

NORDFORSK – NORDIC TRIAL ALLIANCE

Report on the Ethical Review Process for Clinical Trials in the Nordic Countries

The Challenges and Opportunities of the New
Clinical Trials Regulation

Nordic Trial Alliance Working Group on Ethics

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Preface

As part of the Nordic Trial Alliance's (NTA) initiative to increase Nordic collaboration and competitiveness in clinical trials, as outlined by NordForsk and the Nordic Council of Ministers, the NTA Working Group 1 on Ethics has drawn up a report on the ethical review of clinical trials in the Nordic countries.

The report first outlines the current ethical review process for clinical trials in each of the Nordic countries and then reviews future perspectives on and requirements set out in the new EU legislation on clinical drug trials. Finally, proposals are presented as to how to achieve Nordic harmonisation of the ethical review process.

The need for a reform of the current Nordic legislation and practice has emerged from the new EU Regulation No 536/2014 on clinical trials on medicinal products for human use. The new Regulation necessitates significant changes in legislation and practices of the Nordic countries with regard to their assessment processes for clinical trials.

The aim of this report is to establish common ground for a discussion on the need to update and harmonise the ethical review process for clinical drug trials in the Nordic countries, and also to suggest a roadmap towards this end. It is hoped that the report and the processes associated with its production and dissemination will help relevant stakeholders in the Nordic countries to find the best possible solutions for harmonising the ethical review practices for clinical trials in the Nordic countries, in pursuit of improved Nordic collaboration and increased international competitiveness in clinical drug trials.

Our NTA Working Group on Ethics consisted of representatives with different professional backgrounds and experience from all Nordic countries. We thank them all for their hard work and constructive participation in the process of formulating this report. We also warmly thank the project management staff, Lena Nybond and Päivi Rautava, at the Turku Clinical Research Centre (Turku CRC), the joint clinical research support unit of the Hospital District of Southwest Finland and the University of Turku. In the process of writing this report, drafts have

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Tiina Varis, Hospital District of Southwest Finland

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Mika Scheinin, MD, Dr. Med. Sci., Chair, Nordic Trial Alliance Working Group on Ethics

Juliana Tenovuo, Master of Laws, Author of the report, Hospital District of Southwest Finland

Abbreviations

EEA	European Economic Area
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
Fimea	Finnish Medicines Agency
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
NBC	National Bioethics Committee (Iceland)
NEM	National Committee for Medical and Health Research Ethics (Norway)
REC	Regional Ethics Committee
REK	Regional Committees for Medical and Health Research Ethics (Norway)
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TENK	National Advisory Board on Research Integrity (Finland)
THL	National Institute for Health and Welfare (Finland)
TUKIJA	National Committee on Medical Research Ethics (Finland)
Valvira	National Supervisory Authority for Welfare and Health (Finland)
WHO	World Health Organization
WMA	World Medical Association

1. Executive Summary

The aim of this report is to suggest practical solutions for harmonising the ethical review processes for clinical drug trials in the Nordic countries. EU Regulation 536/2014 on clinical trials necessitates changes in the applicable legislation in all of the Nordic countries, a significant part of which concerns the ethical review of clinical trial applications. The fact that the new EU Regulation has already entered into force means that the time for Nordic harmonisation is now.

Harmonising the Nordic procedures of ethical review presents an important as well as unique opportunity for the entire Nordic research area. Although the procedures will to some extent be harmonised between all EU/EEA countries, the Nordic countries will have an advantage if they can achieve complete harmonisation. The Nordic countries share very similar moral values, cultures and health care and legal systems, which means that they have an excellent starting point for taking harmonisation much further than the other EU/EEA countries.

Harmonisation of the procedures of ethical review in the Nordic countries will not only enable the Nordic countries to comprise a unified region in terms of setting up and conducting clinical trials, it will also generate direct and tangible benefits. Harmonising Nordic procedures will increase the competitiveness of the region. Currently, one of the main concerns in the Nordic countries is that their populations are too small to attract multinational clinical trials, as it is considerably more challenging to recruit study subjects than in countries with larger populations. Combining the five Nordic countries into a unified clinical research area for conducting clinical trials would be an ideal solution to this problem, since together, the Nordic countries have approximately 26 million inhabitants. Clinical trials account for a large part of the economic volume of the pharmaceutical industry, both in terms of manpower and investment, which means that an increase in the number and volume of clinical drug trials would have tangible effects on the economies of the Nordic countries. In addition, such an

increase would have positive effects on employment and, of course, on patient care as well. Nevertheless, while it is important to improve the competitiveness of the Nordic countries, the subjects' well-being is the primary concern of all clinical trials. This must be kept in mind when designing different options and suggestions for the future.

The new EU Regulation will require that all Nordic countries must revise their legislation and practices concerning the ethical review of clinical trials, which entails a chance of realising harmonisation that should not be missed. The framework for harmonisation has already been established by the Regulation, which means that the Nordic countries do not need to take radical measures to align their national legislation on the matter more closely. The Nordic countries have been interested in achieving such harmonisation for a long time, and the simultaneous revision of the national legislation resulting from the new Regulation provides a much needed opportunity to realise these plans.

This report presents a variety of potential solutions for harmonisation, formulated in collaboration with numerous Nordic experts in the field of ethical review. To better understand the situation, the report also describes current ethical review procedures in place in the Nordic countries prior to the changes mandated by the Regulation. The requirements and framework of the Regulation with regard to the ethical review process are also presented. Thus, the aim of this report is to present all of the information needed, and to provide suggestions, for creating a new harmonised system for ethical review in the Nordic countries.

2. Background

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). Regulation 536/2014 was published in the official journal of the EU on 27 May 2014 and is legally binding in all Member States, with direct applicability in the Nordic EEA countries, Iceland and Norway.¹ The new requirements set out in the Regulation have to be implemented when the Regulation is applied six months after publication of the new EU trials database and the launch of the associated electronic information exchange platform. The current estimate of the EMA is that the Regulation is to be implemented by the end of 2018. A 3-year transition period is foreseen in Article 98 of the Regulation. During the first year, clinical trial applications may be made either under the new Regulation using the EU portal and database, or under Directive 2001/20/EC. For the next two years, clinical trials authorised under the Directive will continue to be governed by that Directive. Any trials authorised under the Directive and still ongoing 3 years after the Regulation comes into application will from then on be governed by the Regulation.

While the new Regulation and the requirements it stipulates for the legislation of the Member States (and Associated States) will pose challenges for the States involved, it can also be seen as a great opportunity to encourage harmonisation of the legislation and practices of the Nordic countries when it comes to clinical trials and associated ethical review and authorisation procedures. Over the past decades, the Nordic countries as individual countries and cooperatively have already introduced several initiatives to improve the competitiveness of the region and cooperation between the countries. In certain areas of clinical drug trials, active

¹ For the sake of clarity, the term *Member States* in this report refers to both EU and EEA countries.

collaboration has already been established. For example, there are several Nordic networks of clinical researchers organised as working groups or associations in various fields of clinical medicine, most notably within several sub-specialities of oncology. The national funding agencies (medical research councils and their counterparts) collaborate widely, and the Council of Ministers and NordForsk are well-established as platforms for collaboration at the government level.² Additionally, the organisation Nordic Health Research and Innovation Networks (NRI-Networks or, in short, NRI) has evolved as an independent, non-profit entity working to promote health research and innovation in the Nordic region. The NRI is based on a partnership model where the partners are university hospitals, universities and other research organisations; pharmaceutical and medical technology companies and their organisations; and governmental bodies and patient organisations.³ The Nordic countries were also among the first to issue international guidance on Good Clinical Trial Practice⁴, now known as GCP or Good Clinical Practice, as promoted by e.g. the OECD⁵ and WHO.⁶

There are many common features in the current principles and practices of ethical review of clinical trials utilised in all five Nordic countries due to similarities in the health care and legal systems, shared moral and cultural values and adherence to the same international guidance documents (such as the Nuremberg Code and the WMA Declaration of Helsinki, in addition to relevant OECD and EU documents). However, practices are not uniform and significant differences exist with regard to procedures and required documents (see e.g. Appendix 1 and 2).

The current level of collaboration has not been sufficient to harmonise the ethical review practices in the Nordic countries effectively and fully deliver the benefits that harmonisation can offer. The legislation and practices have evolved independently of one another in all five

² <http://www.nordforsk.org/en/about>

³ <http://nordicnetworks.org/>

⁴ Nordic Council of Medicines 1989.

⁵ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice

⁶ WHO 1995.

countries. Therefore, the new Clinical Trials Regulation with its requirements for unified practices in the Member States (and Associated States) may provide the much-needed impetus to finally take Nordic collaboration and harmonisation to a new level. The aim of harmonising practices in the area of clinical research in the Nordic countries is also the main goal of the Nordic Trial Alliance (NTA) network, the initiator of the report at hand. The number of clinical drug trials conducted in the Nordic countries has been decreasing during the past decade (with the exception of Denmark), but there is hope that increased Nordic collaboration and competitiveness will reverse this trend.

In order to achieve improved collaboration and harmonisation of the ethical review processes for clinical trials, the Nordic countries now need a shared vision of the desired state of affairs. Common principles need to be agreed upon and then each country should outline the procedures for the approval process for clinical trials in cases where there is no binding definition in the new EU Regulation, including the ethical review process. The goal should be to agree on common Nordic procedures for the ethical review of clinical trials and a common set of documents required from the applicants. Although the EU Regulation establishes many new requirements for Member States, the harmonisation process will not be complete without harmonisation of the various details left up to the Member States to decide. This report provides suggestions for the elements that need to be specifically harmonised at the Nordic level, as well as some suggestions regarding the tools for implementing these changes.

It should be noted that in an ideal situation, the Nordic countries would harmonise their systems for assessment of applications concerning all health-related research projects on human subjects, including both intervention trials and registry research, and not just the processes regarding clinical trials of pharmaceuticals. However, since the EU Regulation only concerns clinical trials of pharmaceuticals and imposes rather strict timelines for their implementation, the most realistic objective is to harmonise the assessment of clinical trials applications and to hope to achieve wider harmonisation in the not-too-distant future.

3. Clinical Trials and the Function of Ethics Committees

3.1. The Definition of Clinical Trials and Other Medical Research

When discussing biomedical research involving human subjects and clinical trials, a distinction must be made between clinical trials of pharmaceuticals, other types of clinical research, low-intervention clinical trials and non-interventional studies. Since the impetus for changing the current legislation on and practices of ethical review in the Nordic countries and other EU/EEA countries comes from EU Regulation 536/2014, the appropriate definitions for these different kinds of studies should comply with the definitions in the Regulation.

The EU defines clinical trials (of medicinal products) in Article 2 of the Regulation 536/2014 as clinical studies which fulfil any of the following conditions: *“the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.”* The definition of clinical trials refers to the broader category of clinical studies. Clinical studies (on medicinal products) are defined in the Regulation as follows: *“clinical study means any investigation in relation to humans intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; to identify any adverse reactions to one or more medicinal products; or to study the absorption, distribution, metabolism and excretion of one or more medicinal products, with the objective*

of ascertaining the safety and/or efficacy of those medicinal products.” A clinical study other than a clinical trial is called a non-interventional study.⁷

A low-intervention clinical trial is defined as a clinical trial which fulfils all of the following conditions: the investigational medicinal products, excluding placebos, are authorised; according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation, or the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.⁸ Regulation 536/2014 applies to all clinical trials of medicinal products conducted in the Union, apart from non-interventional studies.⁹

3.2. Functions of Ethics Committees and the Division into Regional and National Committees

The definition of ethics committees and the tasks appointed to them depend on national legislation. However, ethics committees also have certain general characteristics that can be internationally recognised. For example, the Declaration of Helsinki sets out basic requirements for ethics committees whose tasks include assessment and review of all types of clinical research involving human subjects; the scope of the Declaration is defined as “*a statement of ethical principles for medical research involving human subjects, including*

⁷ EU Regulation No 536/2014, Article 2.

⁸ EU Regulation No 536/2014, Article 2.

⁹ EU Regulation No 536/2014, Article 1.

research on identifiable human material and data.”¹⁰ Article 23, in its current form, reads as follows:

“The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study’s findings and conclusions.”

