents call for information about the suitability of the investigator. A separate attachment about these issues should be provided to supplement the basic information given on the application form. (Muistilista eettisten toimikuntien jäsenille ja tutkijoille 2009.) Sweden has section 3:1 and Iceland sections A-4 and A-8, which are about the investigator (Application form for approval of clinical trial protocol 2015, Application for Ethical Vetting www.epn.se). In Denmark, this information should be attached as an annex (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011).

In each country, the CV of the investigator should always be included in the application (Tutkittavalle annettavat tiedot kliinisestä lääketutkimuksesta ja suostumusmalli 2016, Application form for approval of clinical trial protocol 2015, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics

2011, Application for Ethical Vetting www.epn.se, www.ettikom.no). Also relevant was documentation on the investigators' medical training, and in Iceland, the publications of the principal investigator should also be listed in the application (Checklist accompanying an NBC application for a Clinical trial 2013). Economic and financial relationships that might have an influence on the neutrality of the investigator are to be listed in the application in each of the five countries, as well (Tutkittavalle annettavat tiedot kliinisestä lääketutkimuksesta ja suostumusmalli 2016, Application form for approval of clinical trial protocol 2015, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Application for Ethical Vetting www.epn.se, www.ettikom.no).

Table 4 Evaluation of the suitability of the investigator in the Nordic countries

| M. | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| CV of the researcher | X | X | X | X | X |
| Documentation of medical/dental training | X | | X | | |
| Publication lists of the principal investigator | | | | | X |
| Economic and financial relations that might have an influence | X | X | X | X | X |

(Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Checklist accompanying an NBC application for a Clinical trial 2013, Application form for approval of clinical trial protocol 2015, Application for ethical vetting www.epn.se/en, Electronic Attachments. 29.6.2015)

## 2.4 Evaluation of the suitability of the facilities

Part N. of Annex 1 of the Regulation 536/2014 is about the suitability of the facilities, which means clinical trial sites, equipment and human resources. There was not much information found on the websites of the Nordic ethical committees. From Iceland or Norway, no information was found.

In Sweden and Denmark, there is a part in the application where the suitability of the facilities should be documented (Guidelines about Notification etc. of a Biomedical Research Project to

the Committee System on Biomedical Research Ethics 2011, Application for Ethical Vetting www.epn.se). In Finland, this information should be included in the application as an annex (Muistilista eettisten toimikuntien jäsenille ja tutkijoille 2009).

Important information to be given includes the suitability of the facilities, equipment, location, human resources and institutions and clinics. In addition, in Finland it is also noted that the safety of the research subjects and personnel should be taken into account, for example preparedness for complications and emergencies and storage and handling of hazardous materials (Muistilista eettisten toimikuntien jäsenille ja tutkijoille 2009).

Table 5 Evaluation of the suitability of the facilities in the Nordic countries

| N. | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| Suitability of facilities and equipment | X | X | | | |
| Suitability of the location where the project is to be completed | | X | | | |
| Suitability of human resources | | X | | | |
| Institutions and clinics | X | X | | | |
| Complication and emergency preparedness | X | | | | |
| Storage and handling of hazardous materials | X | | | | |

(Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012)

## 2.5 Proof of insurance coverage or indemnification

Proof of insurance should be provided in the application, if participants are insured. Also, proof of a guarantee or similar arrangements for compensation of damages may be enclosed in the application. This is left for each member state to consider in Annex 1 section O. of the Regulation 536/2014.

In Finland section 14 of the application form asks for a statement whether there is a valid patient insurance or insurance policies related to IMP-related injuries. If research participants

are not insured, this should be explained in the application and provisions for other types of compensation should be documented. (Clinical trial information leaflet and consent 2016.) In Sweden, insurance coverage should be mentioned in section 3:5 of the application, and in Iceland, in section D-6 of the form (Application form for approval of clinical trial protocol 2015, Application for Ethical Vetting www.epn.se).

It is common for all five countries that it should be stated how the participants are insured or whether they are insured at all. In Iceland, the name of the insurance company as well as the coverage policy should be attached to the application form (Application form for approval of clinical trial protocol 2015). Also, if any compensation or reimbursement plans exist, they should be mentioned in the Danish and Icelandic application forms (Application form for approval of clinical trial protocol 2015, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011).

Table 6 Requirements for proof of insurance coverage and indemnification in the Nordic countries

| O. | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| How are the participants insured | X | X | X | | X |
| Name of the insurance company | | | | | X |
| The coverage policy of the insurance | | | | | X |
| If compensation or reimbursement plans exist, they should be mentioned | | | X | | X |

(Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Application form for approval of clinical trial protocol 2015, Clinical trial information leaflet and consent Template 1 2016, Tutkittaville annettava tiedote kliinisestä lääketutkimuksesta ja suostumusmalli 2016, Application for ethical vetting www.epn.se/en, Information for research participants www.epn.se)

## 2.6 Financial and other arrangements

Part P. of Annex 1 of the Regulation 536/2014 is about the financing of the study. This section should also describe the compensation paid to participants as well as the fees for the

investigator and the trial site. It should also be mentioned if there are any other agreements between the sponsor of the study and the site.

In Finland, the financial arrangements should be described in an attachment (Muistilista eettisten toimikuntien jäsenille ja tutkijoille 2009). Sweden and Norway have sections in their application forms for the financial arrangements and economic relations (Application for Ethical Vetting www.epn.se, www.ettikom.no). In Denmark, there are sections h., i., and j. of the trial protocol, which are about financing of the study and there should also be a document attached to the application form (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011).

It should be stated in the application form what will be reimbursed for the participants, for example compensation for discomfort and inconvenience, lost income from employment, travel expenses or costs of pharmaceutical products (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Muistilista eettisten toimikuntien jäsenille 2009). In Finland and Denmark, details should be provided about the form and amount of remuneration (Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Muistilista eettisten toimikuntien jäsenille 2009) and in Sweden when it is to be paid (Application for ethical vetting www.epn.se). It was also important that the amount of reimbursement shall not have undue influence on the participant's consent (Guide to the Application 2012, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Lääketieteellisiin tutkimuksiin liittyvät taloudelliset selvitykset eettisille toimikunnille ja tutkittaville 2008, Guidelines for applicants www.vsn.is).

