FACULTY OF HEALTH AND MEDICAL SCIENCES
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## Master Thesis

# Transparency in clinical research within the Nordic countries

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In collaboration with the Nordic Trial Alliance Work Package 6 on transparency and registration in clinical research.

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# Foreword

The Nordic Trial Alliance Work Package 6 is working towards raising the awareness of the hampered trial registration, reporting and towards finding possibilities to minimise double registration and reporting within the Nordic countries. "*Report on transparency and registration in clinical research in the Nordic countries"* is funded by NordForsk and is a joint work conducted with highly valued clinical researchers from all the Nordic countries. The involved members have long track records regarding clinical research and management of research units. They have all been deeply involved in national and international collaborative clinical research projects and have a high standing in their national clinical infrastructures and have been chosen to present their own countries in the work package. The report describes the current practices in clinical registration and transparency in the Nordic countries and suggests ways to improve trial registration, publication of trial results, and full study reports, and to develop Nordic best practice for public upload of depersonalised individual participant data. The main goal is to lay the foundation for Nordic registration and reporting of clinical research to the highest international standard.

During the time period from March 2014 to December 2014 I have contributed to the Work Package 6 as an active member, a co-author and worked every day with the report and my thesis at the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital. This master thesis builds on the work done within the Work Package 6 and the report but will be handed in a couple of months before the Work Package 6 report will be submitted to the Nordic Trial Alliance.

I would like to thank Mika Scheinin for suggesting me to get involved in the Work Package 6, the Copenhagen Trial Unit, the Working Group leader and external supervisor Christian Gluud, and all the members of the Work Package 6 for involving me in the project of "*Report on transparency and registration in clinical research in the Nordic countries*". Furthermore, I would like to thank Christian Gluud and Maria Skoog for guidance with in the field of transparency as well as with my following master thesis based on the Work Package 6 report. Also many thank to my internal supervisors Karin Friis Bach and Lona Louring Christrup for insightfully supervising my thesis.

Jenna Saarimäki,
Copenhagen, Denmark,
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# 1. Abstract

**Introduction:** Multiple analyses confirm that the achieved transparency level is not sufficient. The Nordic Trial Alliance Work Package 6 (WP6) is a group of clinical researchers working towards setting transparency on a correct level within the Nordic countries by conducting a joint report on transparency.

**Objective:** To analyse the current situation of trial transparency in the Nordic countries and also the initiatives, policies, and legislations that have impact on transparency. Moreover, to collect the arguments in favour of, and against transparency based on the WP6 experiences and present and discuss the recommendations conducted by WP6 of how to improve transparency within the Nordic countries.

**Background:** Transparency in clinical research is divided into 4 different aspects by WP6 and the AllTrials campaign: registration of clinical trials before enrolling the first participant, publishing results of clinical trials, publishing the full study report, and sharing of depersonalised individual participant data.

**Methods:** The following study is a descriptive analysis based on the report of the WP6. The methods used are: documental analysis, literature review, and focus group sessions.

**Results:** The incentives in place requesting transparency are not fully followed in the Nordic countries. Based on the WP6 experiences, the arguments in favour of transparency are heavier than the ones against. The WP6 set different recommendations for how to improve transparency within the Nordic countries.

**Discussion:** Transparency in clinical research is a topic provoking conversations and opinions. Achieving greater transparency is a joint work and every stakeholder should be taken into account when trying to improve the current situation.

**Conclusion:** Existing initiatives and efforts for greater transparency are not enough as these recommendations are not completely followed. The arguments in favour of and against transparency from the WP6 build a good foundation for conversations between different stakeholders and the recommendations set by the WP6 will improve transparency in the Nordic countries if fully followed.

## 2. Abbreviations

| | |
|---|---|
| ANZCTR | Australian New Zealand Clinical Trials Registry. |
| BMJ | British Medical Journal. |
| CCO | Creative Commons zero license. |
| CERN | Conseil Européen pour la Recherche Nucléaire (European council for nuclear research). |
| ChiCTR | Chinese Clinical Trial Registry. |
| CRiS | Clinical Research Information Service, Republic of Korea |
| ClinicalTrials.gov | A registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. |
| CONSORT | Consolidated Standards of Reporting Trials. |
| CRIStin | Current Research Information System in Norway. |
| CRO | Clinical Research Organisation. |
| CSR | Clinical Study Report. |
| CTRI | Clinical Trials Registry – India. |
| Data | The data recorded for each participant. |
| Depersonalised data | The data recorded for each participant in a depersonalised form |
| DOI | Digital Objective Identification number. |
| DIPD | Depersonalised Individual Participant Data. |
| DMP | Data Management Plan. |
| DRKS | German Clinical Trials Register. |
| EC | European Commission. |
| ECRIN | European Clinical Research Infrastructure Network. |
| EU | European Union. |
| EUDAMED | European Databank on Medical Devices. |
| EU-CTR | EU Clinical Trial Register. |
| EudraCT | European Union drug Regulating Authorities Clinical Trials. |
| FDA | Food and Drug administration. |
| FDAAA 2007 | The US Food and Drug Amendment Act. |
| FDAMA | The Food and Drug Administration Modernization Act. |
| GB | Gigabyte. |
| ICH-GCP | International Community on Harmonisation of Good Clinical Practice |
| ICMJE | International Committee of Medical Journal Editors. |
| IPD | Individual Participant Data |
| WHO ICTRP | World Health Organisation International Clinical Trial Registry Platform. |
| IOM | Institute of Medicine. |
| IMPACT | IMProving Access to Clinical Trial data by the Ottawa Group. |
| IRCT | Iranian Registry of Clinical Trials. |
| ISRCTN | The International Standard Randomised Controlled Trial Number Register. |
| JPRN | Japan Primary Registries Network. |
| Metadata | Data about data. |

| | |
|---|---|
| MRC | The UK Medical Research Council. |
| NordForsk | NordForsk is an organisation under the Nordic Council of Ministers that provides funding for Nordic research cooperation as well as advice and input on Nordic research policy. |
| NTA | Nordic Trial Alliance. |
| NTR | The Netherlands National Trial Register. |
| Pharmacovigilance | The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. |
| Personal data | Data which relate to a living individual who can be identified from those data. |
| PLoS | Public Library of Science. |
| Protocol | Protocol defines the objective(s), design, methodology, statistical considerations and the organisation of a Clinical Trial. |
| PRS | Protocol Registration System. |
| ReBec | Brasilian Clinical Trial Registry. |
| REC | Research Ethic Committee. |
| Registration | Registration of a trial prior enrolling participants to a publicly accessible clinical trial register. |
| Registry | A clinical trials registry is the entity that houses the trial information, and is responsible for ensuring the completeness and accuracy of the information it contains, and that the registered information is used to inform health care decision making. |
| Report | The Nordic trial Alliance Work Package 6 report on transparency and registration in clinical research in the Nordic countries. |
| Reporting | A scientific process addressing efficacy and safety and giving details about design, methods and results of a clinical trial. |
| PACTR | Pan African Clinical trial Registry. |
| RPCEC | Cuban Public Registry of Clinical Trials. |
| SLCTR | Sri Lanka Clinical trials Registry. |
| SPIRIT | The Standard Protocol Items: Recommendations for Interventional Trials. |
| TCTR | Thai Clinical Trials Registry. |
| Transparency | A process with openness and communication so it is easy for others to understand and see what has been done as well as what was intended to do. |
| Trial | A research study that involves human subjects and designed to assess the effects, beneficial and harmful, of healthcare interventions. |
| WHO | World Health Organisation. |
| WMA | World Medical Association. |
| WP6 | Work Package 6. |

## 3. Introduction

The Nordic Trial Alliance (NTA) is a 3-year pilot program (from 2013 to 2015) working towards making it easier to conduct clinical trials in the Nordic countries. Over the past decade the number of trials has decreased significantly in the Nordic area and according NTA, increased cooperation in clinical research would lead to a rise in the number of joint clinical trials and boost the attractiveness of the Nordic countries as partners in clinical research. Numerous trials are carried out jointly as research studies benefit from the similar healthcare systems and research cultures within Denmark, Finland, Norway, Iceland, and Sweden.[1]

In order to keep the well established and developed clinical research on the right track, transparency should be set at the correct level. Transparency is a process and a term which relates to openness and communication. Transparency makes it possible for others to see and understand what has been done and what was intended to be done in clinical research. Multiple analysis and surveys confirms that the current transparency level is not sufficient. Numerous clinical trials remain unregistered and unreported or researchers have not made all of their results available and this selective reporting of trial results lead to biased trial results.[2;3] Consequently, decisions about healthcare may be based on incomplete, wrong, or biased information. The WP6 has reviewed these issues and states that the defected trial registration and reporting is not acceptable. Therefore, the WP6 conducted the "*Report on transparency and registration in clinical research in the Nordic countries*" with the aim of showing good example, and restoring the ethical conditions in clinical research within the Nordic countries. In the report, the WP6 highlights the international initiatives, policies, and regulations concerning transparency which should be followed, reviews the main arguments in favour of and against transparency and develops recommendations which would enhance transparency in the Nordic countries regarding clinical research. These aspects have been taken into account in this master thesis.

### 3.1. The report on transparency and registration in clinical research in the Nordic countries

The report has been carried out as a joint work with members from all the Nordic countries. Denmark has been working as the project leader and making sure the work has been on track and the deadlines have been met. Members from Denmark have been the main authors and collectors for the information. The work has been implemented with four well planned Nordic meetings, several telephone conferences, and individual work inputs. The final meeting will be held in January 2015 when the report will be finalised and handed in to NTA in March 2015.