In Article 2 of Regulation 536/2014, an ethics committee is defined as *“an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients’ organisations.”* Thus, significant features of the functions and operating principles of ethics committees are left for the Member States to define. The only main characteristics mandated by the EU are that the committee must be independent and established by law, and that it shall give opinions regarding the ethical aspects of clinical trials, taking into account the views of laypersons. The definitions of ethics committees in the Nordic countries are presented in Chapter 4.

¹⁰ WMA Declaration of Helsinki.

The ethics committees that assess clinical trials can function on a regional or national level. The new Regulation states that it should be left to the Member State to determine the appropriate body or bodies to be involved in the assessment of applications to conduct a clinical trial and to organise the involvement of ethics committees within the timelines for the authorisation of clinical trials. Thus the EU does not stipulate whether the ethics committees should function at a regional or national level or even whether an actual ethics committee should be the body assessing the application. In all of the Nordic countries, however, the bodies assessing applications for clinical trials have traditionally been either regional or national ethics committees, and it is very likely that this task will be assigned to some kind of ethics committee after the implementation of the new Regulation as well. Ethics committees, more or less in their current mode of operation, will in any case be needed for the assessment of other types of medical research involving human subjects.

As a departure from what has been the norm and what is assumed in the Regulation, the current process should explore whether the ethical review of clinical trials could be conducted on a supranational level in the Nordic countries. Although the Regulation aims at harmonising ethical review at the EU level, it does not completely support the idea of supranational ethical review of clinical trials. The preamble to the Regulation states that “*The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation should not include aspects of an intrinsically national nature, such as informed consent.*” Thus, while the Regulation promotes cooperation in the authorisation process, it does not validate moving the entire assessment process to an international level. While the Regulation does not further define the scope of the aspects that should be reviewed at the national level, it does not appear to promote the idea of an international ethics committee.

4. The Current State of Ethical Review in the Nordic Countries

4.1. The Current Legislation Concerning Clinical Trials and their Ethical Review in the Nordic Countries

In all five Nordic countries, the legal framework for ethics committees includes both acts of legislation and statutes/regulations. The basic operating principles and functions of ethics committees in all Nordic countries are very similar, and they conform to the definition in the new EU Regulation. The ethics committees are mandated by law, they must be independent, and their main task is to review the ethical aspects of different kinds of medical research involving human subjects. Another common feature of the ethics committees is that the research projects must be reviewed by a group involving both experts and laypersons. The countries vary as to whether these tasks are assigned to regional ethics committees alone or divided among regional and national committees.

4.1.1 Finland

The most essential act regulating medical research in Finland is the *Medical Research Act* (488/1999), as amended in 2004, 2010, 2014 and 2015. There is also a *Medical Research Decree* (986/1999), amended by Decree 313/2004, and the *Government Decree on the National Committee on Medical Research Ethics* (820/2010). In addition, some tasks of the ethics committees are specified in the *Biobank Act* (688/2012) and the *Act on the Medical Use of Human Organs, Tissues and cells* (101/2001). Clinical trials are also regulated by the *Pharmaceuticals Act* (395/1987; English translation not available), but the provisions of this Act complement and refer to the Medical Research Act when it comes to ethical review of clinical trials.

4.1.2 Sweden

Medical research carried out in Sweden is regulated by the *Act concerning the Ethical Review of Research Involving Humans* (2003:460), the *Statute concerning the Ethical Review of Research Involving Humans* (2003:615), the *Statute with instructions for Regional Ethical Review Boards* (2007:1069), and the *Statute for the Central Ethical Review Board* (2007:1068).

4.1.3 Norway

Medical and other health care research in Norway is regulated by the *Act on medical and health research* (Health Research Act, 2009). There is also a separate Act regulating research ethics, the *Act on ethics and integrity in research* (2006).

4.1.4 Denmark

In Denmark, the ethical review of medical research is regulated by the *Act on Research Ethics Review of Health Research Projects* (593/2011) and *Departmental Executive order on information and consent for participation and inclusion of trial subjects in biomedical research projects* (1149/2013). Ethical committees are also regulated by the *Act on the Ethical Council* (440/2004, not available in English).

4.1.5 Iceland

In Iceland, the legal basis of medical research and the functions of ethics committees have been established in the *Act on Scientific Research in the Health Sector* (44/2014). Clinical trials of medicinal products are also subject to the provisions of the *Medicinal Products Act*, (93/1994) and the regulations issued on the basis of that Act. In addition, clinical trials of medical equipment are subject to the provisions of the *Act on Medical Devices*, (16/2001) and the regulations issued on the basis of that Act. The most relevant regulation is the *Regulation on Clinical Trials of Medicinal Products in Humans* (443/2004, as amended by Regulations Nos. 907/2004 and 1099/2010). There are also some relevant provisions in the *Health*

Records Act (55/2009), the Act on Patient Insurance (111/2000) and the Act on the Protection of Privacy as regards the Processing of Personal Data (the Data Protection Act, 77/2000).

4.2. The Current Practices of the Ethics Committees in the Nordic Countries

All five Nordic countries have both regional and central ethics committees. However, the practices and number of committees vary among the countries. The functions of the ethics committees in the Nordic countries are described in the following paragraphs.

4.2.1 Finland

In Finland, the National Committee on Medical Research Ethics is referred to by its acronym, TUKIJA.¹¹ In addition to the national committee, there are nine regional research ethics committees established by the five University Hospital Districts.¹²

TUKIJA operates within the National Supervisory Authority for Welfare and Health (Valvira)¹³ and its role is defined by Government Decree 820/2010. According to the decree, TUKIJA has an expert role in matters related to medical research ethics, and one of its tasks is to advise regional ethics committees in matters of ethical principles related to medical research. TUKIJA also provides education on the subject, participates in international collaboration on research ethics issues, and provides information via publications, seminars, a website, etc. on topical issues in the international arena for ethical discussion.¹⁴

The distribution of tasks between TUKIJA and the regional ethics committees is defined by law. TUKIJA is primarily responsible for the assessment of all clinical trials of medicinal

¹¹ <http://www.tukija.fi/en>

¹² <http://www.eurecnet.org/information/finland.html>

¹³ <http://www.valvira.fi/en/>

¹⁴ Statute on the National Medical Research Ethics Committee 2010, Section 2.

products, but it may assign a specific clinical trial to a regional committee for assessment. The regional committee's statement then applies for the entire country. In Section 17 of the Medical Research Act it is stated: "*Prior evaluation of research projects and delivering opinions on them is the responsibility of the ethics committee of the region where the person in charge of the research is based or of the region where the research is to be principally conducted. The National Committee on Medical Research Ethics shall deliver an opinion on clinical drug trials, unless it has delegated the task to a regional ethics committee.*"¹⁵ Thus, the ethical evaluation of clinical drug trials can be conducted by the national ethics committee, even though it is often delegated to an appropriate regional committee. For example, in 2011 TUKIJA received 172 advance notifications of clinical trials, of which TUKIJA reviewed 44 and 128 were delegated to regional committees. In 2014, 35 of the total 157 applications were assessed by TUKIJA and 122 were assessed by regional committees.

According to the Medical Research Act, if a regional ethics committee delivers a negative opinion on a study, the commissioning party (i.e. the applicant, or sponsor of the study; in investigator-initiated trials, the investigator and/or his or her institution has this role) may bring the matter before the same committee for reconsideration. At this stage, at the request of the applicant, the regional ethics committee must seek the opinion of the National Committee on Medical Research Ethics before delivering a new opinion on the matter.¹⁶

The nine regional research ethics committees of Finland are located in Helsinki (four committees), Tampere, Oulu, Kuopio, Jyväskylä and Turku (one each). The largest of the Finnish Hospital Districts, the Hospital District of Helsinki and Uusimaa, has appointed four ethics committees; one of them has a coordinating role and the others deal primarily with certain medical specialities (internal medicine and related fields; the surgical specialities; paediatrics, obstetrics and gynaecology; and psychiatry).¹⁷ The regional committees must

¹⁵ Medical Research Act, Section 17, paragraph 1.

¹⁶ Medical Research Act, Section 3, paragraph 4.

¹⁷ http://www.tukija.fi/en/general_information/ethics_committees

include qualified persons representing expertise in research ethics, medicine, health sciences or nursing science and law. At least two members must be laypersons who are neither health care professionals nor research personnel.¹⁸ Each committee must have a chairperson, at least six other members and an appropriate number of deputy members.

Some special provisions have been laid down for the ethical review of clinical trials of medicinal products in addition to those established for other types of clinical research. If the clinical trial under review includes minors as research subjects, the ethics committee must either include or consult a specialist in paediatrics. If the clinical trial applied for is to be conducted on adults who are incapable of giving valid informed consent, the committee must either include a member with special expertise on the illness and the patient group concerned or consult one by requesting a written opinion.¹⁹

The ethics committee assessing an application for a clinical trial must take into account the following aspects regarding the trial:

- appropriateness of the trial and its planning;
- appropriateness of the assessment of its benefits and risks and justifiability of any conclusions regarding them;
- the research plan;
- suitability of the researcher and staff;
- the Investigator's Brochure containing clinical and other information on the medicinal product or products used in the trial;
- the quality of the facilities and equipment to be used in the trial;
- sufficiency and scope of the written information given to obtain informed consent and the procedure for obtaining consent;

¹⁸ Government Proposal 229/1998 vp.

¹⁹ Medical Research Act, Section 18.

- if applicable, specific justification for the trial to be carried out on persons not able to give valid independent consent;
- the grounds on which potential damages caused by the trial will be compensated and insurance policies and other arrangements for covering a compensation payable due to damages or death;
- the amount of the fee or remuneration to be paid to researchers and the research subjects or the criteria for determining these and procedures potentially related to the matter, as well as the main content of the contract between the commissioning party and the research site; and
- detailed procedures relating to the selection of the research subjects.

The current timelines of the ethical evaluation of a clinical trial are 60 or 90 days from when a valid request for an opinion has been received; the longer timeline applies to advanced therapy investigational medicinal products, for which the time limit can be further extended by up to 90 days if extensive investigations are deemed necessary. The ethics committee may ask for additional information from the applicant once. There is no time limit for giving an opinion on xenogeneic cell therapy projects.²⁰

Finland also has other research ethics committees, not mandated by law, serving fields of scientific research other than medicine that involve human subjects. They are maintained by universities and some research institutions. These committees are not governed by any statutes of formal governance, but have their own informal national network, which is coordinated by the National Advisory Board on Research Integrity (TENK) appointed by the Ministry of Education and Culture.²¹

²⁰ Medical Research Act, Section 10 d.

²¹ <http://www.eurecnet.org/information/finland.html>

4.2.2 Sweden

There are six regional ethics committees reviewing both medical and non-medical research on humans in Sweden. The committees are appointed by and responsible to the Ministry of Education and Research, and operate in the six major universities in Gothenburg, Linköping, Lund, Stockholm, Umeå and Uppsala. Despite their close association with the universities, the committees have their own administration and finances. Thus the internal work of the ethics committees is independent from the universities, even though they may receive administrative help from the university.²²

In addition to the regional ethics committees, there is a Central Ethical Review Board, located in Stockholm. The Central Ethical Review Board is responsible for making decisions on controversial issues submitted to it by the regional ethics committees and for serving as an appeal body for applicants who want to contest or complain about a decision made by a regional committee.²³ In addition to reviewing appeals and referrals, the central board has a supervisory function.²⁴

The six regional boards must have a minimum of two departments. Each department reviews cases within selected fields of research. In regions that comprise larger universities, there may be up to four different departments for review of medical research. Additionally, there is always one separate department for assessing non-medical research on humans.²⁵ A department consists of a chairman and fifteen other members, of which ten must have scientific qualifications and five are laypersons. All members must have deputies. The chairperson and his/her deputy must be a judge or former judge.²⁶

²² <http://www.eurecnet.org/information/sweden.html>

²³ Act Concerning the Ethical Review of Research Involving Humans (2003:460), Section 31.

²⁴ Nordforsk 2014, p. 35.

²⁵ <http://www.eurecnet.org/information/sweden.html>

²⁶ Ethical Review Act 2003, Section 25.