The name(s) of the study sponsor(s) and the amounts of money to be paid to the site by every commercial and non-commercial sponsor should be stated. In Finland, there are more detailed rules on what should be stated in the application about the funding of the study, including the total amount of costs and fees for the investigator(s) (Muistilista eettisten toimikuntien jäsenille ja tutkijoille 2009, Lääketieteellisiin tutkimuksiin liittyvät taloudelliset selvitykset eettisille toimikunnille ja tutkittaville 2008).

It is also similar for all application forms that all economic relationships between the investigator and participants as well as sponsors should be described. For example, ownership

of shares in the sponsor company, employment status and companies owned by investigators that may benefit from the study should be described. (Guide to the Application 2012, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Lääketieteellisiin tutkimuksiin liittyvät taloudelliset selvitykset eettisille toimikunnille ja tutkittaville 2008.)

Table 7 Evaluation of financial arrangements in the Nordic countries

| P. | Finland | Sweden | Denmark | Norway | Iceland |
|---|---|---|---|---|---|
| **1. Reimbursement or remuneration for participation** | | | | | |
| What kind of expenses will be reimbursed | X | X | X | | X |
| Form and amount of remuneration for participation | X | | X | | |
| When is this to be paid | | X | | | |
| Amount of payment shall not have undue influence on giving the consent | X | | | | X |
| **2. The funding of a study and finances** | | | | | |
| Name and amount | X | X | X | | X |
| How and to whom is the subvention paid | | | X | | |
| The total amount of costs | X | | | | |
| Fees for researcher's | X | | | | |
| Resources and arrangements for recruitment | X | | | | |
| Insurance cover | X | | | | |
| **3. Economic relationships** | | | | | |
| All direct and indirect circumstances that could affect the researcher's relationship to the study subject | X | X | X | | X |
| Ownership of shares | X | X | X | | X |
| Employment status | X | X | X | | X |
| Consultancy work for companies financing the study | X | X | X | | X |
| Companies owned by researcher that may benefit from the study | X | X | X | | X |

(Lääketieteellisiin tutkimuksiin liittyvät taloudelliset selvitykset eettisille toimikunnille ja tutkittaville 2008, Muistilista eettisen toimikunnan jäsenille ja tutkijoille 2009, Ennakkoilmoituksen täyttöohje 2010, Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics 2011, Guide to the application 2012, Application form for approval of clinical trial protocol 2015, Application for ethical vetting www.epn.se/en, Guidelines for Applicants www.vsn.is/en/content/guidelines-applicants)

## 2.7 Proof of payment of the handling fee

Proof of payment of the handling fee should be submitted, if applicable (Regulation (EU) 536/2014). There was no information on this found from the websites of the Nordic ethical committees.

## 2.8 Conclusions

All in all, the current legislation and rules on ethical review of clinical trials are quite different in each of the Nordic countries. There was relatively little structured information to be found about the current situation and most of the information was not provided in English. The processes and the application forms differ a lot between the countries. Denmark and Norway have electronic portals, while the other countries only employ qualified and standardized paper versions of the application forms, with a number of free-form attachments. Criteria for these seven issues that are discussed above are also quite different for some parts.

Some of these issues will be to some extent harmonized by the application of the CTA and Assessment report formats of the EU Regulation, but the Regulation still leaves a lot to each member state to decide in the area of these seven topics listed as K-Q of Annex 1 of the Regulation. This is the reason why it would now be very important to harmonize the application and review processes in the Nordic countries, if the countries wish to foster their competitiveness in the field of clinical research. With identical application and review processes it would be easier for investigators and sponsors to start and carry out joint research projects in the five Nordic countries, by engaging in only one application process instead of five different application processes.

# 3 HARMONIZATION OF NATIONAL ASPECTS

## 3.1 Study subject recruitment arrangements

Topic K. of the Regulation 536/2014 concerns study subject recruitment arrangements. The application should include a description of the procedures for inclusion of the study subjects as well as define the first act of the recruitment process. All advertising materials (printed materials, visual, audio) should be attached to the application. Also, all methods used for handling of responses from potential participants should be described. (Regulation 536/2014.)

The Declaration of Helsinki (WMA 2013) gives no direct guidance to section K. of the Regulation. It is mentioned that special attention should be paid to the specific information needs of potential study subjects as well as the methods used in giving the information to the subjects. The Declaration does not specify or identify which materials and methods are appropriate and which are not. Instead, according to Good Clinical Practise Guidelines (EMA 2016), all materials and procedures to be used in subject recruitment, for example advertisements, should be submitted with the trial protocol for evaluation by the competent ethics committee. This is closer to the wording of Regulation 536/2014. The types of allowable recruitment materials and methods are not specified in GCP (Good Clinical Practise).

Also, more detailed information is included in the Declaration than what is in the Regulation. According to the Declaration of Helsinki (WMA 2013), every trial should be registered in a publicly accessible database before the first act of recruitment. It is the investigator's responsibility to provide evidence that it is possible to recruit enough study subjects within the recruitment period, according to GCP (Guidelines for Good Clinical Practise 2016). The responsibility for recruitment activities is not defined in section K. of the Regulation. It appears that the main point of the international ruling as well as in the Regulation 536/2014 is that all recruitment activities and materials should be documented and evaluated by the ethics committee, no matter what the activities and materials are.

In Finland the new Regulation 536/2014 is being applied in the current Draft for the Government Proposal for a new Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017). In the

Draft, the 7 § of the Law on Clinical Drug trials is about the language of the application. The materials concerning section K. part 60 (and also section L.) of the Regulation, including the recruitment materials given to the study subjects, should still be provided in Finnish or Swedish even if many parts of the application can be written in English according to this new Draft. The Draft also lists the same types of advertising materials as in Regulation 536/2014 that should be included in the application. The procedures used to select study participants should be described in the application, as well as any information that is given to subjects who are not chosen for the trial. All in all, comparing the old Finnish ruling on this topic, not much has been changed in the new Draft legislation.