The report was constructed by the WP6 members as two parts of the work. The first part was aimed at compiling information regarding requirements and/or obstacles from the research community, funding bodies, ethics committees, competent authorities, data inspection agencies, institutions, etc. concerning trial registration, and reporting of results, and sharing of depersonalised individual participant data (DIPD). National information for those current procedures and norms for transparency and registration from the Nordic research community was collected using focus points and questioners sent to all members of the WP6. Furthermore, additional information was collected by the WP6 members from websites and written communications with researchers and key persons from above institutions. The collected information was discussed internally and the main barriers to lack of reporting and other transparency issues were identified. The second part of the work was aimed at developing an agreement for common Nordic best practices and Nordic possibilities for meeting a greater transparency level.

The objective of the report is to investigate current demands and practices and develop Nordic best practices for public, prospective registration and reporting of clinical trials of all interventions. Furthermore, to investigate current demands and practices and develop Nordic best practices for public upload of DIPD after reporting of the trial. Hence, the WP6 developed recommendations for how to improve transparency in the Nordic countries.

### 3.2. How I have taken part in the WP6 work

I started my work as an active member of the WP6 in March 2014. The first WP6 meeting in Stockholm was already held and questioners to collect national information on transparency were already created and sent out to the WP6 members from all the Nordic countries. Later on, I assisted by collecting the answers together and got them worded into the report with the other WP6 member Maria Skoog.

Further, I studied the important legislations impacting transparency based on the documents from the Food and Drug Administration (FDA) and the European Commission (EC) and wrote sections about their legislations on transparency to the report. At the second WP6 meeting in Bergen, I gave a presentation about these legislations to the other members of the WP6. As the work with the report went along, I searched information about the important initiatives affecting transparency, e.g., from the Institute of Medicine (IOM), the European Medicines Agency (EMA), the World Health Organisation (WHO), the AllTrials campaign, etc. I also paid close attention to discussions based on planned legislations and policies. Furthermore, in collaboration with the Danish group, I collected arguments against and in favour of transparency and these arguments were discussed and revised at the WP6 third meeting in Copenhagen. During the meeting I also gave a presentation about the three online repositories: Dryad, Figshare, and ZENODO and how they could serve as repositories for DIPD. I continued my work with the repositories by collecting information from their websites, sent few questions to them in order to get more proving information, and with Christian Gluud we also obtained information from the ZENODO launcher Lars Holm Nielsen.

Overall, I have been part of the Danish author group as a co-author and drafted parts to the report which have been further processed by the other members of the group. The report will be finalised by March 2015.

## 4. Objective

To analyse the current situation of trial transparency in the Nordic countries and also the initiatives, policies, and legislations that have impact on transparency. Moreover, to collect the arguments in favour of and against transparency based on the WP6 experiences and present and discuss the recommendations conducted by the WP6 of how to improve transparency within the Nordic countries.

**Research questions:**

1. Are the initiatives, policies, and regulations that should be followed sufficient to secure transparency in the Nordic countries?
2. What are the main arguments in favor of and against transparency according to the WP6?
3. What are the main recommendations from the WP6 to improve transparency within the Nordic countries?

# 5. Background

## 5.1. Clinical studies

The purpose of a clinical study is to add medical knowledge by doing research on human participants.[4] There are two main types of clinical studies: clinical trials (also known as interventional trials and divided into phase I, phase II, phase III, and phase IV trials) and observational studies. In a clinical trial participants receive specific interventions (e.g., medicinal product or medical device) according the trial protocol which defines the objective(s), design, methodology, statistical considerations, and the organisation of the clinical trial.[5] The investigators will determine the benefits and harms of the intervention by measuring certain outcomes in the participants.[4]

In an observational study, health outcomes are assessed in group of participants according to a protocol. Participants may receive different interventions such as drugs or devices as part of their normal medical care and the investigators may observe if those interventions have desired effect on the participants.[4] In contrast to a clinical trial, participants are not exposed to a specific intervention by the investigator (like in a clinical trial). The aim of an observational study is to examine the effect of the exposure. Hence, observational studies may suffer from extraneous and patient related factors which may influence the study results.[6]

In an interventional clinical trial, the experiment can be randomised to an intervention group and a control group receiving placebo or another control intervention, and these groups can be compared. Randomised clinical trials can also involve blinding of which group receives placebo, and which the actual intervention.[6]

## 5.2. The four aspects of transparency and how they are practiced at the Nordic countries

The WP6 follows the AllTrials recommendation and divides clinical trial transparency into 4 aspects: registration, summary results, full report, and DIPD.

### 5.2.1. The registration of clinical trials

Protocols of investigational medical product trials conducted in EU, must be submitted to the national competent authority for trial approval. This is done via the EudraCT (European Union Drug Regulating Authorities Clinical Trials) database. EudraCT is the European clinical trials database for pharmaceutical trials launched from 1st of May 2004 and operated by EMA.[7] Furthermore, before enrolling trial participants into a clinical study the protocol should be registered at a specific public online registry, depending on the type of a study.

Information submitted to the EudraCT is extracted to the public EU Clinical Trial Register (EU-CTR) by EMA. EU-CTR is for interventional medical product trials but it is excluding phase I trials and in 2011, EU-CTR was recognised as a WHO primary registry.[8] Since 2011, application to the EudraCT is recognised as trial registration since the information will be extracted to the EU-CTR but according the WP6 experiences, this practice is not well known within the Nordic countries.

The WP6 has noticed that different kinds of studies within the Nordic countries are most commonly registered at the ClinicalTrials.gov. ClinicalTrials.gov, run by the United States National Library of Medicines, was the first online registry for clinical trials and was made available to the public in February 2000. It is the largest and most widely used registry and results database worldwide and it accepts all kind of clinical studies to be registered.[9]

Eudamed is the European databank for medical devices and the competent authorities of the EU are responsible for entering the device trial information to the Eudamed.[10] The use became obligatory since May 2011, but a disadvantage is that the submitted information is not publically available. This secure web-based portal is working as a central repository for information exchange between the national competent authorities and EC in accordance with the Medical Device Directives.[11] It has been created to strengthen the market surveillance and transparency of medical devices.[10] Furthermore, the trials conducted with medical devices should also be registered at a specific public online registry (e.g., ClinicalTrials.gov).

In addition, the trial protocols need to be submitted to the relevant national ethical review board (REC) for approval depending on the case and the policies of that certain Nordic country. But according the WP6, the trial information submitted to REC registries is not publically available.

Figures 1 and 2 represent the general standards for trial registration practise in the Nordic countries. In contrast to medicinal product or device trials, the protocols for other types of trials do not need to be sent for an approval to any EU organisation. They need to be accepted by REC and further submitted to a certain online registry (e.g., ClinicalTrials.gov) to fulfil, e.g., requirements for journal publication or ethical standards.

**Figure 1: Clinical trial registration for medicinal product and device trials in the Nordic countries.**

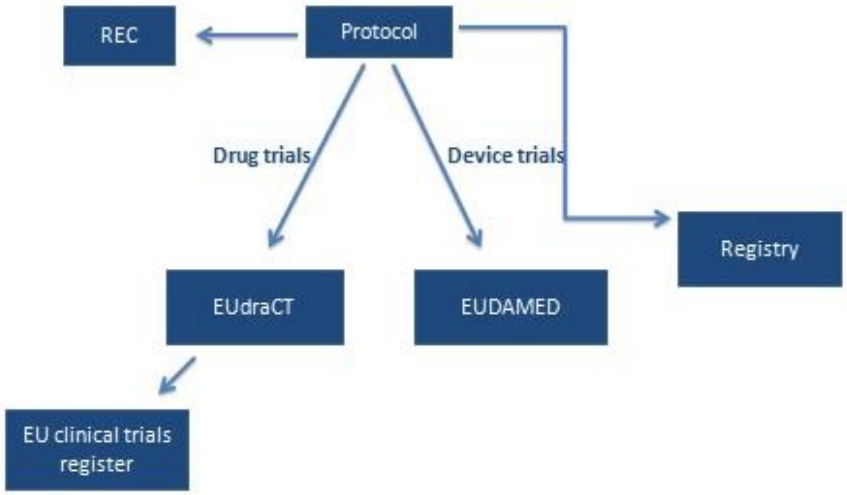
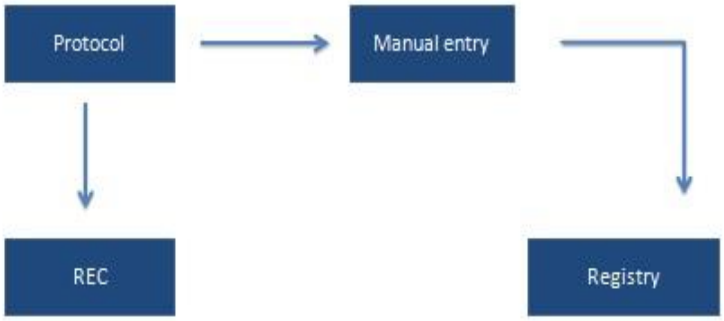



**Figure 2: Clinical trial registration for other types of trials in the Nordic countries.**



**WHO International Clinical Trial Registry Platform**

In 2004, the topic of trial transparency was discussed at the Mexico Global Forum and Ministerial Summit on Health Research (Mexico Summit). As a result of this conversation it was recommended that WHO should engage in trial registration.[12] In 2005, WHO began the push for clinical trial registration by launching the International Clinical Trial Registry Platform (ICTRP).[13] ICTRP standards claim for prospective registration of all clinical trials to a publicly accessible WHO registry meeting certain criteria. The goal is to ensure that information regarding clinical trials involving human beings is accessible to the public in order to improve transparency in clinical research.[13]

The WHO ICTRP has two elements: the WHO network of collaborating clinical trial registries (The registry network containing WHO primary and partner registries and ClinicalTrials.gov) and the search portal for clinical trials registered at the registries mentioned above.[13] One or several WHO primary registries are available in each WHO world region. Table 1 presents the current WHO primary registries and the year they were accepted. It can be noticed that after WHO began the push for trial registration, many registries around the world met the WHO criteria and were accepted as primary registries. Currently, there are also 3 partner registries which have not met the criteria for primary registries but are still submitting trial information to their affiliated primary registries.[14] But there are no Nordic trial registries affiliated with the WHO ICTRP.