The Central Ethical Review Board consists of seven members: a chairperson and six other members, of which four are researchers and two are laypersons. Deputies may be appointed for the members. The chairperson must be a judge or a former judge.²⁷ The decisions of the central board in matters concerning ethical review may not be appealed. Directives or prohibitions issued by the central board in order to ensure compliance with the Ethical Review Act or statutes may be appealed to the general administrative court. Other decisions of the central board concerning matters of supervision may not be appealed.²⁸

According to the Ethical Review Act, the board assessing an application must take into account the same fundamental principles concerning medical research on humans outlined in the Declaration of Helsinki. The research in question may only be approved if it is conducted with respect for human dignity. The Ethical Review Board must take into account human rights and fundamental liberties, while giving consideration to the fact that the research may lead to growth in knowledge. The needs of society and science cannot take precedence over the welfare of the research subjects. The risks of the research to the subject must be counterbalanced by its scientific value, and the research cannot be approved if the anticipated result can be achieved by other means that entail fewer risks to the health, safety and personal integrity of the research subject. Personal data must be handled in a way that conforms with the Ethical Review Act. The researcher must have the necessary scientific competence to conduct the research.²⁹

4.2.3 Norway

In Norway there are seven Regional Committees for Medical and Health Research Ethics (REK) in four health care regions of the National Health Service: the South-East, Western, Central and Northern regions. The South East region has four committees. The committees

²⁷ Ethical Review Act 2003, Section 32.

²⁸ Ethical Review Act 2003, Section 37.

²⁹ Ethical Review Act 2003, Sections 7-11.

are responsible for reviewing all types of medical research involving human subjects, not just clinical trials on medicinal products.

Each REK has nine members.³⁰ The members represent expertise in medicine, psychology, nursing science, law and ethics. Each committee must also have two layperson members, of which one should be recruited from a patient organisation. The term is four years with possibility for one extension.³¹ The regional committees are responsible for the ethical review and approval of research projects involving experiments on human subjects. Appeals concerning decisions of the regional committees can be submitted to the National Committee for Medical and Health Research Ethics (NEM).³²

NEM has 12 members with different professional backgrounds. The members are experts from the fields of ethics, law, psychology and genetics. The committee also has lay representatives, and is traditionally chaired by a physician. The members are appointed by the Ministry of Education and Research for a four-year term. The function of NEM is to be an advisory and appeal body for the regional committees. NEM gives its opinion on issues regarding principles, while the regional committees evaluate actual medical research projects. NEM has also published reports regarding biomedical research and drawn up guidelines for the inclusion of women in medical research. The decisions of NEM are final and cannot be appealed.³³

The Norwegian Biotechnology Advisory Board is an independent body appointed by the Government for a four-year term. The main task of the board is to evaluate the social and ethical consequences of applications of modern biotechnology and to discuss usage which promotes sustainable development. It consists of 15 members, all of whom have a background

³⁰ Hølen Jacob, 2014.

³¹ <http://www.eurecnet.org/information/norway.html>

³² Act on ethics and integrity in research, Section 4.

³³ <https://www.etikkom.no/en/In-English/Committee-for-Medical-and-Health-Research/>

or education which makes them competent to discuss questions regarding modern biotechnology.³⁴

The Regional Committees for Medical and Health Research Ethics (RECs) evaluate the ethical aspects of medical research proposals, and must take into account certain requirements concerning the research. Medical and health research must be organised and carried out in a responsible manner and the research subjects' human rights and dignity must be respected. The subjects' welfare and integrity have priority over scientific and societal interests, and the research must take into account ethical, medical, health, scientific and privacy issues. The research applied for must be described in a research protocol including information on the sources of funding for the project, and the research must be organised under the direction of a person or a body responsible for the research and managed by a project manager. The personal health data and other personal data used in the research project must be protected. Commercial exploitation of research participants, human biological material and personal health data in general is prohibited.³⁵ Research may only be conducted on people if there are no alternative methods that are approximately equally effective. The risks of the research for the participants must be evaluated beforehand, and they must be proportional to the expected advantages for the research participants or for other people. Research may only be combined with treatment if the research is assumed to have health-promoting value for the research participant.³⁶ These provisions of the Health Research Act are equivalent to those found in the Declaration of Helsinki.

4.2.4 Denmark

The health research ethics committee system of Denmark consists of a national committee and 12 regional scientific ethical committees.³⁷ The regional committees are located in five

³⁴ <http://www.bioteknologiradet.no/english/>

³⁵ Act on Medical and Health Research 2008, Sections 5-8.

³⁶ Act on Medical and Health Research 2008, Section 22.

³⁷ <http://www.cvk.sum.dk/CVK/Home/English.aspx>

regions: Copenhagen (6 committees), Zealand (1 committee), Southern Denmark (2 committees), Central Denmark (2 committees) and Northern Denmark (1 committee).³⁸ The regional committees consist of 7, 9 or 11 members of which 3 (or 4 or 5, respectively) are active within health research.³⁹ Most of the regional committees have 11 members.⁴⁰ The members are appointed for four years and may be reappointed twice.⁴¹ Appeals on the decisions of the regional committees can be submitted to the National Committee on Health Research Ethics.⁴²

The National Committee on Health Research Ethics consists of 13 members appointed by the Minister for Health.⁴³ The national committee's responsibility is to work together with the regional committees to ensure that health research projects are carried out in a responsible manner and that the rights, safety and well-being of the participants in such projects are protected while paving the way for development. The national committee has several specified functions. It coordinates the activities of the regional committees and serves as a board of appeal. It also lays down guidelines and gives opinions on issues of a general nature, but not on issues directly related to the approval of an actual research project, except regarding projects of an especially difficult nature.⁴⁴ The national committee monitors the development of research within the health sector, promotes the understanding of ethical issues in relation to health services and biomedical research, and provides consultative statements on biomedical research projects to be implemented in developing countries.⁴⁵

³⁸ Lundgaard Kjøller 2014.

³⁹ Act on Biomedical Research, Section 36.

⁴⁰ Lundgaard Kjøller 2014.

⁴¹ Act on Biomedical Research, Section 36.

⁴² Nordforsk 2014.

⁴³ <http://www.cvk.sum.dk/CVK/Home/English.aspx>

⁴⁴ This includes, for example, research projects on biological materials taken when forensic autopsy has been performed, projects on advanced therapy products, projects involving full genome mapping when the biological material comes from a biobank and exemption from informed consent requirements is sought, and projects on psychosurgery.

⁴⁵ Nordforsk 2014.

The research ethics committees must take the criteria laid down in the Act on Biomedical Research into account when assessing an application. The conditions for granting permission are listed as follows:

- the potential risks of the trial are not unjustifiable of themselves or in relation to the foreseeable benefits of the trial;
- the expected benefits may justify the project;
- the project should lead to new knowledge or investigate existing knowledge;
- there is sufficient reason to undertake the project; and
- expectations as to the project's conclusions are justified.

The competent committee must balance the foreseeable risks and drawbacks in relation to the benefit for the individual trial subject and other patients. The committee must make sure that the foreseeable risks are minimised considering the trial subject's disease and level of development. This assessment must take into account whether the trial subject is able to give valid informed consent or whether informed consent must be obtained in the form of proxy consent.⁴⁶

The Danish Council of Ethics is an independent body which advises the Parliament, the ministries and other public authorities on ethical issues concerning aspects of biotechnology related to human life, the environment and food. The council also works with ethical issues related to the health care sector. The council consists of 17 members appointed by the Minister for Health and other specific ministers, and it includes both experts and laypersons.⁴⁷ The main function of the Ethical Council is to advise and promote debate and awareness.⁴⁸

⁴⁶ Act on Biomedical Research, Section 18.

⁴⁷http://www.etiskraad.dk/da-DK/Om-Raadet/Historie.aspx?sc_lang=en. The other Ministers appointing members for the Council are the Minister of the Environment and Food, the Minister of Higher Education and Science, and the Minister of Business and Growth. All of these Ministers appoint one member.

⁴⁸ Nordforsk 2014.

4.2.5 Iceland

The ethics committee system in Iceland consists of the National Bioethics Committee and two institutional ethics committees. The Minister of Health appoints a National Bioethics Committee (NBC) comprising seven members for a term of four years to consider scientific research projects in the health sector. The committee must include individuals with expertise in health sciences, ethics, law, and data protection.

The NBC has the role of evaluating scientific research projects in the health sector with the objective of ensuring that they are consistent with scientific and ethical principles. If there is doubt as to whether a project is to be deemed scientific research in the health sector, the NBC will make a ruling. The NBC evaluates collaborative projects (collaboration in this case is not specified in the Act on Scientific Research in the Health Sector, No. 44/2014), multinational projects, clinical trials of medicinal products and other prospective scientific research projects in the health sector which are not reviewed by the Health Research Ethics Committees at the major hospitals.

The Health Research Ethics Committee of Landspítali University Hospital grants permission for research projects in the biomedical field to be carried out either at the hospital or in collaboration between Landspítali University Hospital and universities. The Health Research Ethics Committee of Akureyri Hospital grants permission for biomedical research projects to be carried out at the hospital, the University of Akureyri or in collaboration between Akureyri Hospital and universities.⁴⁹ The decisions of the institutional ethics committees may be appealed to the National Bioethics Committee.⁵⁰

⁴⁹ Act on Scientific Research in the Health Sector, no. 44/2014, Article 11.

⁵⁰ Act on Scientific Research in the Health Sector, no. 44/2014, Article 14.

The evaluation process involves the review of possible risks and benefits of the project in question, in accordance with the WMA Declaration of Helsinki and other international ethical guidelines on scientific research in the biomedical field. The legislation requires particular care in the evaluation of studies which require the participation of children or members of vulnerable social groups.

5. EU Regulation No 536/2014 and its effects

5.1. The State of EU Legislation and Other International Guidelines on Ethical Review for Clinical Trials Prior to the New Regulation

EU Regulation No 536/2014 repeals Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Directive 2001/20/EC has been widely criticised by stakeholders for increasing the regulatory burden and costs of conducting clinical trials in the EU; it has been claimed that this has contributed to the significant reduction in the number of trials conducted since the Directive was adopted.⁵¹ This is, of course, one of the main objectives behind the new Regulation – to re-establish the EU’s competitiveness in clinical trials and in pharmaceutical development. However, Directive 2001/20/EC is not the only legal instrument that has been applied in the EU with regard to clinical trials.

⁵¹ Allen & Overy 2014.

The fundamental framework around the Clinical Trials Regulation consists of the Treaty on the Functioning of the European Union (TFEU) and the European Convention on Human Rights.⁵² The TFEU contains provisions concerning the scope of the Regulation's Articles 114 and 168.⁵³ Article 3 of the EU Charter of Fundamental Rights sets out requirements for the rights to the integrity of the person, in particular in the fields of medicine and biology. Article 8 contains provisions for the protection of personal data, and the freedom of science is ensured in Article 13.⁵⁴

One of the most fundamental international sets of ethical principles regarding medical research is the Declaration of Helsinki, which continues to provide guidelines for biomedical research involving human subjects, together with the new Regulation. The Declaration of Helsinki has been developed by the World Medical Association (WMA) and consists of ethical principles addressed primarily to physicians.⁵⁵ The Declaration establishes several general principles, such as the duty to act in the patient's best interest, the duty to protect vulnerable groups and individuals, and that the goal of generating new knowledge in medical research can never take precedence over the rights and interests of individual research subjects.⁵⁶ The Declaration also has an article on research ethics committees, which was approved as an amendment in 1975. The provisions on the ethical review of research protocols are set out currently in Article 23 of the Declaration, which requires transparency and independence in the ethical review, taking into consideration the relevant national legislation and applicable international norms and standards.

The position of the Declaration of Helsinki, as pertaining to clinical trials on medicinal products, has in some regards been challenged during recent years. Most importantly, the Food and Drug Administration (FDA) of the United States and the ICH GCP no longer refer to the latest

⁵² Salokannel 2015.

⁵³ Treaty on the Functioning of the European Union (2012/C 326/01).

⁵⁴ Charter of Fundamental Rights of the European Union (2000/C 364/01).

⁵⁵ Declaration of Helsinki, Articles 1-3.