In the first round of public consultation on the Draft (https://stm.fi/hanke?tunnus=STM077:00/2017) many comments supported the proposal that materials may be submitted in English, apart from the subject recruitment materials and the materials concerning informed consent. For example, the Regional State Administrative Agency of Northern Finland noted that the materials concerning subject information and consent should be provided in both national languages, Finnish and Swedish. The National Institute for Health and Welfare (THL) suggested that also the materials concerning part 60 of section K., on subject information and consent could in some cases be only provided in English. Otherwise this part was quite little discussed.

## 3.2 The information leaflet, the informed consent form and information on the informed consent procedure

Regarding Annex 1 section L. of the new EU Regulation, information given to prospective trial participants should include “all information given to the subjects before their decision to participate or abstain from participation” (Regulation 536/2014). All such information to be given should be attached to the application.

Informed consent should be provided in writing on a standardized form. A description of the information and consent procedures should be attached to the application. There are named situations in which the informed consent and information given should be given particular attention. Such situations include: minors or incapacitated study subjects, cases where the consent is witnessed by an impartial witness, and clinical trials in emergency situations. With

minors or incapacitated subjects, informed consent should be asked from their legally designated representative, i.e. surrogate consent is needed. In cases where an impartial witness is used, it should be mentioned why the witness is needed and the process how the witness is selected as well as the procedure for obtaining consent should be described. In case of research conducted in an emergency situation, one should describe the process of obtaining informed consent from the subject or his or her legal representative to continue the trial. Also, a description of the situation and justification why it was urgent should be included. When the trial is a so-called cluster study, and simplified means are used for obtaining the informed consent, the simplified means should be described in the application. (Regulation 536/2014.)

Chapter V (Protection of subjects and informed consent) of the Regulation 536/2014 includes further regulation of the informed consent, and Annex 1 directly refers to it. It gives frames for the member states to prescribe their national legislation. Article 28 is about the general rulings of the informed consent. Informed consent should be written, dated and signed by the study subject or his/her legally designated representative as well as the interviewer. Article 29 includes a list of what the information given to the subjects should include. The subject should understand the nature, objectives, benefits, implications, risks and inconveniences of the trial, the subject's rights and the conditions of the trial, and possible treatment alternatives. The text should be understandable for a layperson. Consent should be preceded by an interview with a member of the investigational team who must be qualified according to national law, and the interviewer should make sure that the subject understood the information. There should be information about an insurance policy and the study must be identifiable by its unique EU trial number. Later, the results of the study should be informed to the subjects in a manner understandable by a lay person. (Regulation 536/2014.)

Article 30 of Regulation 536/2014 regulates informed consent in cluster trials. It is applicable when the trial is conducted in only one country. Simplified means of consent are allowed when this does not conflict with national law, groups rather than individuals are study subjects, the study is a low-intervention trial and the tested products are used within the terms of their marketing authorisation. (Regulation 536/2014.)

Articles 31-35 of the Regulation are about vulnerable groups of study participants. Article 31 of the Regulation 536/2014 is about clinical trials on incapacitated subjects. As mentioned

above a legally authorised representative should give surrogate consent for participation. The incapable subject should be provided with all information that he or she understands. There cannot be financial incentives for the subjects. It is important that the trial concerns the clinical condition of the subject. (Regulation 536/2014.)

Article 32 of the Regulation regulates clinical trials on minors. The participant's legally authorised representative should give the consent, and the subject should be provided with all information that a person of that age and mental maturity can understand. The wish of a minor who is capable of forming opinions, for example on withdrawing from the study, should be respected. If the minor reaches adulthood during the trial, the subject should be re-informed and should provide renewed, independent consent. No financial incentives are allowed. Participating minors should also be afflicted with the condition that is being investigated, and the condition should be one that primarily appears in children. There should also be a reasonable likelihood that the trial directly benefits the participating children, or that some population of children benefits and there is a minimal risk of injury or harm compared to standard treatment. (Regulation 536/2014.)

Article 33 of the Regulation 536/2014 regulates trials on pregnant or breastfeeding women. They may only participate if the trial provides direct benefit for the study subject (embryo, foetus, child or pregnant or breastfeeding woman), or similar results cannot be achieved with non-pregnant or breastfeeding women and the study benefits others from the group of pregnant or breastfeeding women or embryos or foetuses or children. All possible adverse events should be considered. In these trials, financial incentives are not allowed. Article 34 states that additional measures are needed also when the trial involves persons in military service, persons who are deprived of liberty, persons in residential care or who due to a judicial decision cannot take part on a fully voluntary basis. (Regulation 536/2014.)

Article 35 of the Regulation 536/2014 is about emergency situations. A subject's consent may be obtained after the decision to include the subject in the trial if the decision of entry is made at the time of the first interventional measure of the trial and in accordance with the study protocol. Also, it has to be an emergency situation or other urgent situation, and because of that and the subject's incapacitated condition, the subject cannot give voluntary informed consent prior to his/her entry into the study. There should be scientific evidence that the participant clinically benefits from the study, and justification that there is no possibility to

obtain fully informed surrogate consent. The investigator should make sure that he or she is not aware that the subject has earlier expressed a wish to refuse from all clinical trials. The trial should be directly about the condition that the subjects have, and cannot be conducted in other than emergency situations. Also, the risks of the study should be minimal compared to the standard treatment of the condition. Consent should be obtained as soon as possible from the subject or a legally authorised representative. If the legally authorised representative has given surrogate consent, consent should also be obtained from the subject as soon as possible. If the legally authorised presentative refuses to give consent, he or she should be informed of the possibility to withdraw the results of that subject from the trial. (Regulation 536/2014.)

In the Declaration of Helsinki (WMA, 2013), there is a list of required elements of information that should be provided to potential study subjects before signing of the consent form. The list includes the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects (Declaration of Helsinki, 2013). Its wording is more detailed than that of Regulation 536/2014. The Guidelines for Good Clinical Practise (EMA, 2016) mention that all written information, the consent form and other materials provided to the participants, should be delivered to the ethics committee for evaluation. Also, the written information should be renewed every time when new information that is important for consent for the trial becomes available. In GCP, the wording always refers to written information, compared to the Declaration of Helsinki and Regulation 536/2014 that refer to all information given to participants, whether written or not. There is still a mention in GCP that the investigator should fully inform the subject.