The search portal allows searching in the central database (the WHO ICTRP central repository) containing the trial information provided by the WHO network of collaborating registries.[15] After the trial is identified, the hyperlink gives direction to the relevant registry source. WHO adopted English as the working language for trial registration and to the clinical trials search portal.[12] If the Nordic trial is registered with registry providing information to the search portal, it will appear in the search platform of the WHO ICTRP.

**Table 1: Current WHO primary registries.**[16]

| Name | Abbreviation | Joined |
|---|---|---|
| **Australian New Zealand Clinical Trials Registry** | ANZCTR | 2007 |
| **Brasilian Clinical Trial Registry** | ReBec | 2011 |
| **Chinese Clinical Trial Registry** | ChiCTR | 2007 |
| **Clinical Research Information Service, Republic of Korea** | CRiS | 2010 |
| **Clinical Trials Registry – India** | CTRI | 2007 |
| **Cuban Public Registry of Clinical Trials** | RPCEC | 2011 |
| **EU Clinical Trials Register** | EU-CTR | 2011 |
| **German Clinical Trials Register** | DRKS | 2008 |
| **Iranian Registry of Clinical Trials** | IRCT | 2008 |
| **International Standard Randomised Controlled Trial Number Register** | ISRCTN | 2007 |
| **Japan Primary Registries Network** | JPRN | 2008 |
| **Thai Clinical Trials Registry** | TCTR | 2013 |
| **The Netherlands National Trial Register** | NTR | 2007 |
| **Pan African Clinical Trial Registry** | PACTR | 2009 |
| **Sri Lanka Clinical Trials Registry** | SLCTR | 2008 |

**Partner registries:**[14]

- Clinical Trial Registry of the University Medical Center Freiburg
    - Affiliated registry: DRKS
- DeReG - German Registry for Somatic Gene-Transfer Trials
    - Affiliated registry: DRKS
- Centre for Clinical Trials, Clinical Trials Registry - Chinese University of Hong Kong
    - Affiliated registry: ChiCTR

ClinicalTrials.gov is not defined as WHO primary or partner registry, although it is providing data to the WHO ICTRP. It was established by U.S. federal law and complies with the Food and Drugs Amendment Act (FDAAA) and other applicable laws from USA.[12] Hence it cannot commit to any other standards which may differ from the U.S. requirements. For example, it allows registration 21 days after enrolling the first participant.[17] For greater transparency allowing registration after enrolling the first patient is not optimal, although ClinicalTrials.gov is a globally accepted registry.

**WHO ICTRP Registry Criteria for primary registries**

Criteria that primary registries need to meet in the WHO Registry Network, in order to fulfill the standards of the ICTRP, can be categorized into 6 main areas: content, quality and validity, accessibility, unambiguous identification, technical capacity, administration, and governance.[16]

**Content:** The primary registries have to accept registration of interventional clinical trials submitted by responsible registrants and they need to be open for prospective registrants internationally. The registries need to be able to receive and make publicly available the WHO Trial Registration Data set (see table 2) and attempt to keep submitted information up-to-date and never remove a trial after it has been registered.

**Quality and validity:** The primary registries need to have a mechanism to ensure the validity of the registered data (data registered is complete and accurate, the trial and the person registering the trial exists, etc.). The registries need to provide a publicly accessible audit trail in order to track the changes made for an individual trial to the WHO Trial Registration Data Set.

**Accessibility:** The primary registries need to ensure that the data of all trials will be accessible to the public at any time, that the information is electronically searchable,

and made available to the ICTRP in English. The registries need to allow registrants to submit a trial for registration at any time of the day or week and it needs to be searchable at any time of day or week.

**Unambiguous identification:** The primary registries are demanded to have processes to prevent the registration of a single trial more than once in their database.

**Technical capacity:** Primary registries in the WHO Registry Network will submit all WHO Trial Registration Data Set records in their registry (in English) to the Central Repository. They also have to provide an access to a database for storing and managing the submitted data but they are not required to develop their own databases. They also need to perform security and other provisions against data corruption and loss.

**Administration and governance:** Primary registries need to have support from the government within the country (or region) and be managed by a not-for-profit agency.[16]

The partner registries differ from the primary registries: the national or regional remit is not needed nor is support from the government. The management can be done by any organisation (not only non-profit organisations) and the scope of the registry can also be limited to only a particular indication. Furthermore, the partner registries need to be affiliated with either a WHO primary registry or another International Committee of Medical Journal Editors (ICMJE) accepted registry.[16]

### The WHO 20 items list

The WHO 20 item dataset was developed during the WHO stakeholders meeting in April 2005. At the meeting the pharmaceutical industry announced that disclosure of any five items (the scientific title, intervention(s), target sample size, primary outcome(s) and key secondary outcomes **in bold** in the table 2) could jeopardize the competent investment which underlines the creation of new medicines.[18;19] However, WHO set to the decision that the 20 item dataset is minimum information that must be submitted to a registry, in order for a trial to be fully registered.[20]

Trials conducted in the Nordic countries and registered to a publicly accessible trial registry should also include all the information demanded at the WHO 20 items list.

**Table 2: The WHO 20 items list.[20]**

| |
|---|
| 1. Primary Registry and Trial Identifying Number |
| 2. Date of Registration in Primary Registry |
| 3. Secondary Identifying Numbers |
| 4. Source(s) of Monetary or Material Support |
| 5. Primary Sponsor |
| 6. Secondary Sponsor(s) |
| 7. Contact for Public Queries |
| 8. Contact for Scientific Queries |
| 9. Public Title |
| **10. Scientific Title** |
| 11. Countries of Recruitment |
| 12. Health Condition(s) or Problem(s) Studied |
| **13. Intervention(s)** |
| 14. Key Inclusion and Exclusion Criteria |
| 15. Study Type |
| 16. Date of First Enrollment |
| **17. Target Sample Size** |
| 18. Recruitment Status |
| **19. Primary Outcome(s)** |
| **20. Key Secondary Outcomes** |

### 5.2.2. The reporting of trial results

When researchers conduct a clinical trial, they are expected to report the findings in accordance with basic ethical principles, including positive, neutral, and negative results.[21] These results may be reported as a publication in a scientific journal but also by submitting them to a public trial registry.

ClinicalTrials.gov allows summary results to be entered into templates on their website preferably no longer than a year after the trial has ended.[22] In October 2013, EMA improved the EudraCT database that sponsors may enter trial results in line with the guidance from EC.[23] The information will be extracted to the EU-CTR where the results remain publicly available. Some of the Nordic countries have also their own national

registries for trial results, e.g., Norway has common practices for the research communities to upload summary results in the national Current Research Information System in Norway (CRIStin) database. CRIStin collects information on the principle of open access to everyone.[24] The Capital Region of Denmark research registration system (PURE) is used in Denmark to store research results as open access to public.[25]

### 5.2.3. Clinical study reports

The Clinical Study Reports (CSR) are produced for regulatory and licensing purposes. They contain, e.g., large amount of detailed information about the methods, the statistical analysis plan, the results of all predefined outcomes including adverse events, and the conclusions of the trial.[26] The standard structure and content of the CSR is set out by the International Community on Harmonisation of Good Clinical Practice (ICH-GCP) guidelines E3.[27] According the WP6, public access for these study reports would be vital for transparency.

### 5.2.4. DIPD

Individual participant data (IPD) is the data recorded for each participant from clinical trials and DIPD is data formulated to a format that it is not possible to identify any participants. DIPD can be structured from the facts like the pre- and post-treatment of the participant, treatment group indicator, and clinical characteristics such as age and sex of the study participants.[28] These data are held by the sponsors conducting clinical trials and depending on the regulations concerning the data sharing, it might or might not be released to the public for secondary uses which would be essential for transparency.[29]

According to the WP6 experiences, there are no common practices for sharing DIPD among the Nordic countries. It is because there are no national policies in force demanding this practice or even national laws for securing online sharing of DIPD.

## Repositories for data files

The WP6 has noticed that none of the trial registries allow uploading of full study protocols, CSRs, or DIPD files although the sharing would be vital for transparency. It states that the submission must be done to a suitable online repository which has the capacity to store these files in a safe, searchable, and accessible manner. I have investigated that there are three online repositories readily available. These online repositories permit this kind of submissions and all of them provide digital object identifier (DOI) for every submission allowing the storage to be citable and searchable.

