Value of harmonized Nordic ethical evaluation of clinical trials

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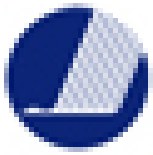
Nordic Trial Alliance, Oslo 30.1.2017



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Nordic Trial Alliance: Mission

- The mission of the NordForsk initiative NTA is to improve the conditions of clinical research in the Nordic countries.
- NTA aims to enhance Nordic cooperation in clinical trials.
- Increased Nordic cooperation will lead to a rise in the quality and number of joint clinical studies and will boost the attractiveness of the Nordic countries as partners in research. It will also promote knowledge transfer as well as increased efficiency and research output.
- The ultimate aim is a common Nordic Clinical Research Area in biomedical research.

About the Nordic Trial Alliance

A part of Sustainable Nordic Welfare

NTA is funded within the Nordic Council of Ministers' program Sustainable Nordic Welfare, and its focus area *Infrastructure for welfare*. The program includes both actual co-operation projects as well as Nordic platforms for dialogue and exchange of knowledge.

NordForsk coordinates

NTA's activities are coordinated by a small Nordic secretariat linked to NordForsk. The secretariat is headed by a coordinator and has wide contacts in the Nordic clinical research communities. All Nordic countries are represented in NTA's management and operations.

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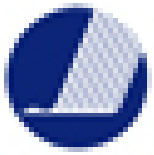
Start of NTA in 2013-2015

- Annual Stakeholder Meetings
- Five projects/working groups:
  1. Ethical Review Process for Clinical Trials
  2. Monitoring of Clinical Research
  3. Transparency and Registration
  4. Collaboration between Industry and Academia
  5. Pediatrics (strategic area)



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Research projects funded by NTA

The following joint research projects have received funding:

- *Assisted reproductive technology and safety in the Nordic countries (Anja Pinborg, Denmark)*
- *Nordic Arthroplasty Register Association - an international quality register study of total joint arthroplasty of four nations (Keijo Mäkelä, Finland)*
- *NordStar (Merete Lund Hetland, Denmark)*
- *BMT in elderly AML - a prospective, controlled, international study (Mats Brune, Sweden)*
- *Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission (Mark Ainsworth, Denmark)*

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NTA projects in 2016

Workshop on cross-border participation in clinical trials

Harmonised Nordic Ethical Evaluation of Clinical Trials

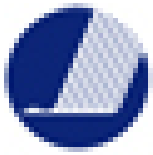
Nordic Conference on Real-World Data

Establishing a Nordic Network for Clinical Trials in Children – stage 2

Nordic Hotspot for Life Science

Nordic Monitoring Network - Network for Monitoring and Quality Assurance of Academic Studies in the Nordic Countries

Nordic network addressing the antimicrobial resistance (AMR) challenge and mapping AMR-related research in the Nordic countries



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NTA today and in the future

Annual meetings

Workshops and working groups

Projects: research projects and infrastructure initiatives

Website for researchers and for patients

The future of NTA will be elaborated during the current Norwegian presidency of the Nordic Council of Ministers in 2017

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New EU Clinical Trials Regulation 536/2014

- Scope: clinical trials on medicinal products for human use (repeals Directive 2001/20/EC)
- Aim: harmonized common procedures, faster and more efficient and predictable authorization of trials – while societal interests and human rights and dignity of participants are protected
- Aim: to foster European competitiveness in clinical trials and drug development
- To be fully implemented by the end of 2018

New EU Clinical Trials Regulation 536/2014

- Ethics committees are important actors of clinical trials, but also a source of national divergence, and so of delay in the authorization of clinical trials
- The new EU Regulation
  - – expressly refers to ethics committees but leaves much to the discretion of each member (and associated) state as long as deadlines for authorization are met
  - – includes restrictions on member states' discretion to regulate ethics committees

Steps and responsibilities

CTA Submission → Assessment → Decision

One submission by Sponsor for all Member States (MS) concerned in the Clinical Trial (CT)