According to GCP Guidelines (EMA 2016), the language of the participant information should be in layman's terms and the information should not revoke any legal rights or release the investigators and sponsors from liability. An opportunity should be given to think about whether or not to participate in the trial, and a possibility to get more detailed information should be given. There is also a list of what the written information should include in GCP Guidelines that is even more detailed than in the Declaration of Helsinki and Regulation 536/2014. This list includes a mention that the trial involves research, the purpose of the trial, the trial treatments and their random assignment, the trial procedures, the subject's responsibilities, those aspects of the trial that are experimental, the reasonable foreseeable

risks or inconveniences to the subject, the reasonable expected benefits, the alternative procedures or courses of treatment that may be available to the subject, the compensation and/or treatment available to the subject in the event of trial-related injury, the anticipated prorated payment, the anticipated expenses, that the participation is voluntary and that the subject may withdraw from the trial at any time, that the study monitor, the auditor and regulatory authorities will be granted access to the subject's original medical records without violating the confidentiality of the subject, that all records identifying the subject will be kept confidential, that the subject will be informed if information becomes available that may be relevant to the subject's willingness to continue participation, the person to contact for further information, the foreseeable circumstances and/or reasons under which a subject's participation may be terminated and the expected duration of the participation in the trial (Guidelines for Good Clinical Practise, 2016). This list is the most detailed of all these three lists. It is obvious that this section is already quite strictly regulated on the international level and that not much is left for national legislators to decide. For example, the guidance found on the websites of the Nordic ethics committees was less detailed than these international lists.

According to the Declaration of Helsinki (WMA 2013), participation in the trial should always be voluntary. Similarly, withdrawing from the study should be possible at any time without providing a reason. It is also important to mention that declining participation in a trial or possible withdrawal of consent should not affect the patient-doctor relationship. Informed consent should be freely given, preferably in writing. In situations where written consent is not possible, non-written consent should be documented and witnessed. Participants should be informed of the results of the research if they wish. Also, according to GCP Guidelines (EMA, 2016), consent must be freely given in writing. Withdrawal or refusal to participate should be possible at any time. The consent form must be signed and dated, and the subject should receive a copy of it. The investigator or other staff should not exert undue influence on the decision-making of the subject. If written consent is not possible, an impartial witness should be used. If the subject is capable of writing, he or she should still sign the consent form as well as the witness. All procedures and materials used in the recruitment, information and consenting of study subjects should be delivered to the ethics committee for assessment.

The Declaration of Helsinki (WMA, 2013) also contains a more detailed analysis of vulnerable subject groups in research. These subjects should be especially protected. Persons belonging

to vulnerable groups should not be used in the trial unless the trial cannot be carried out with participants not belonging to such vulnerable groups. The group in question should also somehow benefit from the trial results. With regard to incapable study subjects, consent should be asked from their legally authorised representative. Such studies can only be conducted when the group of incapable persons benefits from the study and the study cannot be performed in other study subjects. If the incapable person can give assent to participation, such assent should be recorded in addition to the consent of the legally authorised representative. GCP Guidelines (EMA 2016) provide more specific rules. In situations where a legally authorised representative is needed, the ethics committee should assess the ethical concerns. When a legally authorised representative is used, requirements include that the trial cannot be performed with subjects who can give valid independent consent, and the risks for the subjects' health are small. Thus, GCP is in good agreement with the Declaration of Helsinki.

There is also a ruling in the Declaration of Helsinki (WMA 2013) about subjects who are physically or mentally incapable of giving independent informed consent, for example in emergency situations. Consent must be asked form a legally authorised representative. In emergency situations, when the research cannot be delayed and there is no legal representative available, the research can continue without informed consent, if there are specific reasons why subjects with the condition in question are involved in the research and the ethics committee has approved the trial. The participant's consent in these cases should be asked as soon as possible. Also, according to GCP Guidelines (EMA 2016), the ethics committee should assess these requirements before such a trial can be started.

In Regulation 536/2014, all these vulnerable groups as well as the informed consent procedures with them are regulated in a quite detailed manner. The Declaration of Helsinki and GCP Guidelines give frames for this more detailed ruling in Chapter V of the Regulation.

The Declaration of Helsinki (WMA 2013) also contains ruling about materials and data and biobank samples that are collected in the trial. Informed consent must be obtained for using and storing such materials.

According to the Finnish Draft for the Government Proposal for Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017), the documents related to section L. of the Regulation should be provided in Finnish or Swedish, as well as the documents in section K.

Informed consent is regulated in Chapter 3 of the Draft for the Government Proposal for Law on Clinical Drug Trials (2017) in 14 §–18 §. 14 § is about incapacitated subjects. Who is defined as incapacitated is left to national legislation to decide. In Finland, the outcome is that incapacitated subjects are defined as persons with a mental disorder, mental disability or other equivalent condition. Such a subject cannot fully understand the facts relating to the trial in a way that he or she can give fully informed, valid consent for the trial. A legally authorised representative can give the consent in such situations. If a legal guardian has been appointed, the guardian can give the consent. If there is no court-appointed guardian, consent can be given by a close relative or another person who is close to the subject (e.g. a close friend). (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 15 of the Draft of the Government Proposal for Law on Clinical Drug Trials (2017) is about informed consent of minors. The age limits of adulthood are left for national legislation to define. In Finland, under-age persons at least 15 years old can give informed consent unless it is not possible due to lack of maturity, nature of the disease or some characteristics of the trial. Still, the legally authorised representative (parent, custodial parent or guardian) should be informed about the study and the consent. The trial must potentially benefit minors and the risks and burden of participation must be minimal compared to standard treatment. If a minor who cannot give informed consent can express an opinion about participation, written assent from the minor as well as the legally authorised representative's consent is needed; this is a new feature compared to previous legislation in Finland. If the minor refuses to participate or wishes to withdraw from the trial, the investigator should appreciate the minor's opinion. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 16 of the Draft for the Government Proposal for Law on Clinical Drug Trials (2017) is about prisoners and forensic psychiatric patients. According to Regulation 536/2014, member states can impose additional measures about consent of persons who are deprived of liberty, persons in residential care or who due to a judicial decision cannot freely decide on their participation. These two groups mentioned above need additional protective measures according to Finnish legislation. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Cluster trials are regulated in 17 § of the Draft for the Government Proposal Law on Clinical Drug Trials (2017). The definition of a cluster trial is the same as in Regulation 536/2014. The