## Dryad

Dryad was launched in 2008 and is mostly consisting of research data from scientific and medical publications. After September 2013, it started to collect submission fees varying between the members, journals, etc. Researchers based in low income countries have been offered a waiver for the submission fees. Any data format can be submitted but all submissions must be in English, associated with a journal publication, and the data must be made available with the Creative Commons Zero (CC0) license. 10 GB of material can be submitted but additional charges will be granted for larger data packages. The collected data has been devoted to the public domain and all the contents are free to download and reuse. When citing data from Dryad there must be cited both the original article as well as the data package.[30]

## Figshare

Figshare is an online repository launched in 2011 and supported by the technology company Digital Science. It allows researchers to publish all of their data in a citable, searchable, and sharable manner. Any file type can be uploaded as well as file sets (groups of files) and it is free to access the contents. Figshare is offering unlimited storage space for free for data that is made publicly available on their site and 1 GB of free private storage space for users to storage their research. Figshare has also launched a partnership with Public Library of Science (PLoS) journals.[31]

**ZENODO**

In May 2013, The European Organisation for Nuclear Research (CERN) launched this online repository for researchers from all scientific fields to share research results, publications, and datasets. ZENODO is a project launched within the EU funded OpenAIREplus project as part of European wide research infrastructure and it provides public access to its contents as free of charge. Storage space for free is unlimited up to 2 GB but one may upload several files and larger files can be submitted for a fee. It also allows communication with existing online services such as DropBox. Users can also establish communities (e.g., research, conference groups, etc.) and share material only to the community members. It uses the same cloud infrastructure as the research output from CERN.[32]

# 6. Methods

The current study is a descriptive analysis based on the work performed in the WP6 and "*Report of transparency and registration in clinical research in the Nordic countries*".

## 6.1. Document analysis

Document analysis has been used as a qualitative research method to answer the research questions. The documents have been interpreted and analysed to give voice around the topic of transparency. The specific documents have either been found from the different parties' homepages or they have pointed by the WP6 leader Christian Gluud or by other members of the WP6.

## 6.2. Literature review

The literature searches were performed at the Pubmed and ScienceDirect using a variety of available search features and pointed literature based on transparency. Further searches have been conducted from the correspondence reference lists and from homepages and other websites found by using Google. Relevant literature has also been pointed by other members of the WP6 group.

## 6.3. Focus group sessions

Observation during the focus group WP6 meetings has been used as a qualitative research method. During the meetings, the WP6 participants have given open-ended responses conveying thoughts and feelings concerning transparency and these experiences have been taken into account in the thesis.

# 7. Results

### 7.1. The four aspects of transparency according the WP6 Group

(1) **Registration:** knowledge that a trial is ongoing or has been conducted.

- The initial registration of a trial needs to be undertaken prior to enrolling participants and registered in a publicly accessible clinical trial registry. The registration should be done for all clinical trials irrespective of the type of intervention, phase, or disease or condition. All phases from phase I to phase IV should be registered, likewise non-interventional studies such as observational studies should also be registered. Furthermore, the full study protocols should be submitted to a public online repository (e.g., ZENODO) before inclusion of the first participant to the trial.

(2) **Summary results:** a brief summary of the trial's results.

- The WP6 stresses that currently only a minority of the registered studies reports results of the conducted trials and this practice should be changed. Information of the main results and outcomes should be published as soon as possible or at least within a year after the trial has ended. If the summary results cannot be published in a journal, an alternative is to report them through publicly accessible clinical trial registration sites.

(3) **Full report:** full details about the trial's methods and results.

- These full CSRs including information of methods, the results of all predefined outcomes including adverse events etc. should be made publically available as soon as possible. Sharing of full CSRs would help to avoid undeclared post hoc changes to the trial methods and selective outcome reporting. Since the current trial registries do not allow these full reports to be uploaded as files, they should be submitted to an online repository (e.g., ZENODO) within a year after the trial has ended.

(4) **Data:** DIPD from the trial.

- As the trial registries do not allow submission of DIPD files, it should be uploaded to an online repository (e.g., ZENODO) after completion of the trial. The WP6 highlight

that sharing of DIPD is vital for independent reanalysis of trial results and meta-analysis for systematic reviews.

Meta-analysis refers to combining and analysing results from related clinical studies. Using DIPD in meta-analysis instead of aggregated summary data gives benefits both clinically and statistically.[28] It offers better utilization of trial data and helps to demonstrate whether a treatment is effective or not in a certain population or subgroups of such a population (e.g., age; sex; disease severity; etc.). Furthermore, when conducting meta-analysis from several trials, access for DIPD should be provided from all the included trials. This is because the statistical implementation needs be done from a group of patients and meta-analysing DIPD from only a single study is not very useful.[28]

## 7.2. International initiatives, policies and regulations impacting transparency

### 7.2.1. Trial registration and publication of trial results and full CSRs

This section is a collection of the international initiatives, policies and regulations impacting trial transparency on the aspects of trial registration and reporting of trial results and full CSRs. The table 3 presents the timeline for the development of clinical trial registration and this development also affects the practice for trial registration in the Nordic countries.

**Table 3: Timeline for the development of clinical trial registration.**

| Year | Initiative/Policy/Regulation |
|---|---|
| **1997** | Food and Drug Administration Modernization Act Section 113. |
| **2000** | USA ClinicalTrials.gov made available to the public. |
| **2004** | The Cochrane Collaboration supports registration of clinical trials. |
| **2005** | Launch of the WHO's International Clinical Trials Registry Platform (ICTRP). |
| **2005** | The Ottawa Group supports registration of clinical trials. |
| **2005** | The International Committee of Medical Journal Editors (ICMJE) requires registration of clinical trials. |
| **2007** | First WHO primary registries were launched. |
| **2007** | Food and Drug Administration Amendments Act Section 801. |
| **2007** | The European Clinical Research Infrastructures Network (ECRIN) started to require trial registration. |
| **2008** | The World Medical Association revised The Declaration of Helsinki to 7$^{th}$ edition and started to demand registration of all trial protocols and their results. |
| **2013** | The AllTrials campaign was launched. |
| **2013** | The World Medical Association the Declaration of Helsinki 9$^{th}$ edition demanding registration of all clinical study protocols as well as their results. |
| **2014** | The new EU regulation on clinical trials on medicinal product for human use. |

## Food and Drug Administration Modernization Act Section 113

The first U.S. federal law to require trial registration was the Food and Drug Administration Modernization Act (FDAMA) in 1997. FDAMA section 113 required the U.S. Department of Health and Human Services through the National Institutes of Health (NIH), to establish a registry of clinical trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases. In 2000, the NIH released the ClinicalTrials.gov.[33]

## The Cochrane Collaboration

Was formed in 1993 and it is a not-for-profit organisation working as a global independent network of health practitioners, researchers, patient advocates, and others from over 120 countries. It recognises the importance of trial registration and battles with the challenge of making evidence generated through medical research useful for people making decisions about health care. It started to support registration of clinical trials in 2004. The Cochrane Collaboration conducts systematic reviews of randomised clinical trials of health-care interventions and publishes them online at The Cochrane Library. It has a vision of a world of improved health where decisions made for health and health care are based on the high-quality, relevant, and up-to-date synthesised research evidence.[34]

## The Ottawa Group

The Ottawa Group consists of over 100 individuals and organisations worldwide who have signed the Ottawa Statement: a consensus document from 2005 aiming at the implementation of global trial registration for all clinical trials. The Ottawa Statement Part.1 demonstrates internationally recognised fundamental principles for trial registration, Part.2 proposes the implementation of the protocol registration and Part.3 outlines the principles on results reporting. Overall the statement highlights that the public availability of information about all clinical trials is necessary in order to ensure ethical and scientific integrity in medical research.[35]

## The International Committee of Medical Journal Editors

In response to selective registration of trials, ICMJE initiated a policy in 2005 that all medical journal editors should require, as a condition of consideration for publication, that prior enrolling the first patient into clinical trial the investigators need to register information about the trial design into a WHO accepted primary clinical trial registry or to ClinicalTrials.gov. In 2007, ICMJE revised the trial registration policy to apply to all trials, including phase 1 trials. ICMJE also recommends trial results to be published in clinical trial registries but does not require it yet.[36]

## The Food and Drug Administration Amendments Act of 2007

The Food and Drug Administration Amendments Act of 2007 (FDAAA 2007), Public Law 110-85 (signed by George W. Bush September 27, 2007) was designed, in part, to improve transparency in clinical research.[37] It contains a section for clinical trial databases (Title VIII) which requires registration of clinical trials meeting the definition of "an applicable clinical trial", i.e., an applicable prospective clinical device trial or an applicable prospective controlled clinical investigation of a drug, other than a phase I clinical investigations. Generally it concerns trials with drugs and biologics (other than phase I studies) and trials of devices with health outcomes. The applicable clinical trials must be registered through the ClinicalTrials.gov Protocol Registration System (PRS) and the information must be submitted no later than 21 days after enrolment of the first patient.[17]

FDAAA 2007 also requires submission of certain results data. In order to implement registration of results data, ClinicalTrials.gov launched a clinical trial result database in 2008. The results must be reported within 12 months of the trial primary completion date. The primary completion date in ClinicalTrials.gov is defined as: "*the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre specified protocol or was terminated in accordance with the protocol or study termination."* FDAAA 2007 defines the required results as "basic results" which contain summary information of study participants, study outcomes, and adverse events. The results are also made publicly available at ClinicalTrials.gov.[9]

The information required as results to ClinicalTrials.gov are regarded as summary information and it does not include DIPD. "Participant flow" describes the progress of

participants (the numbers of participants who started, completed the trial, etc.). “Baseline characteristics” define the demographics, such as age and sex of the participants, and study-specific measures. “Outcome measures” and “statistical analyses” include a tabular summary of outcome measure values. Also all anticipated and unanticipated adverse events must be included when submitting results of a study.[22]

## The Declaration of Helsinki

The Declaration of Helsinki, developed by The World Medical Association in 1964 and updated several times afterwards, contains ethical principles to offer guidance to physicians doing medical research on human subjects. It is built upon the Nüremberg Code and was the foundation for creation of institutional review boards.[21]