⁵⁶ Declaration of Helsinki, Article 8.

version of the Declaration as applicable guidance on ethical principles regarding clinical trials. Instead, their guidance refers to the 1989 version of the Declaration.⁵⁷ The Amendments of the Declaration approved in 1996, 2000, 2002, 2004, 2008 and 2013 have not been endorsed by the FDA on the grounds that the FDA cannot reach an agreement in respect to these amendments of the Declaration; it holds that the WMA has here overstepped its mandate. The additions not acceptable to the FDA are the amendments from 2004, stating that “*The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists*” (Paragraph 29), and that “*At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study*” (Paragraph 30).⁵⁸ The FDA views Paragraph 29 as an attack on the use of placebos, and agrees with the pharmaceutical industry’s fear that the obligation to avoid placebo controls in all instances where some kind of therapy exists will make it harder to prove the efficacy of a new drug and will increase the costs of development.⁵⁹ In April 2006, the FDA published a regulatory change ending the obligation of clinical trials conducted outside of the US to comply with the Declaration of Helsinki.⁶⁰

The European Medicines Agency (EMA) has also taken a stand on the amendments to the Declaration of Helsinki. In a statement in 2001, the EMA says that although a strict interpretation of Section 29 of the Declaration would appear to rule out clinical trials that use a placebo control arm whenever authorised therapeutic methods already exist, the judicious use of placebo remains essential for some trials in order to demonstrate the value of new medicinal products. The EMA points out that there are a number of conditions that govern and

⁵⁷ <http://www.fda.gov/RegulatoryInformation/Guidances/ucm124932.htm>

⁵⁸ Wolinsky 2006.

⁵⁹ Wolinsky 2006.

⁶⁰ Blackmer 2014.

restrict the use of placebos to avoid their unethical use, and that provided the conditions ensuring the nature of placebo-controlled trials are clearly understood and implemented, the availability of placebo-controlled trials is necessary to satisfy public health needs.⁶¹

Many of the fundamental ethical principles of medical research were already set out in the Nuremberg Code in 1947, but this Code does not include specific requirements for an ethical review process for research projects.⁶²

The International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an international organisation governed by several international contributors,⁶³ has also set out Guidelines for Good Clinical Practice (GCP) which have been recognised internationally as standards for clinical trials. The ICH GCP requires clinical trials to be conducted in accordance with the ethical principles originating in the Declaration of Helsinki.⁶⁴ The ICH GCP defines an independent ethics committee as *“an independent body (a review board or a committee, institutional, regional, national or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s) facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.”*⁶⁵ The ICH GCP sets out a wide set

⁶¹ EMEA 2001.

⁶² <http://www.hhs.gov/ohrp/archive/nurcode.html>

⁶³ The Steering Committee of the ICH is the governing body that oversees the harmonisation activities of the ICH, and it has representatives of the EU, WHO, European Federation of Pharmaceutical Industries and Associations (EFPIA), the Ministry of Health, Labour and Welfare of Japan, Japan Pharmaceutical Manufacturers Association, FDA, Pharmaceutical Research and Manufacturers of America, International Federation of Pharmaceutical Manufacturers and Associations (non-voting member), Swissmedic, and Health Canada. <http://www.ich.org/about/organisation-of-ich/steering.html>.

⁶⁴ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, Section 2.1.

⁶⁵ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, p. 4-5.

of principles for conducting clinical trials of medicinal products, and states that the rights, safety and well-being of the trial subjects are to be the most important considerations.⁶⁶

The Council of Europe's Convention on Human Rights and Biomedicine (also known as the Oviedo Convention), states that (biomedical) research on a person may only be undertaken if *"the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of the research, and multidisciplinary review of its ethical acceptability."*⁶⁷

The World Health Organization (WHO) has also developed Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products, published in 1995. The WHO GCP includes principles addressed to investigators, ethics review committees, pharmaceutical manufacturers and other sponsors, and drug regulatory authorities. Many elements of the WHO GCP are similar to the ICH GCP. The main difference between the two sets of guidelines is that while the ICH GCP seeks to provide a unified standard for the EU, Japan and the US in order to reach harmonisation and facilitate the mutual acceptance of clinical trial data by the regulatory authorities,⁶⁸ the WHO GCP seeks to set globally acceptable standards for the conduct of biomedical research on human subjects. In other words, while the ICH GCP aims at standardisation of clinical trials, the WHO GCP aims to be an informative tool addressed to different target groups and to provide standards that are applicable worldwide, including countries where national regulations or requirements do not (yet) exist.⁶⁹

As mentioned, the new Clinical Trials Regulation of the EU does not overrule ICH GCP or the Declaration of Helsinki. On the contrary, the preamble of the Regulation states that the document is in line with the major international guidance documents on clinical trials, such as the 2008 version of the WMA Declaration of Helsinki and the Guidelines for Good Clinical

⁶⁶ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, p. 9.

⁶⁷ Convention on Human Rights and Biomedicine 1997.

⁶⁸ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, p. 1.

⁶⁹ WHO 1995, p. 100.

Practice.⁷⁰ Specifications regarding compliance with the trial protocol and good clinical practice are also explicitly set out in Article 47.⁷¹

5.2. The New Requirements established by the Regulation

5.2.1 An Overview

Although Regulation No 536/2014 is legally binding in all Nordic countries due to the EEA relevance of the Regulation, the Regulation only establishes certain common general requirements for legislation and practices with regard to ethical evaluation of clinical trials on medicinal products, leaving the question of how to implement these requirements largely up to the Member (and Associated) States. Thus, implementation at the national level – as is typical for EU legislation in general – plays a crucial role in the realisation of the new requirements established by the Regulation. However, the Regulation sets out requirements, for example, in terms of timelines that every Member State must comply with when deciding on the procedures.

As described in the previous chapters, practices of ethical review of clinical trials vary between the Nordic countries. The Regulation will not necessarily prevent differences in national practices, for instance due to lack of regulation of the competent ethics committee or committees, as long as the ethical review meets the standards established in the Regulation. The Regulation states that a clinical trial is to be subject to scientific and ethical review and must be authorised in accordance with the Regulation: *“The ethical review shall be performed*

⁷⁰ It has to be noted that the version of the Declaration of Helsinki to which the Regulation refers to is the 2008 version, not the latest 2013 version. The 2013 revision includes, for example, the duty to compensate and treat subjects who are harmed as a result of participating in research and a prohibition on carrying out research on a vulnerable group unless it is responsive to the health needs or priorities of this group and cannot be carried out in a non-vulnerable group. The revised version also includes obligations with regard to the publication and dissemination of the results of the research.

⁷¹ EU Regulation No 536/2014, Article 47.

by an ethics committee in accordance with the law of the Member State concerned. -- Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation for the assessment of the application for authorisation of a clinical trial.”⁷² The requirements for the ethical assessment are summarised in the preamble of the Regulation:

“It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial and to organise the involvement of ethics committees within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State. When determining the appropriate body or bodies, Member States should ensure the involvement of laypersons, in particular patients or patients' organisations. They should also ensure that the necessary expertise is available. In accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence.”

The most essential and significant new requirements with regard to the assessment process of the applications set by the Clinical Trials Regulation are presented in the following paragraphs.

5.2.2 The Requirement for Independence

As can be noted from the definitions above, stringent requirements are set for the independence of the ethics committee or other organ performing ethical review. The same requirements are repeated in Article 9 of the Regulation, which also specifies that “*Member*

⁷² EU Regulation No 536/2014, Article 4.

States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence. In order to guarantee independence and transparency, the Member States shall ensure that persons admitting and assessing the application as regards the aspects addressed in Parts I and II of the assessment report have no financial or personal interests which could affect their impartiality.” The persons assessing the applications are also to make an annual declaration of their financial interests. The Member States must ensure that the ethical assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience, and at least one layperson must participate in the assessment.⁷³

The requirements of Article 9, combined with the other requirements for the assessment process, mean that even though it is left to the Member States to determine the appropriate body or bodies for assessing ethical aspects of applications, the requirements for such a body are strictly regulated. Article 9 is not directly addressed to ethics committees, but applies to everyone participating in the assessment of applications and therefore in practice is important to the function of ethics committees.

The requirement for independence set by the Clinical Trials Regulation is also strict compared with the other applicable international guidance documents. For example, ICH GCP only requires that at least one member of the ethics committee assessing the application is independent of the institution/trial site, and only those members who are independent of the investigator and the sponsor of the trial should vote or provide an opinion on a trial-related matter.⁷⁴

⁷³ EU Regulation No 536/2014, Article 9.

⁷⁴ ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice, Section 3.2.1.

It must be noted that the members' independence from the clinical trial site is not further defined in the Regulation. It is thus unclear what is meant by the clinical trial site, which is often understood in discussions as the hospital, research centre or institution where the clinical trial is conducted. Thus, the clinical trial site does not necessarily equal the legal entity employing the investigator, which would be impractical or even unfeasible. For example, a large national or regional health care organisation or a city (the owner of the city hospital) should not be defined as a clinical trial site, as this would exclude all of its employees from the evaluation process. In any case, the requirement for independence from the clinical trial site may pose a challenge, especially if the ethical assessment of applications is assigned to regional ethics committees. The regional committees often function under the organisation where the clinical trials are conducted, which means that the members of the regional committees may automatically become challengeable in the evaluation of trials conducted in the same large hospital or hospital district.⁷⁵

The new requirements for independence from the trial site may also lead to a situation in which it becomes difficult to find sufficient expertise required for the assessment of an application in a multi-site study in a small country. It may be especially challenging to find enough qualified members to assess an application concerning clinical trials on vulnerable populations. The Regulation stipulates that if the subjects are minors, the application must be assessed with specific consideration given to paediatric expertise. If the subjects are incapacitated subjects, specific consideration must be given to the application on the basis of expertise in the relevant disease and the patient population concerned. In both cases, it is also possible to ask for external expert advice on the clinical, ethical and psychosocial problems in the field of the relevant disease or patient population. If the subjects are pregnant or breastfeeding women,

⁷⁵ Southerington 2014.

expertise is needed in the relevant condition and the population represented by the subjects concerned.⁷⁶

Due to Article 9 of the Regulation, it can be problematic to ensure the functionality of the ethics committees with regard to enough members with no conflicting interests and with sufficient expertise to evaluate the application. The Regulation does not preclude asking for outside expert opinion, but the timelines set by the Regulation can make this difficult or even impossible in practice.

5.2.3 The EU Portal and Submission of Applications

The Regulation also stipulates the creation of a new interface for submitting applications for the authorisation of a clinical trial. This portal is called the EU portal, and it will be the entry point for the submission of data and communication of information relating to clinical trials in accordance with the Regulation. The data and information submitted through the EU portal is to be stored in the EU database.⁷⁷ Through the EU portal, the application will be accessible to all of the Member States concerned, and the sponsor submitting the application is to propose one of the Member States concerned as the reporting Member State.⁷⁸

The EU portal not only serves as a portal for submitting the applications, but is also a comprehensive electronic platform or tool for communication between the sponsor(s), the reporting Member State, other Member States and the EU. In addition to communication during the authorisation process of an application, the EU portal is used for informing the Member States concerned of the withdrawal of an application, an application for a subsequent addition of another concerned Member State, the authorisation procedure for a substantial modification of a clinical trial, notifications concerning the start of a clinical trial, the end of subject recruitment, the end of a clinical trial, serious breaches of the Regulation, information

⁷⁶ EU Regulation No 536/2014, Article 10.

⁷⁷ EU Regulation No 536/2014, Article 80.

⁷⁸ EU Regulation No 536/2014, Article 5.

relevant for subject safety and communication of urgent safety measures taken to protect subjects. If the requirements of the Regulation are no longer met, the Member State concerned must take corrective measures and inform all other Member States concerned through the EU portal. Also the reports of possible Member State inspections are submitted through the EU portal.⁷⁹

A summary of the results of a clinical trial in all Member States concerned must be submitted to the EU database within one year, or as soon as possible after that, from the end of the clinical trial.⁸⁰

5.2.4 The New Timelines Established in the Regulation

The timelines for trial authorisation set in the Regulation are relatively strict. The authorisation procedure for a clinical trial is regulated in Chapter 3 of the Regulation, and includes several parts. A single electronic application will be submitted via the EU portal, thus starting the validation process.