Draft Proposal speculates that according to the Convention on Human Rights and Biomedicine of the Council of Europe (ETS No. 164, 1997), it would not be possible to give consent only by not opting out, i.e. by not expressing one's wish not to participate in a trial. The Draft Proposal concludes that such simplified consent for a cluster trial would not be possible according to current national legislation. It is also speculated whether it would actually be possible to impose additional national conditions for consent for cluster trials. It is stated in Regulation 536/2014 that simplified means to get consent for cluster trials are only allowed when it does not conflict with national law. This issue is thus still undecided in the Finnish legal reform. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 18 of the Draft Proposal is about handling of personal data after withdrawal of consent, and it is also still unfinished. All in all, this section L. of the EU Regulation is very strictly legislated already on the international level, and this Finnish Draft Proposal may be adding several national features and restrictions. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

In the first round of public consultation concerning the Draft Proposal (https://stm.fi/hanke?tunnus=STM077:00/2017), these clauses 14–18 of the Draft for the Law on Clinical Drug Trials were widely debated and many divergent views were expressed.

Most commentators thought that 14 § and 15 § of the Draft were acceptable. About 15 §, it was commented that consent from one parent should be sufficient in most cases, by for example CRST Oy (Clinical Research Services Turku) and the Finnish Paediatric Association (the latter also pointed out that that the second parent should not resist). (https://stm.fi/hanke?tunnus=STM077:00/2017.)

Some commentators argued that 16 § of the Draft (concerning prisoners and forensic psychiatric patient) should be more detailed, and that the definition of "direct benefit" is opaque as well as the definition of who should be expected to benefit from the trial. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

Clause 17 on cluster trials evoked variable opinions. For example, the Finnish Society of Intellectual Disability Medicine thought that it should not be possible to use simplified means to get consent for cluster trials. Most commentators thought that using simplified means to get informed consent for cluster trials would be appropriate, and for example the National

Institution of Health and Welfare (THL) thought that would be a welcome reform in the new legislation. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

About the unfinished 18 § of the Draft, the Data Protection Agency pointed out that according to EU's GDPR (General Data Protection Regulation 2016/679), there is no room left for national legislation in this respect. CRST Oy suggested that the Draft should include a clear statement, that study subjects should be allowed to provide irrevocable consent for the further use of their study data after possible withdrawal of consent for participation. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

## 3.3 Evaluation of the suitability of the investigator

Section M. is about the suitability of the investigator. The CTA should include a list of planned trial sites, with planned numbers of subjects at the sites as well as the name and position of each site's principal investigator. There should also be a list of all investigators, their curriculum vitae and other relevant documents, for example evidence on relevant previous training or experience in clinical trials and patient care. Also, any economic relationships and interests that might influence the investigator should be mentioned. (Regulation 536/2014.)

According to the Declaration of Helsinki (WMA 2013), only persons with appropriate scientific and ethical training and qualifications are allowed to carry out clinical trials involving human subjects. It is not specified what the appropriate qualifications are. A physician or other health care professional who is competent and qualified must always supervise the trial according to the Declaration of Helsinki. GCP (Guidelines for Good Clinical Practise 2016) mentions that every individual carrying out the trial should have qualified education, training and experience for their tasks in the trial. This wording is quite similar as that used in the Declaration of Helsinki. GCP also mentions that investigators should be qualified with regard to all applicable regulatory requirements and should prove their qualification by documentation when required.

Also, information about funding, sponsors of the investigator as well as institutional linkages and conflicts of interest should be mentioned in the study protocol (Declaration of Helsinki, 2013). GCP (Guidelines for Good Clinical Practise 2016) defines that it is the ethics committee (Institutional Review Board or Independent Ethics Committee), who is the considering body

that evaluates the investigators' qualifications. A current curriculum vitae and other relevant documents should be delivered to the ethics committee. It is noted as well that it is important that the investigator of the study is aware of the principles of GCP and the regulatory requirements. It is also noted in GCP that medical decisions on patient care should always be made by a qualified physician (or dentist).

With regard to this section M., the Declaration of Helsinki and GCP provide more detailed ruling than Regulation 536/2014.

According to the Finnish Draft for the Government Proposal for Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017), topic M. of Regulation 536/2014 is legislated in 4 § of the Draft Proposal. According to Regulation 536/2014, an investigator is a person who is responsible for conducting the trial at the trial site. The investigator should be a physician (or dentist) or should belong to another profession that according to national legislation in the member state is qualified to perform the trial. In 4 § of the Finnish Draft Proposal it is proposed that the investigator should be either a physician or a dentist, with appropriate scientific qualifications. Other members of the research group should be qualified for their tasks, as well, according to the second paragraph of 4 §. Each member of the group should be familiar with the informed consent procedure and EU legislation about the trial. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 5 of the Draft Proposal is about the sponsor of the study and situations when the sponsor is not a legal entity located in the European Union. The sponsor should in such cases have a legal representative in the European Union, with responsibility to see applicable European legislation is taken into account and its obligations are followed. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

The Draft Proposal has clearly more detailed ruling about this topic than Regulation 536/2014. About the needed documents, there is no more information than in the Regulation, but about the qualifications of the investigator and the sponsor there exist some national requirements. Compared with the current legislation on this topic in Finland, the obligations are more clearly defined, and the requirement that the investigator in a clinical drug trial should be a physician (or dentist) is retained as it was in the earlier legislation.

There was a lot of discussion on this section in the first consultation round of the Draft Proposal. Many commented that 4 § is defined in the Draft in an appropriate way. Some commented that the definition of investigator was unclear, muddling the definitions of physician, investigator and researcher. The Academy of Finland speculated that the definition is problematic because only physicians or dentists can be called investigators. The National Supervisory Authority for Welfare and Health (Valvira) then argued that this distinction is important because it differs from the definition of the investigator that exists in the Medical Research Act (488/1999). (https://stm.fi/hanke?tunnus=STM077:00/2017.)