The 7th revision of the Declaration of Helsinki was adopted in October 2008 and it contains important requirements concerning prospective registration of clinical trials and disclosure of research results.[21] In 2013, the 9th revision of the Declaration of Helsinki rephrased and stated more clearly the important transparency requirements from the previous 7th edition and encompassing all research studies involving human subjects.[38]

The ethics committees in every research institution in every country should strictly follow the Declaration and it would verify a strong position towards securing the universal trial registration and trial results disclosure.[21;39]

| The 7th revision[21] | The 9th revision[38] |
|---|---|
| Paragraphs 19: "*Every clinical trial must be registered in a publicly accessible database before the recruitment of the first subject.*" | Paragraphs 35: *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject."* |

| The 7th revision | The 9th revision |
|---|---|
| Paragraphs 30: *"Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."* | Paragraphs 36: *"Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication."* |

## The AllTrials campaign

Is a campaign launched in January 2013 and demands for all the past and present clinical trials to be registered and their full methods and summary results to be published. It is an initiative from Bad Science, the British Medical Journal (BMJ), Centre for Evidence-based Medicine, The Cochrane Collaboration, The James Lind Initiative, PLoS journals, and Sense About Science. In the USA it is led by Darthmouth's Geisel School of Medicine and the Darthmouth Institute for Health Policy & Clinical Practice.[40]

According the campaign, there are four levels of information in the clinical trial reporting:

1. Knowledge that the trial has been conducted, from a clinical trials registry.
2. A brief summary of the trials results.
3. Full details about the trial's methods and results.
4. DIPD.

The AllTrials campaign is concerned with the first three and is calling for all trials registered/all trials reported. The petition has been signed by over 80,000 people and over 500 organisations including regulators; medical schools and universities; medical bodies and Royal Colleges; research funders and more than 200 patient groups from across the world.[40]

## The European Clinical Research Infrastructures Network

The European Clinical Research Infrastructures Network (ECRIN) is integrating clinical research in Europe by connecting and coordinating national centres and networks. The ECRIN Scientific Board has the obligation to evaluate all protocols submitted to the ECRIN, before operational support for management of the multinational clinical trials.[41] After 2007, the ECRIN Scientific Board started to require for clinical trial transparency as an acceptance criteria to the services:[42]

-*"Commitment to register the trial in a public trial registry before including the first participant, for example on ClinicalTrials.gov."*

-*"Commitment to publish results irrespective of findings."*

-*"Commitment to make raw anonymised datasets available to the scientific community upon legitimate request to the sponsor or principal investigator once the trial is completed."*

**New EU regulation on clinical trials on medicinal product for human use**

On the 16th of June 2014, the new EU regulation on clinical trials on medicinal product for human use entered into force, and will become applicable no earlier than 28th May 2016. According to the new regulation, EMA shall set up and maintain in collaboration with the Member States and the Commission, a user friendly EU portal at Union level where can be submitted information about the conducted clinical trials. EMA shall also establish a new publicly accessible EU database and the information submitted to the EU portal will be stored at the EU database. The database will be publicly available unless confidentiality can be justified with the matters mentioned at the article 81(4). Personal data of the subjects will not be publicly accessible. The regulation's entry into application is linked with the full functionality of the EU portal and Database since the EU portal and Database will eventually replace the EudraCT.[43]

This regulation highlights that the information from CSR of trials should not be reflected as commercially confidential. The regulation requires that before the trial has begun (involves all trial phases) it must be registered in a publicly accessible and accepted registry. Hence, the regulation introduces new registration requirements for phase 1 trials in Europe.[43]

According the new regulation, detailed summaries of the results must be submitted to the EU portal within a year after the trial has ended (meaning the last visit of the last subject or at a later point as defined in the protocol). This is irrespective of the outcome of the study. If this is not possible within a year, the protocol shall specify why and when the results are going to be submitted. There must also be included a summary of results that is understandable to a lay person. Once a decision on marketing authorisation has been granted, the procedure for marketing authorisation has been completed, or the application has been withdrawn, the full CSRs must be made publicly available in 30 days after the above-mentioned procedures. If the sponsors are not able to fulfil these requirements there will be penalties imposed for non-compliance.[43]

**Are these policies, regulations, and initiatives enough to secure transparency in the Nordic countries?**

As an answer, the policies, regulations, and initiatives already in place are not sufficient to secure trial transparency in the Nordic countries.

One month after the ICMJE policy went into effect, the number of trials registered at the ClinicalTrials.gov increased from 13 153 to 22 714 registered trials.[44] Today ClinicalTrials.gov contains over 170 000 trials. In response to increasing registration habit, many local registries around the world met the ICTRP criteria and were recognised either as a primary or partner WHO registry.[45] Hence, the developing of trial registration and a trial registries' network has improved.

Although the overall numbers of registered trials has increased since 2005, there is no complete list of all clinical trials.[46] The AllTrials campaign emphasizes that numerous surveys on the registration status of published trials and reporting of their results conducted by, e.g., Huser et al., in 2013[47], Jones et al., in 2013[2], Van de Wetering et al., 2012[48], Scherer et al., in 2012[49], and Mcgee et al., in 2011[50], provides evidence that the initiatives have not been sufficient to secure all clinical trials to be registered or their results to be reported. Approximately 40% of clinical trials concerning medicines in current use are still not registered, including trials conducted in the Nordic countries.[51] The AllTrials campaign is stressing that when we do not even know that some trials have taken place neither will we get to know the results from them.

Furthermore, the WP6 is concerned that the new EU regulation is not going to be sufficient to secure trial registration and results publication neither in EU nor in the Nordic countries. The WP6 bases its opinion to FDAAA 2007 since it demands registration and results reporting for trials conducted under the US law but has not reached adequate compliance. Numerous of trials in USA are still not registered or their results are not reported.[2;52]

According to the WP6, the most effective way to ensure prospective registration for all trials would be to make trial registration as a condition for ethical approval from RECs. An example of this is already in place since in 30th of September 2013, the Health Research Authority in UK started to demand trial registration before their approval.[53] The WP6 is also recommending that the Nordic countries should formulate a legislation

to secure publication of trial results since the new EU regulation might not be sufficient to secure this practice.

### 7.2.2. Sharing of DIPD

The next major step of transparency would be the sharing of DIPD for public use.[54] There are already organisations and parties in place planning or debating for policies of how such data should be shared and re-used and they are represented on the table 4.

**Table 4: Timeline for the development of sharing DIPD.**

| Year | Initiation/Policy/Regulation |
|---|---|
| **2013** | The Ottawa Group announced the IMPACT initiative. |
| **2014** | Horizon 2020 open research data pilot. |
| **2014** | PLoS journal data sharing policy. |
| **2014** | European Medicines Agency (EMA) data sharing policy. |
| **2014** | Institute of Medicine (IOM) data sharing policy. |
| **2015** | New EU regulation for data protection. |
| **In the future** | International Committee of Medical Journal Editors (ICMJE) data sharing policy. |

**European Medicines Agency**

EMA is the European Union medicines agency evaluating medicinal products. It has been releasing access to clinical trial reports on request, as a part of its access-to-documents policy from 2010. In October 2014, the Agency adopted a policy on publication and access to clinical trial data (defined as clinical reports and DIPD).[55]

The implementation of the policy is divided into two phases:

1. The publication of clinical data is related to the clinical reports only.
2. Later on EMA will review various aspects of IPD especially how to submit IPD for scientific reviews, how to provide access to IPD, and what are the conditions that need to be fulfilled for accessing the data.[56]

**Institute of Medicine**

IOM is an American non-profit organisation organised in 1970 and providing national advice on issues relating biomedical science, medicines, and health. Furthermore, it is emphasizing that clinical trials are a crucial way to determine the safety of medical interventions. According to IOM, shared DIPD could facilitate new analyses and improve the understanding of a particular therapy or condition. Researchers who conduct a study and later on analyze the individual data have represented a significant investment but still these data are not publicly shared. This is because there exist some barriers to share DIPD from clinical trials, although it would benefit both the researcher and citizens. Therefore, IOM is conducting a consensus study to recommend guiding principles and build a framework for responsible sharing of DIPD. The scope will be limited to interventional clinical trials and the responsible data manager (data repositories, industry sponsors, or clinical trial researchers) would make the data available to the public via open access or restricted access.[29]

The project started in August 2013 and it is sponsored by AbbVie Inc., Amgen Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome Fund, Doris Duke Charitable Foundation, Eli Lilly and Company, FDA, Genentech, GlaxoSmithKline, Johnson & Johnson, Merck & Co. Inc., NIH, Novartis Pharmaceuticals Corporation, Novo Nordisk, Pfizer Inc., and Sanofi-Aventis.[29]

In January 2014, IOM released the interim report for public comments "Dis*cussion framework for Clinical Trial Data Sharing: Guiding Principles, Elements and Activities*" and the comments could be submitted at the two public workshops or at the project's website. IOM is expected to release the final report for strategies and practical approaches in December 2014.[29]

**The Ottawa Group**

In 2013, The Ottawa Group announced the IMPACT (IMProving Access to Clinical Trial data) initiative. It aims to define methodologies and develop standards for public disclosure of raw data of clinical trials and thus contribute to the implementation of the Ottawa Statement that calls for public disclosure of participant level data.[57]

**International Committee of Medical Journal Editors**

ICMJE is highlighting that sharing of DIPD is crucial to verify the published clinical trials and to utilize the input that trial participants have given when enrolling to trials. It has given contribution to the IOM data sharing policy and currently, ICMJE is in the process for considering setting a policy on data sharing.[58]