5.2.4.1 The Submission of an Application

The reporting Member State is to notify the sponsor and the other Member States concerned that it is the reporting Member State through the EU portal within six days of submission of the application dossier. Within 10 days of submission of the application dossier, the reporting Member State must validate the application taking into account considerations expressed by the other Member States concerned, and notify the sponsor through the EU portal whether the proposed clinical trial falls within the scope of the Regulation and whether the application dossier is complete in accordance with Annex I of the Regulation.⁸¹

The Member States concerned may communicate to the Reporting Member State any considerations relevant to the validation of an application within seven days of the submission

⁷⁹ EU Regulation No 536/2014, Chapters II–XIII.

⁸⁰ EU Regulation No 536/2014, Article 37.

⁸¹ The content of the list is described in the chapter 7.1.

of the application dossier. If the reporting Member State does not notify the sponsor within 10 days of submission of the application dossier, the clinical trial is deemed to fall within the scope of the Regulation and the application dossier is considered complete and valid. If the reporting Member State finds that the application dossier is not complete or that the clinical trial does not fall within the scope of the Regulation, it is supposed to inform the sponsor through the EU portal and set a maximum of 10 days for the sponsor to comment on the application or to complete the application dossier through the EU portal. Within five days of receiving the comments on the completed application dossier, the reporting Member State then notifies the sponsor of whether or not the clinical trial falls within the scope of the Regulation and whether the application dossier is complete. If the reporting Member State does not notify the sponsor within five days, the clinical trial applied for will be deemed to fall within the scope of the Regulation and the application dossier will be considered complete. However, if the sponsor does not provide comments or complete the application dossier within those 10 days, the application will be deemed to have lapsed in all Member States concerned.

The date on which the sponsor is notified that the application dossier is complete and the clinical trial falls within the scope of the Regulation is the validation date of the application. If the sponsor is not notified, the validation date is the last day of the time period reserved for the notification to the sponsor.⁸²

5.2.4.2 Part I of the Assessment Report

After submission of the application, the reporting Member State must assess it in compliance with the Regulation. In Part I of the assessment, the reporting Member State must assess whether the clinical trial is a low-intervention clinical trial if so claimed by the sponsor, and whether it complies with the requirements of the Regulation with respect to the anticipated therapeutic and public health benefits of the clinical trial and the risks and inconveniences for

⁸² EU Regulation No 536/2014, Article 5.

the research subjects. The reporting Member State must also assess compliance with the requirements concerning the manufacturing and import of the proposed investigational medicinal products and auxiliary medicinal products set out in the Regulation, compliance with the labelling requirements set out in the Regulation, and the completeness and adequateness of the Investigator's Brochure.⁸³

The reporting Member State must draw up an assessment report, of which the aspects listed above form Part I. Concerning the aspects of Part I, the assessment report must present one of the following conclusions: the conduct of the clinical trial is acceptable in view of the requirements set out in the Regulation, the conduct of the clinical trial is acceptable in view of the requirements set out in the Regulation but subject to compliance with specific conditions which shall be specifically listed in that conclusion, or that the conduct of the clinical trial is not acceptable in view of the requirements set out in the Regulation. This assessment report must be submitted through the EU portal to the sponsor and the other Member States concerned within 45 days from the validation date.

If the clinical trial involves more than one Member State, the assessment process will include three phases, of which an initial assessment phase is performed by the reporting Member State within 26 days from the validation date, a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all Member States concerned, and a consolidation phase performed by the reporting Member State within seven days from the end of coordinated review phase. The date on which the final Part I of the assessment report is submitted by the reporting Member State is the official reporting date.⁸⁴

The 45-day deadline for submission of Part I of the assessment report can be extended by 50 days for clinical trials involving an advanced therapy investigational medicinal product or a

⁸³ EU Regulation No 536/2014, Article 6.

⁸⁴ EU Regulation No 536/2014, Article 6.

medicinal product as defined in Point 1 of the Annex to Regulation (EC) No 726/2004⁸⁵ for the purpose of consulting experts. Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor. For the purpose of obtaining and reviewing such additional information, the reporting Member State may extend the period of 45 days by a maximum of 31 days. The sponsor must submit the requested additional information within the period set by the reporting Member State, which is not to exceed 12 days from the receipt of the request. The Member States concerned are to jointly review any additional information provided by the sponsor together with the original application within a maximum of 12 days of the receipt of the additional information. The further consolidation must be performed within a maximum of seven days of the end of coordinated review. If the sponsor does not provide the additional information within the set time period, the application will be deemed to have lapsed in all Member States concerned. The request for additional information and the additional information are submitted through the EU portal.⁸⁶

5.2.4.3 Part II of the Assessment Report

In Part II of the assessment report, each Member State concerned must assess the application for its own territory. The Member States concerned must consider the application's compliance with the requirements for informed consent as set out in the Regulation, compliance with the requirements set out in the Regulation for the arrangements for rewarding or compensating study subjects and investigators, compliance of the arrangements for recruitment of subjects with the requirements set out in the Regulation, compliance with the Data Protection Directive

⁸⁵ In the annex of Regulation No 726/2004 concerning Community procedures for the authorisation and supervision of medicinal products for human and veterinary use, the definition used for medicinal products referred to in the Clinical Trials Regulation is: medicinal products developed by means of one of the following biotechnological processes: recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, or hybridoma and monoclonal antibody methods.

⁸⁶ EU Regulation No 536/2014, Article 6.

95/46/EC (soon to be replaced by the General Data Protection Regulation that was approved by the EU in December, 2015), compliance with the suitability of individuals involved in conducting the clinical trial as defined in Article 49 of the Regulation, compliance with the requirements for the suitability of clinical trial sites, compliance with the damage compensation rules defined in Article 76 and compliance with the applicable rules for the collection, storage and future use of biological samples from the study subjects. The assessment of these aspects constitutes Part II of the assessment report.⁸⁷

Each Member State concerned must complete Part II of the assessment and provide a report, including its conclusion, within 45 days from the validation date and submit it to the sponsor through the EU portal. For justified reasons, and within the 45-day period, each Member State concerned may request additional information from the sponsor regarding the aspects listed above. For the purpose of obtaining and reviewing this additional information, the Member State concerned may extend the assessment period by a maximum of 31 days. The sponsor must submit the requested additional information within the period set by the Member State concerned, which is not to exceed 12 days from the receipt of the request. Upon receipt of the additional information, the Member State concerned is to complete its assessment within a maximum of 19 days. If the sponsor does not provide additional information within the time period stipulated, the application will be deemed to have lapsed in that Member State. The request and the additional information are submitted through the EU portal.⁸⁸

5.2.4.4 Decision on the Clinical Trial

Each Member State concerned must notify the sponsor through the EU portal whether the clinical trial is authorised, authorised subject to conditions, or refused. The notification must be made by a single decision within five days from the reporting date (the date on which the

⁸⁷ EU Regulation No 536/2014, Article 7.

⁸⁸ EU Regulation No 536/2014, Article 7.

final Part I of the assessment report is submitted by the reporting Member State), or from the last day of Part II of the assessment report, whichever is later. The authorisation of a clinical trial can be made subject to conditions only if the conditions in question cannot by their nature be fulfilled at the time of that authorisation.⁸⁹

The conclusion of the reporting Member State made in Part I of the assessment report is considered to be the conclusion of the Member States concerned. However, any Member State concerned may disagree with the conclusion of the reporting Member State if it believes that participation in the clinical trial would lead study subjects to receive inferior treatment compared with normal clinical practice in that country, if the clinical trial is considered to be in infringement of the national laws of the Member State concerned, or if it has considerations about subject safety and data reliability and robustness. The dissenting Member State must communicate its disagreement with a detailed justification through the EU portal to the Commission, to all Member States and to the sponsor. The dissenting Member State must refuse to authorise the clinical trial. It must also refuse to authorise the clinical trial if it finds that the aspects addressed in Part II of the assessment report are not complied with or if an ethics committee has issued a negative opinion which is valid for that Member State. The Member State concerned must provide for an appeal procedure in respect of such refusal.⁹⁰

If the clinical trial is acceptable or acceptable subject to compliance with specific conditions, the Member State concerned is to include in its decision its conclusion on Part II of the assessment report. If the conclusion of the Reporting Member State in Part I of the assessment report is that the clinical trial is not acceptable, that conclusion is deemed to be the conclusion of all of the Member States concerned. If the Member State concerned has not notified the sponsor of its decision within the timelines, the conclusion on Part I of the assessment report is deemed to be the decision of that Member State. The date on which the

⁸⁹ EU Regulation No 536/2014, Article 8.

⁹⁰ EU Regulation No 536/2014, Article 8.

decision of the authorisation of a clinical trial is communicated to the sponsor is the notification date. If the sponsor has not been notified, the notification date is the last day of the five days allotted for notification. If a clinical trial has not included study subjects in a Member State concerned within two years from the notification date, the authorisation expires in the Member State concerned unless an extension at the request of the sponsor has been approved.⁹¹

5.2.4.5 Summary of the Timelines

As the assessment timelines set in the Clinical Trials Regulation are relatively complex, a short summary of the number of days given for each stage of the procedure is necessary. The validation process of an application consists of two parts, and it has to be completed in a maximum of 25 days, including the request for the sponsor to complete the application dossier.

Part I of the assessment report consists of three phases, the first of which (the initial assessment phase) has to be completed in 26 days, with the possibility of an extension by 50 days in certain situations, the second of which (the coordinated review phase) has to be completed in 12 days with the possibility of an extension by 12 + 7 days, and the third of which (the consolidation phase) has to be completed within 7 days.

Part II of the assessment report has to be completed within 45 days, with the possibility of an extension by 12 + 19 days. The decision on a clinical trial has to be given within five days from the reporting date.

The Clinical Trials Regulation also includes provisions for the authorisation procedure for a substantial modification of a clinical trial. This procedure consists of similar phases as the initial authorisation procedure, but the time limits given for each phase are shorter. The

⁹¹ EU Regulation No 536/2014, Article 8.

authorisation procedure for substantial modifications is described in Chapter III of the Regulation.

A schematic summary of the authorisation process is presented in Appendix 3 of this document.

6. Why We Need a Harmonised System in the Nordic Countries

There are several reasons why the Nordic practices of ethical review of clinical research should be harmonised. Not only would such harmonisation be beneficial for the Nordic countries in fostering collaboration and competitiveness, it would also support the objectives of EU Regulation 536/2014. The Regulation states that Directive 2001/20/EC had aimed to simplify and harmonise administrative provisions governing clinical trials in the Union, but harmonisation has only partly been achieved. The Regulation points out that while future clinical trials will most likely target more specific patient populations, it may be necessary to involve several countries in the trials in order to include sufficient numbers of patients. This of course indicates that the harmonisation is not only recommendable but even necessary.

As we now know, the aim of Directive 2001/20/EC to simplify and harmonise the initiation and performance of clinical trials in the EU was not met in full. Instead, Directive 2001/20/EC created many additional burdens for the conduct of academic (investigator-initiated) trials that are run independently of the pharmaceutical industry, but did not sufficiently succeed in harmonising and simplifying applicable legislation in the Member States.⁹² The implementation of the Directive has led to a situation where both the regulatory burden and cost of conducting

⁹² Delawi, Dhert and Oner 2008.

clinical trials in the EU have increased, possibly contributing to the significant decline observed in the number of trials initiated and conducted since the Directive was adopted.⁹³

Dissatisfaction with the Clinical Trials Directive was the reason why the stakeholders requested the preparation of the new Regulation, calling for the EU to provide a better basis for harmonisation, in order to improve the competitiveness of European clinical trials. The harmonisation of practices in clinical trials is thus in the best interest of the stakeholders, including the European pharmaceutical industry – incoherent approaches between the Member States, failure to respect legal timelines and the lack of formal coordination mechanisms in the Member States have resulted in an increased workload for the industry and lowered the attractiveness of the EU as a favourable environment for conducting clinical trials.⁹⁴

The importance of a country's competitiveness and attractiveness when it comes to conducting a clinical trial cannot be overlooked. Approximately 4 400 clinical trial applications are submitted every year in the EU, and clinical trials are an essential part of clinical research in order to develop new medicinal products and therapies and to improve the treatment of diseases.⁹⁵ The research-based pharmaceutical industry invested an estimated EUR 30 630 million in research and development in Europe in 2013. The industry directly employs more than 690 000 people and generates three to four times more employment indirectly, which means that conducting clinical trials is of great importance not only with regard to the improvement of medical treatments, but also for the economies of Europe.⁹⁶

While the new Clinical Trials Regulation provides a promising basis for international cooperation and, as a legally binding document, has the potential to be more successful in achieving its goals than the Clinical Trials Directive, it still leaves plenty of room for national

⁹³ Allen & Overy 2014.