On clause 5 of the Draft Proposal the opinions were on behalf and against. Some commentators asked for clearer definitions on who is responsible for what. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

## 3.4 Evaluation of the suitability of the facilities

According to topic N. of Annex 1 of the Regulation 536/2014, the suitability of the facilities should be on the responsibility of the head of the clinic or another responsible person. A written statement should be attached to the application stating that the facilities are suitable for the study. Facilities include the clinical trial site, equipment, human resources and descriptions of expertise (Regulation 536/2014).

In the Declaration of Helsinki (WMA 2013), not much is said about this topic. The design and performance of the trial must be clearly described in the trial protocol (Declaration of Helsinki 2013). There is no detailed list of the characteristics of the facilities that must be mentioned; a general statement requires that all relevant details should be covered in the trial protocol.

GCP Guidelines (EMA 2016) provide a more detailed analysis of this topic. It is noted that the manufacturing, handling and storing of the investigational products should follow GMP (Good Manufacturing Practise). It is also important that the investigator is familiar with the use of the investigational products. There should be also available a list of qualified personnel to whom the investigator has delegated significant study tasks. Adequate staff should be available, and it should be ensured that the staff is adequately informed. The investigator must ensure that there are adequate facilities to run the trial properly and safely. (Guidelines for Good Clinical Practise 2016.)

The Finnish Draft for the Government Proposal for Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017) does not include much further ruling about the facilities. All in all, the sponsor is responsible for ensuring sufficient and qualified human resources, equipment and facilities and that the trial can be run safely. This section attracted rather few comments in the first consultation round of the Draft Proposal.

## 3.5 Proof of insurance cover or indemnification

Section O. of Annex 1 is about proof of insurance, a guarantee or similar arrangements, which shall be attached to the application. (Regulation 536/2014.)

According to the Declaration of Helsinki (WMA 2013), investigators or health care professionals are responsible for the protection and safety of the study subjects during the trial. The research protocol should include information about compensating the study subjects in cases of any harm arising as a consequence of the trial. Also, it is mentioned that the compensation should be appropriate, and that adequate medical treatment of the harmed subject must be arranged.

In GCP Guidelines (EMA 2016), there is also ruling about the sponsor of the research. The sponsor should provide insurance or indemnify the investigator against claims arising from the trial. It is also the sponsor's duty to cover the costs of trial-related injuries. Also, the safety of the study subjects is outlined in many articles of the text. (Guidelines for Good Clinical Practise 2016.)

The Finnish Draft for the Government Proposal for Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017) has in its clause 6 ruling on insurance or other indemnification. There must be an insurance policy or other systems to ensure compensation in case of damage for trial subjects (Draft for the Government Proposal on Law on Clinical Drug Trials 2017). The wording of Regulation 536/2014 means that now also other forms of indemnification than an insurance policy may be valid. Other forms of indemnification may be rare in practise but will be possible to use.

According to the Draft Proposal, a competent ethics committee in Finland should evaluate whether the insurance or indemnification is sufficient for the trial concerned (for example evaluate the risks). The main point is to ensure coverage of any personal damages. Compared to the current legislation in Finland, the main change seems to be that according to EU legislation, also other types of indemnification than insurance are considered valid. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

In the first round of consultation on the Draft Proposal many commentators saw that the new clause 6 is clear enough and in line with Regulation 536/2014. The Ministry of Justice pointed out that it was unclear for how long the proof of insurance or indemnification must be in force. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

## 3.6 Financial and other arrangements

Section P. of Annex 1 of Regulation 536/2014 is about financial and other arrangements. The financing of the clinical trial should be described. There should be information about the financing and reimbursement paid to participants and the fees to the investigator and the trial site. Also, other arrangements and financial ties between the investigator, the trial site and the sponsor must be mentioned. (Regulation 536/2014.)

The Declaration of Helsinki (WMA 2013) gives frames for further legislation on this section P. All relevant information about funding, sponsors and incentives for subjects should be available for review, also how subjects who may be harmed because of their participation will receive treatment or compensation (Declaration of Helsinki 2013). Similar guidance is given here for national legislation as is included in EU Regulation 536/2014. According to GCP Guidelines (EMA 2016), compensation and financial aspects between sponsors and investigators should be documented for the ethics committee. So, each of these documents contains similar requirements and the same issues are left for national legislation to define.

Also, according to GCP, it is the responsibility of ethics committees to make sure that all information about payments to subjects is properly presented to the study subjects in a written information leaflet or other written document. In the written information, there should be mentioned also the compensation to study subjects, the estimated amount of

payment and estimated expenses. (Guidelines for Good Clinical Practise 2016) All in all, Regulation 536/2014 gives the same frames to national legislation as these two international documents.

In Finland, this topic is handled in Chapter 5 of the Draft for the Government Proposal for Law on Clinical Drug Trials (Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi 2017). Clause 27 of the Draft Proposal is about the medications related to the study as well as other products and arrangements to be used. All of them should be delivered free of charge to the study subjects. If there are exceptions, they should be justified. Criteria for such possible exceptions can be provided by a Government Decree. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 28 of the Draft Proposal is about payments to study subjects. The study subject, his or her legally authorised representative or other support person cannot be paid for the participation. This is in reference to Regulation 536/2014 that rules that there should be no inappropriate economic incentives for participation. Remuneration can be paid for loss of earnings and other costs. More details about remuneration can be provided by a Government Decree. There is also a mention that all information about financing, fees paid to participants, the investigator and the trial site should be provided to the ethics committee, in agreement with Regulation 536/2014. Further details are left to be decided later by a Government Decree. All in all, not much more detail is given in the Finnish Draft Proposal than what is already stated in the EU Regulation, and a lot is left to be decided by a Government Decree. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Especially clause 27 of the Draft Proposal gave rise to many comments in the first round of public consultation (https://stm.fi/hanke?tunnus=STM077:00/2017). Some thought that there should be no possibility to make exceptions to the free delivery of study drugs to the participants, they should always be free of charge. For example, one ethics committee pointed out that costs for study drugs would be against the principle of equality. Others thought that it may sometimes be reasonable that study subjects have to pay for the drugs if there is a justified reason. Still, the main rule should be that the study drugs are free of charge for the subject. (Draft for the Government Proposal on Law on Clinical Drug Trials 2017.)