Furthermore, BMJ which is one of the ICMJE journals, has already announced its policy on data sharing: "*From January 2013 trials of drugs and medical devices will be considered for publication only if the authors commit to making the relevant anonymised patient level data available on reasonable request*."[59]

**Public Library of Science**

PLoS journals have revised their data-sharing policy in order to increase access to research data: "*Authors must make all data available, without restriction, immediately upon publication of the article".* After 3rd of March 2014, all authors submitting to a PLoS journal are asked to provide a statement describing where and how the dataset underlying findings, can be accessed. This Data Availability Statement should be provided on the first page of the published article.[60]

## Horizon 2020

Horizon 2020 is the EU Research and Innovation funding program (2014-2020) with the aim at securing Europe's global competitiveness in research, technology, and environment.[61] Horizon 2020 is opening new opportunities for clinical research in Europe and it is investing over €300 million for clinical trials.[62]

EC is highlighting that one way to enhance economic performance and improve the capacity to compete through knowledge is an open access to publicly-funded research. During the Horizon 2020 program, EC is encouraging a culture of sharing scientific publications and data with open access. Via open access, research results can be disseminated more broadly and faster for researchers, innovative industry, and citizens. This would boost the visibility of European research and improve the access for small and medium-sized enterprises to the latest research for utilization. There exists two roads for open access and they have been divided between green open access (self archiving with immediate or delayed open access) and gold open access (publisher is providing immediate open access).[63]

The open research data pilot is an innovation of Horizon 2020 and it applies to two types of data: "*The data that includes associated metadata, needed to validate the results presented in scientific publications as soon as possible*" and *"other data that also includes associated metadata, as specified and within the deadlines laid down in a data management plan (DMPs)."* [64] Projects (including the ones conducted at the Nordic countries) participating into this pilot are required to deposit the data, if possible to a data repository (e.g., ZENODO) and allow third parties to access, exploit, and disseminate the research data. Projects or individuals that are not covered in the scope of this pilot may participate in voluntary bases as opt in and they will be monitored and receive same kind of support as the other projects. Projects are, however, allowed to "opt out" from the pilot in the cases of conflicts with obligations to protect results, confidentiality, or security and with rules to protect personal data.[64]

## New EU regulation for data protection

The risk that people could lose control over their personal data has been increasing since the growing globalisation and data flow over the online environment. On 21st of October 2013, Civil Liberties members of parliament voted on the new EU regulation

for data protection reform which will update the existing legal principles set in 1995. The current EU data protection directive 95/46EC does not contain several aspects like globalisation and technological developments (e.g., social networks). This new regulation for data protection is expected to reach agreement in 2015 and then have a 2 years enforcement period and let people have better control over their personal data. In the future, this regulation will also protect individual participant data, consequently affecting the use of data collected in clinical trials.[65]

**Other parties**

The need for data sharing has also been recognised by a variety of international organisations, research funders, and others, including the Organisation for Economic Co-operation and Development, WHO, NIH, the Bill and Melinda Gates Foundation, the Hewlett Foundation, the US Congress, the UK Medical Research Council, the Wellcome Trust, and BioMedBridges.[66] Furthermore, some pharmaceutical companies have started to release DIPD on request. For example, in May 2013 GlaxosmithKline established an online system to enable researchers to request access to anonymised participant level data.[67]

**Are these going to be enough to secure sharing of DIPD in the Nordic countries?**

Sharing of DIPD will be the next challenge to improve transparency. It is difficult to predict exactly how these initiatives will be taken forward and if they will be enough to secure sharing of DIPD to the public within the Nordic countries. According to the WP6, there might be needed a Nordic legislation to secure sharing of DIPD and this issue will be further discussed at the next WP6 meeting in January 2015.

## 7.3. Arguments in favour of and against transparency

Transparency in clinical research is a worldwide issue and provokes opinions and conversations between stakeholders. In the following chapter are listed the main arguments in favour of and against transparency based on the WP6 experiences. Due to the members' affiliations, it needs to be taken into account that these arguments are based on an academia point of view and the WP6 maintains the weight on arguments in favour of transparency. Pharmaceutical industry or other stakeholders might have different weighting of arguments on transparency.

### 7.3.1. Arguments in favour

Trial registration and results publication

i. The safety of the trial participants and ethical treatment should be priorities above all other considerations on clinical research. Potential trial participants need to be informed about the trial by registering it and need to know the results of other relevant ongoing and completed trials before signing an informed consent. This should be irrespective of trial phase or whether the intervention is approved for marketing or not.

ii. Registration of trials would enable better communication between the researchers and enhance scientific knowledge development. Consequently, the quantity of research duplication and redundant trials could be decreased.[68] Researchers need all the available evidence on conducted trials before initiating further trials in order to prevent causing needless harm for participants. Therefore, the too early terminated trials should also be published. Especially publishing results from phase I trials is essential in order to decrease the amount of redundant studies and to give better protection for patients not to go through a similar study which has already shown significant adverse events.

iii. Transparency and quality of trial protocols and registration would fulfil ethical standards.[21] The Declaration of Helsinki is stating that investigators conducting research on humans should register the clinical study and publish its results. Also a moral contract between participants and researchers is demanding for transparency regarding clinical research protocols and results. Participants

might put themselves at risk when joining a trial in order to improve medical knowledge and the absence of full disclosure of result is disrespectful towards these participants as well as to all others.[69]

iv. Full transparency would decrease reporting bias. Historically, positive clinical trial results are more likely to be published and this causes bias in the scientific literature with overestimation of benefits and underestimation of harms. Negative or inconclusive trials do not often get published, due to both ignorance from journal editors and researchers' lack of persistence. This leads to a waste in clinical research since interventions without any true effect ends up to be marketed and used although the trial data might not show significant potency for the intervention. As a result, the published clinical trials cannot be considered as representative of the total output of clinical research.[68;70]

Publishing the full CSR and DIPD

v. Lack of full disclosure of the full CSR and DIPD is disrespectful for trial participants since one major reason for trial participants to participate in clinical trials is to advance clinical knowledge. Then selection through editing of which data advanced this knowledge represents unlawful expropriation. Investigators or industry may own interventions and should have the opportunity to protect such interventions through patents. However, this does not entail the right to expropriate DIPD and clinical results of such interventions.

vi. Transparent publication of DIPD for meta-analyses would lead to improved pharmacovigilance and to a greater balance in assessing between benefits and harms of medical interventions. Secondary analyses and independent verification of original findings are possible with full transparency. The greatest enemy of exact meta-analysis is the selective publication of data and it weakens the proper understanding of the balance between benefits and harms of interventions. IPD gives better utilization of trial data than aggregated and this helps to demonstrate whether a treatment is effective or not in a certain population but also in subgroups of such a population (e.g., age; sex; disease severity; etc.).[28] For example, in a review of vitamin D supplementation for prevention of mortality in adults conducted by Bjelakovic et al., it was noted that having access to the individual participant data would have helped to analyse

the results gained in this meta-analysis.[71] Furthermore, full transparency could generate and stimulate new use of data, in that way data can benefit research and hypothesis outside its original collection aim.

vii. Transparency for publication of results, full CSRs, and DIPD files would improve decision making on medicines, devices, and all other medical interventions since it would lower the amount of unnecessary drugs prescribed for patients. This would also have a benefit for decreasing the amount of reimbursements in healthcare.

### 7.3.2. Arguments against

Trial registration and result publication

i. Protocol registration prior to initiating the trial might give more challenges and burdens for investigators if there is a need for amendments during the trial. This also demands for a good version control of the clinical trial registry in order to keep accurate track for amendments.

ii. Transparent registration of trial protocols and trial results to the registries may hamper the chances for getting trial results published also on a journal. This could impair the benefits of publishing trial information at the registries from the companies and academia point of view. On the other hand, ICMJE does not see such transparency as a problem for publishing the results on their journals.[72]

Publishing the full CSR and DIPD

iii. People can be concerned that transparency for making DIPD available to public gives the possibility to identify patients and this could raise issues in patient consent. The fear of being recognised might be relevant in low population countries (for example in Iceland) or with trials containing only few selected patients (trials with rare diseases or orphan drugs).

iv. Transparency can raise a fear of patient information being used for purposes the patient has not consented to (for example if the data collected from a clinical

trial is used later on for developing another intervention). Making use of the data for other purposes would be problematic if the patient's own ideology or religion is not agreeing with developing this new intervention. On the other hand, receiving benefits from healthcare and the demand for new/better interventions set some obligations for population. Patients taking part to clinical trials can do their input for advanced healthcare by allowing sharing of their data from clinical trials.

v. Generating data into a form which is sufficient and readable for the public costs money and is time consuming. It also demands for more work from the researchers. Although this can be considered as a small cost compared to the total price of developing a new intervention, it needs to be taken into account since someone needs to pay and maintain the infrastructure. Fortunately, there are possibilities for uploading full study protocols, CSRs, and DIPD files to online repositories (e.g., ZENODO) with no cost.

vi. Controlling the production of expensive research efforts is a necessary part on clinical research. Forcing complete disclosure of methods, results, and DIPD might increase risks for making industrial R&D economically unstable.[69;70;73] Such fears, however, do usually not commit in the potential economic gains of open access.

vii. Some companies are afraid that publishing full study protocols, CSRs and DIPD files might break intellectual property rights for their interventions and could release commercially sensitive information to the public and further the research ideas could be stolen.[70;74] Possible loss of market exclusivity and competitive advantage concerns pharmaceutical companies. They must have knowledge over things that are not obvious to everyone else and full transparency might put this competitive advantage on pharmaceutical market at risk and it drives pushback from industry.[73;74] If the full study protocol needs to be published, the investigator might leave out a lot of information in order to protect some valuable knowledge (e.g., methods which cannot be patented) and this could lead to a publication of superficial protocol. However, an effective ethical committee system could stop such protocols from being launched.