Part I: coordinated assessment by RMS and CMS

Part II: each CMS, same timelines

Each CMS: Single decision for Part I and Part II

Aspects of Part I – coordinated assessment

- Whether the CT is a low-intervention clinical trial
- Anticipated therapeutic and public health benefits taking into account characteristics of and knowledge about the IMPs, relevance of the CT, reliability and robustness of the data generated in the CT
- Risks and inconveniences for the trial subject taking into account characteristics of and knowledge about the IMPs and auxiliary medicinal products, characteristics of the intervention compared to normal clinical practice, safety measures, including provisions for risk minimization measures, monitoring, safety reporting, and the safety plan
- Risks to subject health posed by the medical condition for which the IMP is being investigated
- Compliance with the requirements concerning the manufacturing and importation of IMPs and auxiliary medicinal products (Chapter IX)
- Compliance with the labelling requirements (Chapter X)
- Completeness and adequateness of the Investigator's Brochure

Aspects of Part II – compliance to be evaluated by each country

- with the requirements for informed consent
- with the requirements for rewarding or compensating investigators and subjects
- with the requirements for recruitment of subjects
- with data privacy rules
- with Articles 49 and 50 (suitability of investigators and trial sites)
- with Article 76 (damage compensation and insurance)
- with the applicable rules for the collection, storage and future use of biological samples

Assessment of Part II – what?

An assessment report template has been drafted for Part II. It addresses the following topics in a structured manner:

- Informed consent forms
- Written information to study subjects
- Protection of personal data
- Biological samples
- Compensation to subjects
- Recruitment
- Suitability of investigators
- Suitability of the facilities
- Proof of insurance cover or indemnification
- Financial and other arrangements
- Medical care of the subjects

Assessment of Part II – how?

The assessment report template provides boxes to tick and some guidance for the evaluation. Much appears to be left to be decided on the national level:

- Informed consent forms may be subject to “additional specific national requirements”
- Written information to study subjects must be “adequate” and “additional specific national requirements” may be placed
- Data protection must comply with EU rules, but further detailed points must be filled in by member states at the national level
- Biological samples: further detailed points must be filled in by member states
- Compensation to subjects: no undue influence exerted, no financial incentives to minors and other vulnerable subjects – no mention of specific national requirements
- Recruitment procedures and materials: “appropriate”, “acceptable”, “adequate”
- Suitability of investigators: “sufficient” training and experience
- Facilities: are they “adequately described” and “suitable”?
- Are arrangements for damage compensation in accordance with national law?
- Financial and other arrangements: are agreements “adequate”?

Common Nordic procedures for the ethical evaluation of clinical trials: why?

- Small populations, few patients in each country, but together we are 26 million
- Now: many different forms to fill in each country, different requirements for information, not cost-efficient to start a trial
- Soon: new Part II assessment procedures, unique for each country or harmonized?
- Similar moral and cultural values and similar public health care systems provide a good basis for harmonization
- Harmonization would benefit both academic and industry-sponsored research and would promote joint Nordic trials

Language requirements

Article 26

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.

Can we all agree that English will be acceptable as the common language?

Alternative ways to achieve harmonization

1. Joint multi-national Nordic ethics committee for clinical trials
2. Mutual recognition of ethical assessments performed by one country
3. Harmonized Nordic procedures for ethical review

How to best achieve harmonization?

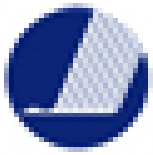
- A detailed analysis of the differences between Annex I of the Regulation and the currently required information in the Nordic countries will have to be performed.
- An analysis of the legislation pertaining to items K-Q of Annex I is needed in each country, and this legislation should be harmonized.
- The Nordic countries should produce joint templates and guidance for documentation related to items K-Q – this is the task of the current NTA extension project.
- Urgent request to the Nordic ministries: Set up a joint ministerial task force!

How to best achieve harmonization?

- Establishment of a Nordic Clinical Research Area is not a project, it is a process.
- Each Nordic country must now revise its own Ethics Committee system for evaluation of clinical trials, striving for Nordic harmonization.
- Present and future actions should be coordinated by a joint Nordic body, who provides templates, guidance, education and oversight.
- Harmonization should be extended to cover all clinical research, not just clinical drug trials.

NTA WP1 on Ethics

- Report published in February 2016 at http://nta.nordforsk.org/news/report-on-the-ethical-review-process-for-clinical-trials-in-the-nordic-countries
- Extension project 2016-17: common documents and other tools for implementation
- Contact: Mika Scheinin (NTA Project Leader), University of Turku and Turku University Hospital, email mschein@utu.fi



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