Clause 28 was also discussed in the consultation round. One ethics committee for example pointed out that there should be more clear legislation about the principles of allowable remuneration to study subjects, while details and the allowable incentives should be left for the ethics committee to assess on a case-by-case basis. The University of Turku and Crown CRO Oy argued that the maximum sums in euros should be removed from the Government Decree. Also, CRST Oy pointed out that strictly defined remuneration restrictions and a fixed maximum sum of remuneration do not make it possible to keep the subjects in the study for long enough. (https://stm.fi/hanke?tunnus=STM077:00/2017.)

## 3.7 Proof of payment of the handling fee

Section Q. of Annex 1 is about the proof of payment of the CTA handling fee, which should be attached to the application if necessary. (Regulation 536/2014.)

This section is quite clear and GCP or the Declaration of Helsinki do not have further ruling or regulation about this issue. Also, the Finnish Draft Proposal contains no further information on this topic Q.

# 4 CONCLUSIONS

All in all, the present analysis shows that these seven sections of Annex 1 of Regulation 536/2014 that are left to the member states to consider and regulate in more detail were handled in quite different ways in each of the Nordic countries. Some similarities were also found. Because the aim of the first part of this study was to identify the materials and instructions related to the countries' current practises in these matters on the websites of the national ethics committees, and the current legal basis was left out of the study, rather little material was found. In the tables presented, where the instructions given in the different Nordic countries were compared, many entries were left blank, not necessarily because lack of regulation but rather because the information was hard to find from the websites. There were for example portals where the investigator should be registered in order to get the information, as in Norway. So, this study shows that it is important to know the national legislation and perhaps also the language of the country where the trial is to be conducted. Also, good command of the guidance provided by GCP and the Declaration of Helsinki is essential. This international guidance that is now also implemented by Regulation No 536/2014 of the European Union gives a solid framework for any national regulation in Europe.

Regulation 536/2014 aims to harmonize the application process for clinical drug trials in all EU member states and affiliated countries. Annex 1 of the Regulation leaves these seven issues handled in this study to each member state to define in more detail. Still, the international ruling is important and provides a framework for the application process also in these issues. The Declaration of Helsinki as well as GCP Guidelines contain clearly defined principles with regard to these seven issues. For example, part L. of Annex 1 of the Regulation 536/2014, about the subject information leaflet and the informed consent process, is quite detailed. Thus, the principles to be followed in national legislation are quite clearly defined.

As an example of ongoing implementation of Regulation 536/2014 in the member states, the Finnish Draft for the Law on Clinical Drug Trials is analysed, showing how these seven sections are thought to be implemented in Finland. Some arguments and comments from experts and stakeholders were reviewed as available on the Ministry's website (http://stm.fi). Many of these seven issues left to member states to regulate in more detail were discussed in the first

public consultation round of the Draft Proposal. For example, part L. (on informed consent) and part M. (on the investigator) were widely debated and the consultation round clearly left some disagreement with regard to how these issues should be regulated in Finland. Also, there were interrelationships of the upcoming Law on Clinical Drug Trials and other EU regulations that were seen as problematic, especially with regard to personal data protection as governed by the European Union's GDPR (General Data Protection Regulation 679/2016). Each of the five Nordic countries are now drafting their own national legislation on these seven issues, K.-Q. of Annex 1. There is a lot of international legislation and guidance that must be considered but there is still room to make national decisions.

All in all, the main aim of Regulation 536/2014 is to harmonize the CTA process in all EU member states and affiliated countries. The issues left for each member state to regulate will inevitably lead to some variation between the countries in the CTA process. All five Nordic countries are now establishing by law their own national procedures with regard to these sections K.-Q. of Annex 1 of the Regulation. The application process will therefore to some extent differ between the countries, and in order to run a multinational Nordic trial, five different applications will have to be prepared. Similar application processes in the Nordic countries would foster collaboration between these countries. It would be easier to start joint trials in the Nordic countries, and this would foster the competitiveness of the Nordic countries in the field of clinical drug trials. Also, the study start-up process would be made easier for applicants, if all information about requirements and clearer instructions for the application process would be easily available on the websites of the national ethics committees. To start a clinical trial, there is a lot of legal regulation to embrace before the trial can be conducted. Making the ethical evaluation process similar and easier for applicants would foster clinical trials also in the Nordic countries.

# REFERENCES


Advertising Recruit Participants. The National Bioethics Committee, Iceland. www.vsn.is/en/content/advertising-recruit-participants. Read 30.12.2016.

Act on research Ethic Review of Health Research Programme. 8. October 2013. http://www.nvk.dk/english/. Read 12.1.2018.

Application for ethical vetting. Ethical vetting. www.epn.se/en. Read 29.12.2016.

Application form for approval of clinical trial protocol. 27. January 2015. The National Bioethics Committee, Iceland. www.vsn.is. Read 30.12.2016.

Clinical trial information leaflet and consent, Template 1. 27.6.2016. TUKIJA. www.tukija.fi. Read 30.12.2016.

Checklist accompanying an NBC application for a Clinical trial. January 2013. The National Bioethics Committee, Iceland. www.vsn.is. Read 30.12.2016.

Consent. 17. September 2015. The Norwegian National Research Ethics Committees. https://www.etikkom.no/en. Read 12.1.2018.

Consent to Participate in Clinical Trial. 7.12.2011. TUKIJA. www.tukija.fi. Read 30.12.2016.

Declaration of Helsinki. October 2013. The World Medical Association. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Read 27.3.2018.

Electronic Attachments. 29.6.2015. The Norwegian National Research Ethics Committees. https://helseforskning.etikkom.no/ikbViewer/page/frister/elektronisk/medbrukere/elektroniskvedlegg?p_dim=35380&_ikbLanguageCode=us. Read 30.12.2016.

Electronic communications and Language Requirements. 26.3.2012. The Norwegian National Research Ethics Committees. https://helseforskning.etikkom.no/reglerogrutiner/administrativerutiner?p_dim=35023&_ikbLanguageCode=us. Read 9.1.2018.

Ennakkoilmoituksen täyttöohje, TUKIJAn ohje. 17.12.2010. TUKIJA. www.tukija.fi. Read 30.12.2016.

Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics, No 9154. 5 May 2011. National videnskabsetiske komite. www.dnvk.de. Read 30.12.2016.

Guideline for good clinical Practise E6 R2. 1 December 2016. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf. Read 27.3.2018.