## 7.4. The WP6 recommendations for improving transparency

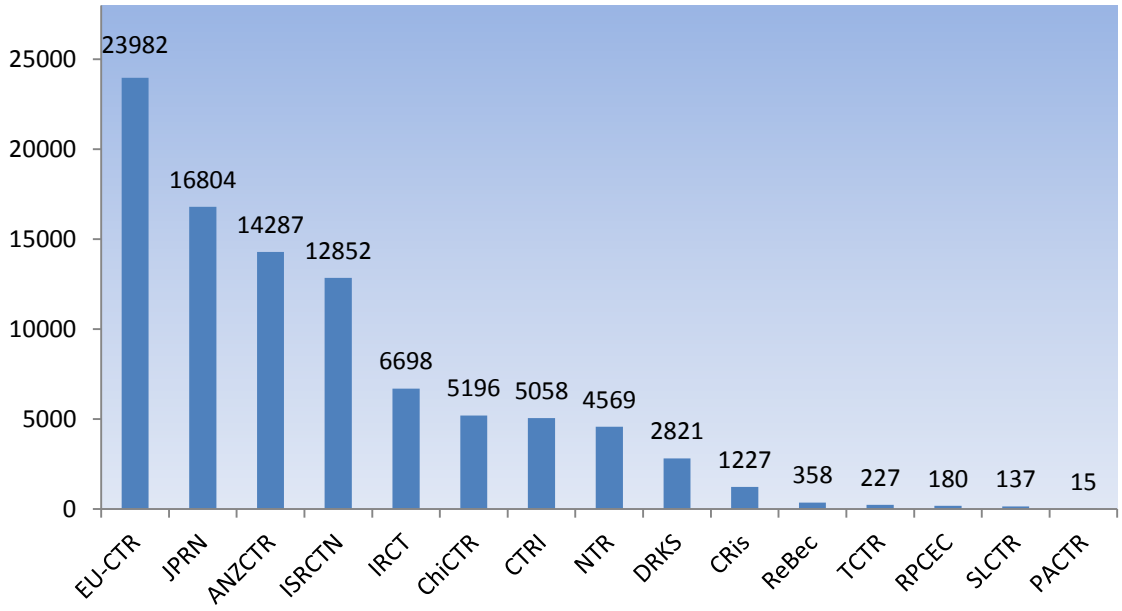
During 3 face to face meetings and 4 telephone conferences, the WP6 came up with recommendations for how to enhance the transparency of clinical research within the Nordic countries.

### 7.4.1. Clinical trial registration for medicinal product, device, and all other types of trials to ClinicalTrials.gov

The WP6 recommends that all clinical trials for medical products, devices, and all other types of trials should be prospectively registered to ClinicalTrials.gov before enrolling the first participant to the trial. It would build knowledge and availability of ongoing research, prevent selective reporting and publication bias, and prevent unnecessary duplication of research. Hence, all the trials could also be found and searched via the WHO ICTRP.

ClinicalTrials.gov allows registration of all kind of trials to the same registry which is a big advantage for transparency. With more than 175 000 registered studies on September 2014 from over 187 countries, it is the largest and most widely used registry today worldwide and also among the Nordic countries. Figure 3 presents the number of registered trials in the WHO primary registers and it can be noticed, that ClinicalTrials.gov is the most used registry.

**Figure 3: The number of clinical trials registered at the WHO primary registers on September 2014.**




Compared to the EU-CTR (see table 5), ClinicalTrials.gov has qualities currently supporting greater transparency.

**Table 5: Comparison of ClinicalTrials.gov and EU-CTR.**

| | ClinicalTrials.gov | EU-CTR |
|---|---|---|
| **Origin of the registry** | USA | EUROPE |
| **Launched** | 2000 | 2011 |
| **Clinical studies** | All kind of clinical studies. | Interventional medicinal product trials. |
| **Trial phases for interventional trials** | All phases. | Phases II-IV. |
| **Trial registration and results submission** | Manually to the boxes on the website or an alternative link to the results. | Information extracted from the EudraCT. |
| **Amendment tracking** | YES | NO |

All clinical studies (interventional, observational, device trials, etc.) and all trial phases can be registered on ClinicalTrials.gov and the information will be publicly available. It also has a feature facilitating tracking for protocol changes for registered clinical trials. Following of changes made throughout a trial that could bias final trial results is important for transparency.[75] Moreover, to ClinicalTrials.gov the researchers can submit results information manually which gives an advantage to provide more broaden scope of the results than the results information extracted straight from the EudraCT to the EU-CTR. Also the researchers may provide a link to the results at ClinicalTrials.gov if the results have been published e.g. on a journal.

In addition, this recommendation supports the new EU regulation for clinical trials. The new regulation is demanding to record also phase 1 trials in a publicly accessible and free of charge database which is a primary or partner registry of, or a data provider to the WHO ICTRP. Currently, EU-CTR excludes phase 1 studies which have been submitted to the EudraCT.

### 7.4.2. New Nordic legislations

The WP6 is concerned that the new EU regulation might not be enough to ensure trial registration and result publication within the Nordic countries. It recommends that RECs should start to demand trial registration as a condition for an approval of a clinical trial. Furthermore, the Nordic countries should enforce trial result publication via a legislation but this issue will be further discussed at the WP6 final meeting in January 2015.

### 7.4.3. Improving protocols by adding items to WHO 20 items list

Trial protocols and existing protocol guidelines differ greatly in quality and content and the problem is recognised worldwide.[76] Therefore, "*the Standard Protocol Items: Recommendations for Interventional Trials"* (SPIRIT 2013) were developed. The SPIRIT 2013-checklist consists of 33 items to be addressed in protocols and draws from GCP E6, WHO, ClinicalTrials.gov and ICMJE.[77]

Furthermore, the CONSORT 2010 statement: "*Updated guidelines for reporting parallel group randomised trials"* was formulated to improve reporting for randomised controlled

trials. The statement is a checklist of 25 items which updates the practice for reporting, based on new methodological evidence and accumulating experience.[78]

The WP6 reviewed the SPIRIT 2013 checklist and CONSORT 2010 statement and recommended that five items: monitoring plan, statistical analysis plan, data management plan including open access policy for publication and data, safety reporting and conflicts of interest (**in bold**, see table 6) should also be added to the WHO 20 items list in order to improve the quality of trial registration. Suggested items would also put pressure on the researcher to have these topics in place before launching the clinical trial. This way trust could be enhanced towards the public and reassured the existence of safety, quality, and design features from all trials are disclosed before the inception of a trial.

**Table 6: The recommended extended trial registration data set by the WP6**

| |
|---|
| 1. Primary Registry and Trial Identifying Number |
| 2. Date of Registration in Primary Registry |
| 3. Secondary Identifying Numbers |
| 4. Source(s) of Monetary or Material Support |
| 5. Primary Sponsor |
| 6. Secondary Sponsor(s) |
| 7. Contact for Public Queries |
| 8. Contact for Scientific Queries |
| 9. Public Title |
| 10. Scientific Title |
| 11. Countries of Recruitment |
| 12. Health Condition(s) or Problem(s) Studied |
| 13. Intervention(s) |
| 14. Key Inclusion and Exclusion Criteria |
| 15. Study Type |
| 16. Date of First Enrollment |
| 17. Target Sample Size |
| 18. Recruitment Status |
| 19. Primary Outcome(s) |
| 20. Key Secondary Outcomes |
| **21. Monitoring plan** |
| **22. Statistical analysis plan** |
| **23. Data management plan including open access policy for publication and data** |
| **24. Safety reporting** |
| **25. Conflicts of interest** |

### 21. Monitoring plan

It is the sponsor's responsibility that the trial is monitored in compliance with the ICH-GCP. However, the GCP guidelines were drafted back in 1996 and have not been updated since. The section for monitoring has been constructed very broadly and the research methods have significantly progressed afterwards.[79] By adding a monitoring

plan to the required items for registration, it would strengthen GCP. Good communicating strategy between sponsors, clinical research associates and study sites will have a high value in the monitoring plan and helps to keep the study on track.

### 22. Statistical analysis plan

Results for the primary outcome and other trial results can be fully affected by the used method for statistical analysis. When more than one analysis strategy is applied for a specific primary outcome, there is a possibility for inaccurate evaluation and further on selective reporting of the trial results. This will raise ethical issues and reliability for the trial results will be jeopardised. Missing data can be handled with different statistical methods and they can all lead to different results and conclusions.[76]

### 23. Data management plan including open access policy for publication and data

When the data management process has been well planned, reported, and implemented with appropriate staff, it will help to avoid mistakes that might jeopardise the validity of data. Reporting of security measures will enhance the protection of data and decrease unauthorised access to or loss of participant data. When the data entry and coding are conducted by different persons, definitions for the data management plan and standard coding practice will decrease the risk of errors and data misinterpretation. Furthermore, the different methods for data entry can affect the trial in the regards of accuracy, cost, and efficiency.[76] Sharing the methods for data management will benefit other researchers when they can learn from others' experiences and therefore produce more accurate data while enhancing the cost-effectiveness of the trial.