⁹⁴ Atzor, Gokhale and Doherty 2013, p. 75.

⁹⁵ Bengtström & Nybond 2012.

⁹⁶ EFPIA: The Pharmaceutical Industry in Figures 2014, p. 4.

variation since it only sets up a framework in the form of timelines, certain requirements and a common communication platform for the process. This is why it would be beneficial to harmonise systems in the Nordic countries to implement the aims of the Regulation as efficiently as possible in the region.

Taking harmonisation in the Nordic countries further than what the Regulation requires would give the Nordic countries unique standing as an arena for clinical trials. One of the key problems with regard to performing clinical trials in the Nordic countries is that their populations are obviously much smaller than those in some competing regions such as East Asia, Eastern Europe or the Americas. Each of the Nordic countries on its own will have difficulties in recruiting sufficient numbers of subjects for trials, but when evaluated together as a region, a population of 26 million makes them much more competitive. Seamless collaboration among the Nordic countries would provide a wider basis for the recruitment of study subjects, improving the competitiveness of the region in a global context.⁹⁷ This could bring important clinical research to the Nordic countries and help to change the current situation, where the number of clinical trials has been steadily decreasing over the past decade. As mentioned before, an increased number and volume of clinical trials would have favourable effects on the quality of health care, bring more income to the states concerned and have positive effects on employment. The time for such Nordic harmonisation is now, since the Clinical Trials Regulation both established the framework and guidelines for harmonisation and forces the Member States to adjust their legislation and practices in any case, creating an opportunity for the Nordic countries to collaborate in carrying out similar reforms of their legislation and practices with regard to the ethical evaluation of clinical trials on pharmaceuticals. Even if no legal pressure similar to clinical trials exists for harmonising the ethical evaluation of other types of biomedical research involving human subjects, this could be achieved as a by-product

⁹⁷ Bengtström & Nybond 2012.

of the process, and would likely benefit Nordic competitiveness and collaboration in other fields of clinical research as well.

7. Recommendations

7.1 Documents Required Now and in the Future

According to a report drawn up for the joint seminar of the NTA Work Package on Ethics - ethical evaluation of clinical trials (WP1) and the Finnish National Committee on Medical Research Ethics, held in Helsinki on 9 October 2014, there is considerable variation among the five Nordic countries as regards current requirements for the documents for ethical review in each country. The number of required documents ranges from eight in Norway to 17 in Finland. The number of required documents in Denmark, Iceland and Sweden is 11, 10 and 12, respectively. However, the differences between the numbers do not reveal the full truth about the situation, since the contents of these documents are distributed differently between the countries. Thus, even though Finland requires nine more documents than Norway, much of the same information found in individual Finnish documents is included in a more combined version in the documents required in Norway. Appendix 1 contains a list of the documents currently required in the Nordic countries.

According to the Clinical Trials Regulation, the application dossier for the authorisation of a clinical trial must contain all required documentation and information necessary for the validation and assessment of the application.⁹⁸ The required documents are listed in Annex I of the Regulation. According to the list, the application must contain the following:

- a cover letter,
- the EU application form (CTA),
- the trial protocol (for which the Annex stipulates several content requirements),

⁹⁸ EU Regulation No 536/2014, Article 25.

- an Investigator’s Brochure,
- documentation relating to compliance with good manufacturing practice (GMP) for the investigational medicinal product,
- an investigational medicinal product dossier (IMPD),
- an auxiliary medicinal product dossier,
- documentation on possible scientific advice and paediatric investigation plan (PIP),
- contents of the labelling of the investigational medicinal products,
- study subject recruitment arrangements (information per Member State concerned),
- the subject information leaflet, the informed consent form and information on the informed consent procedure (information per Member State concerned),
- evaluation of the suitability of the investigator (information per Member State concerned),⁹⁹
- evaluation of the suitability of the facilities (information per Member State concerned),¹⁰⁰
- proof of insurance cover or indemnification (information per Member State concerned),
- information on financial and other arrangements for the study (information per Member State concerned),
- proof of payment of the handling fee (information per Member State concerned), and
- certification that individual study data will be handled and processed in compliance with EU legislation on data protection.

⁹⁹ The required documents for the suitability of the investigator are quite comprehensive: the Regulation requires a list of the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites, description of the qualifications of the investigators in a current curriculum vitae and other relevant documents, information on any previous GCP training or experience obtained from work with clinical trials and patient care, and any conditions, such as economic interests and institutional affiliations that may influence the impartiality of the investigators.

¹⁰⁰ The requirements with regard to the facilities are also quite extensive: the Regulation requires a duly justified written statement on the suitability of the clinical trial sites adapted to the nature and use of the investigational medicinal product, including a description of the suitability of facilities, equipment, human resources and description of expertise, issued by the head of the clinic or institution at the clinical trial site or by some other responsible person according to the system in the Member State concerned.

The documents required in the event of a significant modification of the study protocol are listed in Annex II of the Regulation.

A detailed analysis of the differences between Annex I of the Regulation and the currently required information in the Nordic countries will have to be performed before the new procedures are defined. A full analysis will not be possible before the EU portal for CTA submission is published; the portal will contain guidance for the content and preparation of required documents. It must be determined whether individual Member (and Associated) States will be allowed to impose additional requirements on clinical trial applications beyond those mandated by the Regulation, its Annex I and the submission portal.¹⁰¹ Additional documents cannot be required by individual States, but the content of the documents and their interpretation may be subject to national variation. For example, in Finland, a separate ethical assessment of the trial is currently required from the person in charge of the trial (national coordinating PI). No mention of such a document is included in the Regulation or its Annex I. Still, as discussed in more detail below, the Helsinki Declaration states that the protocol should contain a statement on the ethical considerations related to the trial and indicate how the principles of the Declaration have been addressed. In a multinational trial, the protocol is commonly written by the company sponsoring the study, and the investigators have little or no personal involvement in its ethical assessment. What will be lost if a personal assessment is no longer required at the national level? Are the members of the ethics committee capable of assessing these aspects of the study protocol if the protocol is written in a foreign language (i.e., English)?

¹⁰¹ In Annex I of the Regulation, the requirements set for the content of the protocol are stated as being only the minimum requirements, thus implying that the Member States can set additional requirements for the protocol. However, no such mention is made in the other documents listed in the Annex.

7.2 The Results of the Finnish Survey

As mentioned earlier, the ways by which the Member States arrange the ethical review and delegate tasks to the ethics committees is left to the Member States to decide. In Finland, the Ministry of Social Affairs and Health conducted a survey in June 2014 to find the best possible arrangements for reviewing clinical trials in Finland to ensure that the procedure would be compatible with the timelines set in the Regulation. The survey was sent to the regional ethics committees, the national committee (TUKIJA), the Finnish Medicines Agency (Fimea), the National Supervisory Authority for Welfare and Health (Valvira) and to the National Institute for Health and Welfare (THL). The questionnaire presented four different options. The first option was to keep the current system and make the timetables of the regional committees more flexible so that they could meet the timelines of the Regulation. The second option was to form a smaller national committee consisting of officials and incorporating external experts to provide sufficient expertise. The third option was to establish an ethics committee that would function as a private company. The fourth option was to establish a virtual committee through the use of modern information and communications technology.

The results of the survey were almost unanimous. TUKIJA, Valvira, Fimea and all of the regional ethics committees except for those of the Hospital District of Helsinki and Uusimaa stated that the best option would be to form a new national committee consisting of officials. The two essential arguments presented by almost all of these respondents were that the current system of regional committees would not be able to function within the timelines set by the Regulation and that the autonomy of the committees would not be at the level required by the new Regulation, since the regional committees function under the hospital districts hosting the trials. All of the entities in favour of the establishment of a new national committee for clinical drug trials still wanted to keep the current regional committee system for other types of studies, and to delegate only the evaluation of clinical drug trials to the new national committee. The entities wish to preserve the possibility to appeal against negative opinions. It was also pointed out that since the new national committee would have to be quite restricted

in its number of members, it would be necessary to have a wide network of experts that the committee could consult. The respondents wanted to improve and make use of information technology, but they did not want it to replace the current system of actual meetings. It was suggested that the new national committee should have close cooperation with Fimea, and that Fimea should be the recommended reporting organ and national contact point for the EU portal.

The ethics committees of the Hospital District of Helsinki and Uusimaa presented a dissenting opinion. According to them, it is not reasonable to establish a new national committee just for clinical trials. The reviewing process should be left to the regional committees, and their independence should be safeguarded. It was felt that ethical evaluation should remain independent of the regulatory agency, Fimea.

The results of the survey show that, at least in Finland, the overall system of ethical review should be renewed because of the new timelines and requirements for independence of the committees. However, the situation in the Nordic countries may vary considerably, since the largest problem in the Finnish regional ethics committees appeared to be the lack of sufficient resources to arrange enough meetings for the ethics committees to meet the new timelines.

7.3 Other Relevant Notes

7.3.1 Standardisation of Protocols

The study protocol is an essential part of the application for a clinical trial. The Declaration of Helsinki states that every clinical trial should be based on a protocol. In the Clinical Trials Regulation, a protocol is defined as a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial.¹⁰² The requirements for the protocol are more detailed in the Declaration of Helsinki, which stipulates that the

¹⁰² EU Regulation No 536/2014, Article 2.

protocol should contain a statement of the ethical considerations and indicate how the principles of the Declaration have been addressed.¹⁰³ Thus the protocol includes essential information on the clinical trial, and without a thorough protocol, the clinical trial cannot be assessed.

Since the protocol is such an important part of the application for a clinical trial, it must be as clear and unambiguous as possible. In fact, clinical study protocols are relied upon by several different parties – funding agencies, research ethics committees, regulatory agencies, scientific medical journals, systematic reviewers, etc. – to appraise the conduct and reporting of clinical trials. Often, however, actual study protocols do not meet all requirements set for them.¹⁰⁴

An effective solution for the problems with study protocols could be to standardise their content and structure. This would also be recommendable when harmonising the Nordic system with regard to the Clinical Trial authorisation procedure, as it would not only enhance the quality of the protocols, but it could also increase their clarity, making the assessment of clinical trials applications more rapid and efficient. The potential ability of the standardisation of protocols to accelerate the authorisation procedure should not be underestimated, as efficient procedures are necessary in order to meet the new timelines set by the Regulation.

The standardisation of clinical study protocols has already been a subject of international debate for some time, and various models of standardisation have been suggested. One of these suggestions is the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) collaboration, an international initiative that aims to improve the quality of clinical trial protocols by defining an evidence-based set of items to address in a protocol. It was launched by an international group of stakeholders in 2007 with the primary aim of

¹⁰³ Declaration of Helsinki, Paragraph 22.

¹⁰⁴ Chan A-W et al. 2013.

improving the contents of trial protocols.¹⁰⁵ The SPIRIT Statement has created a 33-item checklist and a flow diagram that include a recommendation for a minimum set of scientific, ethical and administrative elements that should be addressed in a clinical trial protocol.¹⁰⁶ The SPIRIT checklist is a noteworthy suggestion as a tool for standardisation because it was made in collaboration with a large group of experts in the field with the intention of improving the quality of protocols. The checklist was also pilot-tested and an implementation strategy was developed at a stakeholder meeting. The SPIRIT checklist has also been explained with examples of each section of the checklist in an article by a group of experts, so it is very easy to interpret the checklist.¹⁰⁷ As standardisation of protocols is not mandated by the Regulation, standardisation requirements cannot be set by the Member States; however, a joint Nordic recommendation towards protocol standardisation (e.g. as outlined by the SPIRIT Statement) would help to foster harmonisation and efficient and high-quality CTA review in our region.