Guide to the application. 2012. Ethical vetting of research involving humans. www.epn.se/en. Read 29.12.2016.

Biobanks. The National Bioethics Committee, Iceland. www.vsn.is/en/content/biobanks. Read 30.12.2016.

Guidelines for Applicants. The National Bioethics Committee, Iceland. www.vsn.is/en/content/guidelines-applicants. Read 30.12.2016

Infoskriv barn under 12 år. 2015. Regional Committees for Research and Health Ethics. https://helseforskningen.ettikom.no. Read 29.12.2016.

Infoskriv generell biobank. 2015. Regional Committees for Research and Health Ethics. https://helseforskningen.ettikom.no. Read 29.12.2016.

Infoskriv voksne. 2015. Regional Committees for Research and Health Ethics. https://helseforskningen.ettikom.no. Read 29.12.2016.

Infoskriv ungdom 12-16 år. 2015. Regional Committees for Research and Health Ethics. https://helseforskningen.ettikom.no. Read 29.12.2016.

Information leaflet on genetic/pharmacogenetic research and sample consent form, Template 2. 27.6.2016. TUKIJA. www.tukija.fi. Read 30.12.2016.

Information for research patients. Ethical vetting. www.epn.se/en. Read 29.12.2016.

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningprojekt. Den videnskabsetiske komitesystem. www.dnvk.dk. Read 30.12.2016.

Informed consent. The National Bioethics Committee, Iceland. www.vsn.is/en/content/informed-consent. Read 30.12.2016.

Lausuntohakemus kliinisestä lääketutkimuksesta. 2010. TUKIJA. www.tukija.fi. Read 30.12.2016.

Lausuntopyyntö luonnoksesta hallituksen esitykseksi laiksi lääkelain sekä Lääkealan turvallisuus- ja kehittämiskeskuksesta annetun lain muuttamisesta. STM. https://stm.fi/lausuntopyynnot. Read 9.1.2018.

Lepola, P, Needham, A, Mendum, J, Sallabank, P, Neubauer D, de Wildt S. Informed consent for paediatric clinical trials in Europe. 25. Arch Dis Child. 2016;101:1017-1025.

Luonnos hallituksen esitykseksi eduskunnalle Luonnos hallituksen esitykseksi eduskunnalle laiksi kliinisestä lääketutkimuksesta ja eräiksi siihen liittyviksi laeiksi. 2017. STM. https://stm.fi/hanke?tunnus=STM077:00/2017. Read 9.1.2018.

Lääketieteellisiin tutkimuksiin liittyvät taloudelliset selvitykset eettisille toimikunnille ja tutkittaville, Tukijan ohje. 4.3.2008. TUKIJA. www.tukija.fi. Read 30.12.2016.

Medical Research Act 488/1999. Ministry of Social Affairs and Health, Finland.

Muistilista eettisen toimikunnan jäsenille ja tutkijoille. 7.2.2001, päivitetty 17.4.2009. TUKIJA. www.tukija.fi. Read 3012.2016.

National information: Finland. EUREC. http://www.eurecnet.org/information/finland.html Read 12.1.2018.

National information: Norway. EUREC. http://www.eurecnet.org/information/norway.html. Read 12.1.2018.

National information: Sweden. EUREC. http://www.eurecnet.org/information/sweden.html. Read 12.1.2018

Perspectives on medical research conducted on children. 2013. Final Report of the Working group Appointed by the National Advisory Board on Health Care Ethics. www.tukija.fi. Read 30.12.2016.

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. 16 April 2014.

Report on the Ethical Review Process for Clinical Trials in the Nordic Countries, The Challenges and Opportunities of the New Clinical Trials Regulation. January 2016. Nordic Trial Alliance Working Group on Ethics. https://nta.nordforsk.org/news/report-on-the-ethical-review-process-for-clinical-trials-in-the-nordic-countries. Read 29.12.2016

Request for Participation in a clinical trial. Regional Committees for Research and Health Ethics. https://helseforskningen.ettikom.no. Read 29.12.2016

Statute concerning the ethical vetting of research involving humans (2003/615). Ministry of Education and Cultural Affairs, Sweden. 9 October 2003. www.epn.se/en. Read 12.1.2018.

Suostumus lääketieteelliseen tutkimukseen, täsmennys ohjeeseen. 5.11.2010. TUKIJA. www.tukija.fi. Read 30.12.2016.

The Act concerning the Ethical Review of Research Involving Humans (2003/460). 5 June 2003. The Ministry of Education and Cultural Affairs, Sweden. www.epn.se/en. Read 12.1.2018.

The Bioethics Committee System. The National Bioethics Committee. http://www.vsn.is/en/content/bioethics-committee-system. Read 12.1.2018

The Health Research Act. 18. February 2016. The Norwegian National Research Ethics Committees. https://www.etikkom.no/en. Read 12.1.2018.

The Legal Framework. The National Bioethics Committee, Iceland. www.vsn.is/en/content/legal-framework. Read 9.1.2018.

The System of Health Research Ethics Committees. February 2017. NVK. http://www.nvk.dk/english/the-system-of-health-research-ethics-committees. Read 12.1.2018

Tutkittavien rekrytoimisen yleisiä periaatteita, TUKIJAn ohje. 16.2.2016. TUKIJA. www.tukija.fi. Read 30.12.2016.

Tutkittaville annettava tiedote kliinisestä lääketutkimuksesta ja suostumusmalli, asiakirjamalli 1 versio. 27.6.2016. TUKIJA. www.tukija.fi. Read 30.12.2016.

Valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan toimintaohje. 30.6.2017. TUKIJA. www.tukija.fi. Read 12.1.2018.

Vejledning om anmeldelse, inberetningsplit mv. (sundhetdsvidenskablige forskningprojekter). 6 January 2014. Den Nationale Videnskabetiske Komite. www.dnvk.de. Read 30.12.2016.

Vulnerable Groups including Children. The National Bioethics Committee, Iceland. www.vsn.is/en/content/vulnerable-groups-including-children. Read 30.12.2016.

Withdrawal of Consent. The National Bioethics Committee, Iceland. www.vsn.is/en/content/withdrawal-consent. Read 30.12.2016.