### 24. Safety reporting

Safety reports from clinical trials are intended to protect trial participants and they must be exact, relevant, and meaningful. Evaluation of adverse effects is essential when monitoring the condition of trial participants and further conducting the safety reporting. Also the provided timeframe for recording adverse effects will affect the results and quality of received data.[80]

### 25. Conflict of interest

A conflict of interest is a situation in which financial or other competing interests for principal investigators, for the overall trial and each study site, have potential to compromise or bias professional judgement on clinical research. All parties involved with the research in question should disclose any conflicts of interest before trial inception.[81]

## 7.4.4. Using ZENODO as the repository for full study protocols, full CSRs, and DIPD

Table 7 presents and compares the main qualities of the online repositories: Dryad, Figshare, and ZENODO. The WP6 assessed and compared all of these repositories, their qualities and settled to recommend that the files of full study protocols, full CSRs, and DIPD should be submitted to the ZENODO repository.

The decision is based on the facts that ZENODO has been launched within an EU funded project and it has a long-lasting sustainability plan for funding and for free access. Thus, it is already a demand for Nordic research funded within Horizon 2020s data pilot to upload data to ZENODO.[64]

ZENODO has been praised for its user-friendly format and for a quick submission process and its connection to CERN spurs on trust to its storage capacity since CERN signals for considerable knowledge and experience in building and operating large scale digital repositories. ZENODO also has a function for closed submission which is an advantage for researchers being worried that their research data would be used before their research has been published. The submitted data can be released to open-access when researchers desire to do so.[82]

**Table 7: Comparison of the three online repositories**

| | Dryad | Figshare | ZENODO |
|---|---|---|---|
| **Specific research area** | Data underlying the international scientific and medical literature. | All fields of science. | All fields of science. |
| **Launched** | 2008 | 2011 | 2013 |
| **Sponsors** | Financial support from members and data submitters. | Figshare is an independent body that receives support from Digital Science. | Launched by CERN under the EU FP7 project openAIREplus. |
| **Digital Object Identifier (DOI)** | Yes | Yes | Yes |
| **Submission fees** | Started to charge submission fees in September 2013. | No | No but for very large amount of data there may be charges in the future. |
| **Registration for an online account** | Yes | Yes | Yes |
| **Access to contents** | Free | Free | Free |
| **Users can upload files in any format** | Yes, also encouraged to include a ReadMe file that provides additional information to make sense of the files. | Yes | Yes |
| **Checking for uploaded contents** | Basic checks on each submission. | N/A | Basic checks on each submission. |
| **Maximum file size** | 10 GB | Unlimited storage space for research. | 2 GB files and several files can be submitted. |
| **Private space** | No | 1 GB | Allows closed access uploads. |
| **Language** | All submissions must be in English. | Not specified. | For textual items, English is preferred, but all languages are accepted. |

# 8. Discussion

Transparency in clinical research is a hot topic worldwide and policies, regulations, plus other initiatives impacting transparency are already in place. The WP6 states that the major task is to make these initiatives to engage everyone and to set the clinical research in the Nordic countries back on the correct ethical track. The trial registration has been demanded by ICMJE, the Ottawa Group, and the Cochrane Collaboration almost for 10 years now but these policies have not yet succeed to secure all trials to be registered. Relying on the ethical aspects and on the researcher's objective to get a publication, do clearly have only limited power to secure trial registration. The newest initiative, the AllTrials campaign is working on by engaging researchers to sign the petition for all trials registered/all trials reported. The campaign is benefitting from the flourishing social media and the petition has already been signed by 80 000 people.

The enforcement for transparency could be achieved by regulatory roads. Therefore, the international regulations for trial registration and result publication should be brought more forward and all countries which have trial activities should also have regulations securing transparency. RECs in every country should start to demand trial registration as a condition for their approval. The new EU Clinical Trials regulation shows a good example for requiring trial registration for all trial phases as a part of the approval process for new clinical trials on medicinal products. It also demands trial results to be reported within a year the trial has ended as well as making public the full study reports. However, FDAAA 2007 has already been requiring trial registration and reporting since 2007 for all other trials except phase 1 trials but clearly this has not been enough to secure transparency in the USA.[2;52] Hence, The WP6 is stressing that the new EU regulation will likely not bring transparency in clinical research to a desired level.

The new EU regulation covers all clinical trial phases, including phase 1 studies and it has been placed to boost clinical research in Europe.[43] However, the process of the early drug development contains a lot of sensitive information which can be considered as commercially confidential. Outside of EU none of the regulations require publication of phase 1 studies and hence sponsors might start to feel tempted to perform phase 1 studies outside of Europe.[83] This would result in an unfortunate outcome of the new regulation implementation. Therefore, other initiatives demanding publications of

phase 1 studies worldwide would be desired. For example, the ICMJE revised policy in 2007 is an advantage since it is requiring registration of phase 1 studies as well.

Also the registration system for clinical trials still calls for streamlining and more international standardization.[51] ICTRP has set requirements for the WHO primary and partner registries but the AllTrials campaign is stressing that the worldwide proliferation of registries has lead to different requirements and not all of the registries are part of the ICTRP network. This might limit the transparency of registered items and reported results since it is not possible to find all trials that have been conducted on a particular intervention from a single portal, although the trials would have been registered somewhere. In an ideal situation, there would be only one place to register trials worldwide.[51] With keeping this in mind, the WP6 recommendation for registering all trials at the ClinicalTrials.gov would be well founded.

The most efficient way to improve transparency in clinical research is to perform joint work and have building conversations with different stakeholders. Transparency is a topic provoking different opinions depending on what is your role in clinical research. Hence, researchers from academia and industry might have different opinions and values and especially industry has stated concerns for transparency.[73] On the other hand, when patients enroll to a clinical trial, they give consent for clinical research in order to improve their own health or advance clinical knowledge which would benefit society. Hiding the results from a clinical trial is disrespectful towards these patients.

The WP6 came with recommendation ideas on how to improve transparency in the Nordic countries. They touched all four aspects of transparency and brainstormed to give ideas for greater transparency. The recommendation for trial registration in the ClinicalTrials.gov supports improved registration practice for all trial phases but there are some problems which need to be taken into consideration. ClinicalTrials.gov follows FDAAA 2007 and allows registration up to 21 days after the first participant has been enrolled in a trial.[17] For greater transparency, all the trials should be registered before enrolling the first patient and the key protocol items should be at the public domain already at the trial inception. However, in order to get all of the already conducted trials registered, like the AllTrials campaign is calling for, retrospective registration is also important.

Moreover, this recommendation might lead to double registration on medicinal product trials conducted in EU since the information of medical product trials is automatically extracted from the EudraCT to the EU-CTR. If the trial is furthermore registered to ClinicalTrials.gov, the trial will be registered twice and the information might vary between these two registries due to human errors. This also concerns for reporting of the trial results since they will also be extracted to the EU-CTR. With phase 1, device and all other types of trials this is not a problem since EU-CTR does not support registration for these types of trials.

The WP6 recommendation for suggesting extensions to the acknowledged WHO 20 items list is well justified, since that list was set already 10 years ago and the structure and protocols for trials have developed after this. All of these five items have major benefits for registered protocols but also some challenges which need to be taken into account when setting this recommendation into force. The demanded information on trial protocols depends on the local regulations and standards set by the different authorities. For example, detailed information of statistical analysis plan may not always be included in the study application sent to ethical review boards.[76] Furthermore, the quality of the monitoring plan varies between the trial phase, disease being evaluated, the experience level of clinical research associate/investigator, site performance, etc. Disclosing conflict of interest at the data list is important in order to strengthen the decisions made in clinical research. Concerns are growing that financial aspects in clinical research may influence the judgments on the primary interest and goals of medicine. These kind of conflicts may jeopardize the quality of patient care and publics' trust on medicines.[84]

The most recent aspect of transparency is the sharing of full CSRs and DIPD for public. There are well planned initiatives in place looking for best ways to share DIPD that would benefit the society without jeopardising intellectual property rights or patients' privacy. Hopefully, the expected EMA and IOM policies for data sharing in 2015 will present a major leap forward after they have been set into force. The WP6 highlights the importance of sharing DIPD, full study protocols and CSRs, and recommends that ZENODO should be presenting as the main repository for storing these kinds of files. The personal communication with the launcher of ZENODO Lars Holm Nielsen gave a positive impression that ZENODO could develop co-operation with clinical researchers and secure safe storage.

The work with finalising the WP6 report goes on until March 2015 when it will be handed to NTA, and all of the recommendations will be further discussed with the WP6 members.

### 8.1. Limitations

The following limitations are noted for this thesis:
A lot of policies and initiatives affecting transparency are only recently launched and their full effects on clinical research are not yet seen and thus difficult to interpret. Moreover, some of them are still on the planning phase and their positions have not yet been settled before handing in the thesis. Especially the data sharing policy from IOM, which will be settled later in December 2014, could be a valuable reference to interpret how data sharing should be conducted at the Nordic countries. Furthermore, the final WP6 meeting will be in January and the previous recommendations will be discussed again. Hence, some amendments might be expected to the present draft of the report upon which this thesis is based on.

# 9. Conclusion

Existing initiatives and efforts provoking greater transparency are not enough as these recommendations are not completely followed. It seems like more incentives or punishments for non compliance are needed in order to achieve greater transparency. Entrenched habits and fears for open access should be overcome and the new era for transparent clinical research with improved practices should be welcomed with open minds. This includes the sharing of full CSRs and DIPD for public from every conducted trial. The arguments in favour of and against transparency from the academia point of view, build a good foundation for conversations between different stakeholders since transparency cannot be achieved without everyone's contribution. The work of the WP6 is an excellent example of a joint work of countries designing the way towards greater transparency and the suggested recommendations will improve transparency in the clinical research if fully followed within the Nordic countries.

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