7.3.2 Remarks for Optimal Results

There are also other essential factors needed to carry out efficient harmonisation of the ethical review of clinical trial applications in the Nordic countries. First of all, applications should be written in a common language, most logically English. The Clinical Trials Regulation does not require the application dossier to be submitted in English and the language of the dossier is left to the Member State concerned to determine. However, Article 26 concerning language requirements states that the Member States should consider accepting documents other than those addressed to the study subjects that are written in a commonly understood language in the medical field.¹⁰⁸ Thus, even though the language of the application is not determined by the EU in a binding manner, it is recommendable to submit the application dossier in English. The Nordic countries should together adopt English as the required language for applications

¹⁰⁵ Chan A-W et al. 2013.

¹⁰⁶ <http://www.spirit-statement.org/spirit-statement/>

¹⁰⁷ Chan A-W et al. 2013. The examples for the Sections of the checklist have been presented in this article.

¹⁰⁸ EU Regulation No 536/2014, Article 26.

in order to facilitate international cooperation and to make the Nordic countries more approachable as a region for conducting multinational clinical trials.

Another necessary requirement for the harmonisation of the CTA review and approval is that the rules and principles according to which clinical trials are conducted in the Nordic countries – especially those that affect the harmonisation and collaboration between the countries – should be defined by duly appointed officials in a legally binding manner. The practices should be unambiguous and binding, since it has already been proven with the implementation of the Clinical Trials Directive that a system based on voluntary compliance does not work efficiently enough. It should not be left to regional or national ethics committees to impose additional requirements for the ethical review of CTAs.

7.4 Joint or Harmonised Nordic Ethical Evaluation – Pros and Cons

7.4.1 A Joint Nordic Committee

In principle, there appear to be three basic approaches to common ethical review procedures in the Nordic countries. The first and most radical alternative is the establishment of a joint, centralised supranational ethics committee for all five countries. Although this is the most radical option, a joint committee would be the best way of ensuring an efficient process in terms of reviewing applications within the timelines. A joint committee could also increase the reliability, scientific quality, independence and transparency of the evaluation process.

A joint Nordic committee would reduce the workload of the national committees, since all multinational clinical trials on medicinal products planned in the Nordic countries would be delegated to the joint Nordic committee. The competent authority in each country would submit the CTA to the joint committee for ethical review, and the results of the ethical review would be communicated back to the competent authorities, to be taken into account in their evaluation and their decision on the clinical trial. It must be noted, however, that national committees would still need to be maintained to review CTAs submitted from individual

countries. While all countries would have to be represented in the joint committee, it may not be necessary to include several experts from each country in every evaluation, especially for applications that only concern some of the countries. One possible solution would be to have a limited number of permanent members in the committee and to establish a wide group of experts to be called upon for assessments within their areas of expertise. This would also include patient representatives. This would ensure that all assessments are conducted with the required expertise, while keeping the number of committee members at a reasonable level. Membership would constitute an almost full-time task for the actual members. Finding sufficient numbers of experts for the joint committee to draw on would also be easier than at the national level, since the pool is larger and the question of independence would not become as challenging as it may in a national endeavour.

The Regulation does not explicitly support the establishment of a joint Nordic committee. Section 6 of the Preamble states that international cooperation in the ethical assessment process should not include aspects of a strictly national nature, such as informed consent. However, Section 18 of the Preamble states that it should be left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment of the application. Thus, the Regulation does not preclude Member States from mandating a supranational body to perform the ethical assessment, as long as the body is appropriately mandated and national aspects concerning informed consent and other such aspects listed in Annex I of the Regulation are taken into account. While the Regulation clearly requires CTA assessment by each Member State involved, it does not prohibit cooperation in the process. A joint Nordic ethics committee would include members from all five Nordic countries, which would mean that there would always be a representative from each country to assess national aspects, including language. Even if the ethical assessment were to be made by the joint committee, each country (i.e. its competent authority) would still have to submit its decision individually via the EU portal. This would leave room to check the evaluation of national

aspects before submitting the decision to the EU portal, thus ensuring that national aspects are evaluated properly.

Even if a joint Nordic committee would be ideal in terms of harmonisation, organising the committee would be challenging. The time allotted for implementing the new Regulation is limited, and implementation of concerted reforms of this magnitude may prove to be demanding. It should also be noted that the process of renewing the ethical review system to comply with the requirements of the Regulation has already been started in all of the Nordic countries, which may entail that these countries will not find enough flexibility in their national plans for the establishment of a joint committee. For example, Denmark has already set up a Coordination Working Group on the Implementation of the new Clinical Trials Regulation, an IT Working Group, a Working Group on Analysis of Procedures and Legislation and a Working Group on Clinical Trial Application Fees, which means that the effort to introduce the necessary alterations of the Danish system is already in progress. The substance of the proposal in Denmark is that regional committees would assess all incoming CTAs, with each committee meeting three times a month, and one secretariat serving all committees. These committees are supposed to assess both Part I and Part II of the CTA.¹⁰⁹ Another considerable problem with the joint Nordic committee proposal is that it may have a negative impact on public trust on the ethical review system. Since people are used to ethical evaluations being conducted nationally – often even regionally – it may be difficult to accept a supranational review system. However, since all five countries would be represented in the joint committee, there is no real risk of neglecting the national aspects of each country.

¹⁰⁹ Lundgaard Kjøller 2014.

7.4.2 Mutual Recognition Procedure

The second option would consist of a mutual recognition procedure. One country would perform a thorough ethical review of the CTA and the other Nordic countries would accept the conclusions of such a review, apart from the documents written to the study participants and the other nationally regulated documents listed in Annex I. These would have to be evaluated at a national level for appropriateness and be available in the local language(s) as needed. A mutual recognition procedure would be a compromise solution, since all countries would have to fully maintain their national organisations. It would still considerably lessen the amount of work for each individual country, since the evaluation of multinational projects would be conducted between the countries on a rotational basis.

One possible way of organising the evaluation process between the five countries would be to assign the responsibility to each country for one month at a time. However, if one of the countries is the reporting Member State, it would be logical for this to be the country conducting the full ethical review. The division of the review duties between the countries would in any case have to be very clearly defined beforehand, because the timelines prevent any negotiations once a CTA has been submitted.

Adapting the mutual recognition procedure may also pose some problems. First of all, it would most likely not increase the public's confidence in the system, and it would require that the committees in the various countries have a very high level of trust in each other. In the mutual recognition procedure, it would not be possible to review the whole CTA nationally after the first evaluation and still comply with the required timelines, so the trust would have to be complete and unanimous. It would also be problematic for the country responsible for the ethical review to assess aspects of a strictly national nature for other countries, and thus the assessment of these aspects would have to be left to the countries concerned (as the Regulation also requires). In this scenario, the timelines would again become an issue since the ethical review would have to be done by both the country responsible for the overall review and all the countries concerned. While assessing the national aspects, the country concerned

would still have to review the entire application dossier, which could mean that no time would be saved.

Overall, even though the mutual recognition procedure would demand less from the organisational reform processes, it would most likely be much less cost-effective than a joint Nordic committee since the national aspects would still have to be reviewed nationally in all five countries, and it would be necessary to go through almost the entire protocol and CTA in order to have enough context for the evaluation. Thus, since the joint Nordic committee would be more cost-effective, faster, and probably less prone to diminished public trust, it could be seen as a more recommendable option than a system of mutual recognition.

7.4.3 Maintaining the Evaluation at the National Level

The third option is to reform the legislation and procedures in each country in a coordinated manner in order to harmonise the procedures. The requirements set for the documents to be submitted for ethical review and their interpretation should be identical in all five countries. The ethical review of these documents, when actually performed by the committees in the five countries, should proceed according to commonly agreed principles in order to be predictable and uniform. This constitutes a challenge, as the ethical review should be independent of undue influences. How can efficient, predictable high-quality ethical review be conducted in a decentralised system encompassing five countries? Minimum requirements to achieve this are close collaboration between the countries on all levels, clearly defined and coordinated procedures within the countries, procedures for quality assurance and appeal, and a sufficient commitment to the resources of the ethics committees.

To facilitate harmonisation of the procedures in each of the Nordic countries, a supranational Nordic body coordinating all of the committee systems in the five countries could be established to provide guidance, document templates, education and oversight. This body would not require large membership and there would be no need for large financial

investments; a small group of experts and a minor support staff would be enough to achieve and maintain similar procedures in the Nordic countries.

While this option may not be ideal in terms of efficient harmonisation, its strength would lie in requiring less radical and complicated reform of national legislation and organisations than the other two options, and the countries would be able to keep their national processes intact, which would also mean that the national committees would not have to give up their jurisdictions. Still, harmonisation based merely on an institution providing guidance and guidelines, without a strong legal mandate, cannot be seen as an optimal tool for harmonisation, and the international organ could not be given the legal authority to interfere in cases where the national committees do not comply with the joint recommendations. Additionally, as in the other options, an essential issue to consider is compliance with the timelines set by the Regulation. While the joint coordinating organ should be able to give guidance and consultation regarding the assessment of applications, it would not be possible to ask for guidance for the evaluation of individual CTAs within the timelines.

7.4.4 Important Notes Regarding Each Option

When determining the best possible solution for harmonised processes of the ethical assessment of CTAs in the Nordic countries, there are certain aspects that need to be considered in all three of the above-mentioned options. The basis of the harmonisation, no matter which option is chosen, is that the documents the countries require for the assessment process would have to be harmonised and agreed upon in advance. In other words, none of the Nordic countries can require, for example, additional documents to clarify aspects of the research protocol, unless these are agreed upon between the countries.¹¹⁰ The agreement between the countries would also have to include the national aspects and the way that such national aspects are going to be reviewed. The assessment of all aspects of the CTA would

¹¹⁰ However, it has to be taken into account that the requirements set for the documents that are submitted to the EU portal are not yet published in detail. Thus, it may be possible that the portal leaves no room for variation whatsoever and there is no issue of national variation.

have to be harmonised even if the national committees are maintained; it is essential to ensure that applications will be assessed in the same way in all of the Nordic countries.

One essential aspect to be considered while harmonising the procedures is the appeal process. The most logical way to arrange the possibility for appeal would be to maintain the bodies of appeal at the national level. Thus, even if the ethical assessment is carried out by a joint Nordic committee, appeals would be addressed to national entities. Preserving the bodies of appeal at the national level would not be problematic, since the Regulation only requires Member States to provide a possibility to appeal the entire decision on a CTA, which is always made by each State individually, not on the ethical assessment alone.¹¹¹

Although all of the three options suggested above have their pros and cons, it should be kept in mind that one of the main objectives of harmonisation is to reduce bureaucracy and increase the speed and efficiency of the processes. Thus, the model of execution is secondary as long as these objectives are met. Under no circumstances should the harmonisation increase the bureaucracy and complicate the CTA process for the applicant.

¹¹¹ EU Regulation No 536/2014, Article 8.

8. Concluding Remarks

If conducted properly, harmonisation of the ethical review procedures for clinical trials in the Nordic countries can only lead to positive results. EU Regulation 536/2014 aims for considerable harmonisation, but still leaves room for national variation especially in the ethical review. This means that further harmonisation of the procedures would give the Nordic countries a unique standing compared to other European countries.

The three recommended alternative solutions developed in collaboration with professionals of the ethical review process in the Nordic countries are:

1. A joint Nordic committee to perform ethical review of clinical trials that involve more than one of the Nordic countries.
2. A mutual recognition procedure, in which one of the Nordic countries (for example the reporting country) would be responsible for the ethical review and the other countries would automatically recognise the result of the review.
3. Maintaining the ethical review of both national and international clinical trials at the national level, leaving the responsibility for the organisation to the countries to decide individually. A supranational body would provide coordination, document templates and guidance, and the requirements and standards of the ethical review would have to be agreed upon between the countries.

All of these suggestions for harmonisation have their pros and cons. While a joint Nordic committee would be the most effective way of harmonising the ethical review procedures, it may be too complex and radical for all of the Nordic countries to accept. A mutual recognition procedure would be a compromise between the solutions, but it may be too uncertain and slow to ensure compliance with the timelines set by the Regulation. Maintaining the ethical review at the national level would not be ideal for harmonisation, but the threshold for implementing this solution would be lower than for the other two options. Furthermore, since

this option would be the least demanding with regard to changes in legislation and existing organisations, it may be the most realistic option given that the EU has not allowed much time for the implementation of the Regulation.

In addition to the suggestions outlined above, there are certain aspects that need to be taken into account when implementing the harmonisation process. The language of the documents that are not meant for the study subjects should be English in order to ensure seamless communication between the countries and reduce the burden on applicants. The changes in the system with regard to harmonisation should be governed by duly appointed and mandated officials so that the legal validity and practical implementation of the changes can be guaranteed – voluntary harmonisation by independent ethics committees is unlikely to be successful. The documents and standards by which the countries evaluate CTAs should be the first elements to be harmonised, since it is extremely important that applicants can trust that the outcome of the ethical review will be similar in all five Nordic countries, and that only one application dossier is needed for the review process.

Regardless of which suggestion is adopted, harmonising procedures in the Nordic countries is in the best interests of all parties. The way the harmonisation is conducted is not the most essential part of the challenge; what is essential is achieving the harmonisation so that it meets the standards required to give the Nordic countries the benefits they need for restoring their attractiveness as clinical trial sites. The tools presented in this report are not the only possible measures for harmonisation, but rather examples to draw attention to the importance of the issue and the uniqueness of this opportunity, and to provide models to point out potential different approaches and methods for undertaking the harmonisation process. If harmonisation is achieved and proves to be functional, it could serve as a model for harmonising the procedures in other areas of medical research as well, paving the way towards a common Nordic research area in clinical research.

Appendix 1: Documents Required for Ethical Review in the Nordic

Countries¹¹²

Number	Mandatory document/information	Denmark	Finland	Iceland	Norway	Sweden
1	Cover letter	X		X		X
2	Application Form / Request for a Statement	X	X	X	X	X
3	Information on whether the application has been assessed through the VHP (Voluntary Harmonised Process) and whether the application is a national one	X				
4	EudraCT Form				X	X
5	Trial protocol	X	X	X	X	X
6	Protocol summary in local language	X	X			X
7	Research plan intended for laypersons	X				X
8	Identification of medical/health area	X				

¹¹² Anu Sulamaa, 2014. It has to be noted that this list of documents is based on individual research work on publicly available documents, and the information may not be completely accurate or unambiguous. The information required for the documents listed in the table may vary between the countries. Thus, some of the documents mentioned on the list may be included in other documents in some countries (for example, Norway requires information on almost all of the topics mentioned even though the number of separate documents seems relatively small), and this list is merely approximate and intended to indicate the variety of documents that may be required by different countries.

9	ICD-10 code	X				
10	Statement on the scientific relevance of the study	X				
11	CV of the National Coordinating Investigator / Chief Investigator in a country	X	X	X	X	X
12	National coordinating investigator's statement on ethical aspects of the study (ethical assessment)	X	X			
13	Investigator's Brochure		X	X	X	X
14	Information about handling of study drug(s)					X
15	Notification of Adverse Events and SUSARs	X				
16	Description of trial subjects to be included in the trial	X				
17	Number of participants and inclusion/exclusion criteria for participation	X				
18	Description of the care of participants at study site and monitoring of health					X
19	Testimonial from operations manager or equivalent concerning resources and the safety of those participating in the research.					X
20	Recruitment plan	X	X			

21	Template(s) of advert(s) planned to be used for recruitment of clinical trial subjects	X	X	X	X	X
22	Subject Information Leaflet(s), Informed Consent Form(s) and Proxy consent as applicable	X	X	X	X	X
23	Description of the process to obtain informed consent	X	X			X
24	Justification for the study in case the study involves persons who are not capable of giving independent consent (minors & other vulnerable groups)	X	X			
25	Any materials given to study subjects (e.g. questionnaires, diaries, instructions on how to handle study drug, etc.)	X	X	X	X	X
26	List of countries where study will be conducted	X				
27	List of study sites within the country	X	X			X
28	Copies of permits required for the study, including that of the Medical Director of a hospital, as applicable			X		
29	National coordinating investigator's statement on all study sites' equipment and appropriateness for the study		X			
30	List of all investigators within a country (at least one per site)		X			X

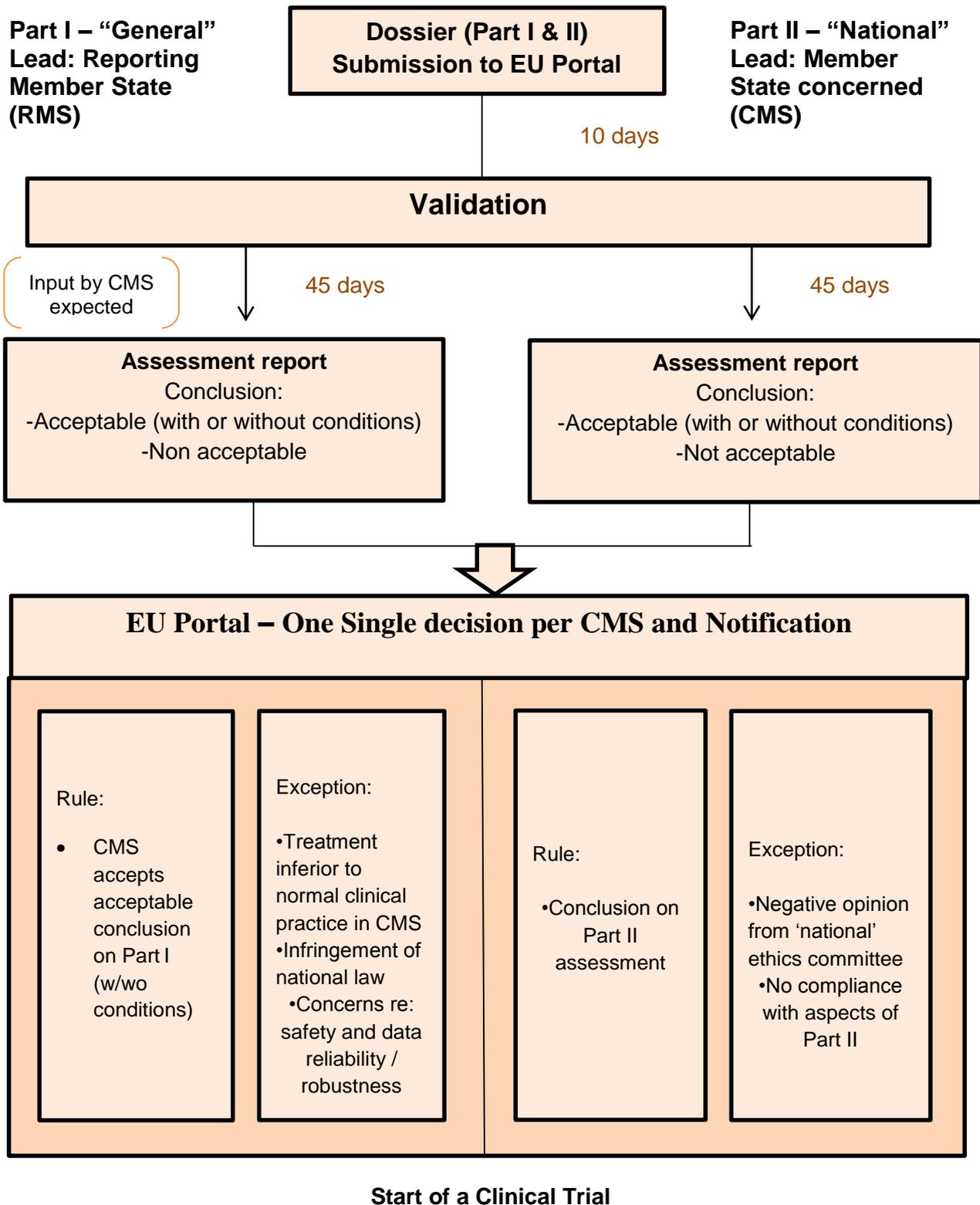
32	A statement on the National Coordinating Investigator's and all principal investigators' (at study sites) qualifications and suitability		X			
33	Description of information collected, who will have access to the information, and measures to ensure confidentiality	X	X			
34	Description of data processing and analysis of results	X				
35	Identification of research on biological material as part of the trial, if any	X				
36	Description of export of research materials (data or samples)	X				
37	Identification of storage place for research materials together with destruction plan	X				
38	Study budget / Payments, fees and compensation	X	X			
39	Financial compensation / remuneration to research participants	X	X		X	X
40	Insurance coverage for study subjects	X	X	X		
41	Other permits applied for: depending on the type of the project, permission may also be required from others, e.g. Data Protection Authority or the board of a biobank. Details of such applications or copies of permits obtained should be enclosed.	X				

Appendix 2: The Ethics Committees in the Nordic Countries

	Finland	Sweden	Denmark	Norway	Iceland
Legal basis	Medical Research Act 1999, Medical Research Statute 1999, Biobank Act 2012, Act on the Medical Use of Human Organs and Tissues 2001, Pharmaceutical Act 1987	Act concerning the Ethical Review of Research Involving Humans 2003, Statute concerning the Ethical Review of Research Involving Humans 2003, Statute with Instructions for Regional Ethical Review Boards 2007, Statute for the Central Ethical Review Board 2007	Act on Research Ethics Review of Health Research Projects 2011, Act on the Ethical Council 2004	Health Research Act 2009, Act on Research Ethics 2007	Act on Scientific Research in the Health Sector 2014, Medical Devices Act, Act on Patient Insurance, Act on Artificial Fertilisation and Use of Human Gametes and Embryos for Stem-Cell Research, Protection of Privacy Act, Act on Biobanks, Regulation on Clinical Trials of Medicinal Products in Humans
Term of office (REC)	4 years	4 years	4 years, may be reappointed twice	4 years with the possibility of one extension	4 years
Administrative basis	Regional committees are appointed by the University Hospital Districts, national committee operates under the National Supervisory Authority for Welfare and Health	Regional committees are appointed by and responsible to the Ministry of Education and Research	The national committee is appointed by the Minister for Health	The national committee is appointed by the Ministry of Education and Research	Institutional Review Boards functioning in the two University Hospitals. The national committee is appointed by the Minister of Health
Possibility to appeal	Possibility to bring the matter for reconsideration by the same committee, regional committee must at the request of the applicant seek the opinion of the national committee	Yes, to the national committee	Yes, to the national committee	Yes, to the national committee	Yes, to the national committee
Number of RECs	9 committees established by the 5 University Hospital Districts	6 regional committees located in the six large universities	12 regional committees placed in 5 regions	7 regional committees for medical and health research	Two institutional ethics committees placed in University Hospitals

<p>Members of the RECs</p>	<p>Chairperson + at least 6 other members, at least two of whom must be laypersons, and the rest have to represent research ethics, medicine, health science or nursing science and law</p>	<p>Chairperson + 15 other members, 10 of whom must have scientific qualifications and 5 are laypersons</p>	<p>7, 9 or 11 members 3, 4 or 5 of whom respectively have to be active within health research</p>	<p>9 members, representing medicine, psychology, nursing, law and ethics. Two lay representatives, one of whom should be recruited from a patient association</p>	<p>7 members to evaluate research protocols from the perspective of science, ethics and human rights.</p>
<p>Duties of the National Committee</p>	<p>Expert role in matters related to medical research ethics, advising regional committees in matters of ethical principles related to medical research, providing education on the subject, participating in international collaboration in issues of research ethics, and providing information on topical issues in the international ethical discussion in the field in the form of publications, seminars, websites etc., reviewing clinical trials not delegated to the regional committees; delivering opinions on appeals</p>	<p>Making decisions on controversial issues submitted to it by the regional ethics committees and serving as an appeal body for the regional committees, the committee also has a supervisory function</p>	<p>Ensuring with the regional committees that health research projects are carried out in a responsible manner, coordinating the activities of the RECs, laying down guidelines and giving opinions on issues of general nature, monitoring the development of research, promoting the understanding of ethical issues in research and providing consultative statements on research projects to be implemented in developing countries</p>	<p>Being an advisory and appeal body for the regional committees, giving opinions on issues regarding principles, and publishing reports and guidelines for biomedical research.</p>	<p>Evaluating scientific research protocols in the health sector with the objective of ensuring that they are consistent with scientific and ethical principles and human rights, evaluating collaborative and multinational projects, clinical trials of medicinal products and other prospective scientific research projects, participating in public and academic debate in bioethics, giving advice and preparing advisory opinions on subjects within its remit. Procedures of NBC apply also in the work of institutional review boards.</p>

Appendix 3: Summary of the Authorisation Process¹¹³



¹¹³ Michaux 2014.

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