

# Transparency and Registration in Clinical Research in the Nordic Countries

By the Nordic Trial Alliance Working Group  
on Transparency and Registration



norden

NordForsk

Transparency and Registration in  
Clinical Research in the Nordic Countries

**Nordic Trial Alliance**  
NordForsk  
Stensberggata 25  
NO-0170 Oslo  
[www.nta.nordforsk.org](http://www.nta.nordforsk.org)

Design: jnd.no  
Printed by: 07 Group

ISSN 1504-8640



# Transparency and Registration in Clinical Research in the Nordic Countries

By the Nordic Trial Alliance Working Group  
on Transparency and Registration

# Table of Contents

<b>Preface</b>	<b>4</b>
<b>The Nordic Trial Alliance Working Group on Transparency and Registration</b>	<b>6</b>
<b>Conflicts of Interest</b>	<b>7</b>
<b>Abbreviations</b>	<b>8</b>
<b>1. Executive summary</b>	<b>16</b>
<b>2. Background</b>	<b>20</b>
<b>3. Introduction to transparency</b>	<b>30</b>
<b>4. International policies and regulations impacting the future of transparency</b>	<b>36</b>
4.1 The Declaration of Helsinki	36
4.2 The Food and Drug Administration Amendments Act of 2007	36
4.3 The European Clinical Research Infrastructures Network (ECRIN)	37
4.4 European Medicines Agency	37
4.5 Horizon 2020	38
4.6 Regulation on clinical trials on medicinal product for human use	39
4.7 EU Regulation for data protection	40
<b>5. Arguments in favour of and against transparency</b>	<b>44</b>
5.1 Arguments in favour	44
5.2 Arguments against	49
<b>6. Does publication of trial protocols or trial results in registers impede journal publications?</b>	<b>54</b>
<b>7. Registries and repositories</b>	<b>58</b>

<b>8. Status of the Nordic countries</b>	<b>62</b>
8.1 Current national procedures for public, prospective registration and reporting of clinical trials of all interventions	62
8.1.1 Available registries	
8.1.2 Other public databases available in the Nordic countries	
8.1.3 What type of research – interventional and non-interventional – is registered?	
8.1.4 When is registration conducted?	
8.1.5 What items are registered?	
8.1.6 The full protocol including statistical analysis plan	
8.1.7 Level of help with registering study and results	
8.1.8 Updating and quality of registered information	
8.1.9 Reuse of information from registries – for what purposes?	
8.1.10 Governance of access to summary results	
8.2 National wishes and foreseeable problems regarding registration of protocols, statistical analysis plans, and reporting of summary data	67
8.3 Status of Open Access	68
8.4 Current national procedures for public upload of depersonalised or anonymised individual participant data after the report of the trial	69
8.4.1 Registries/data repositories in the Nordics available for individual participant data	
8.4.2 Governance of access to individual participant data	
8.4.3 Requirements and common practices of storage, use, and quality checks of individual participant data	
<b>9. Recommendations for the Nordic countries</b>	<b>74</b>
9.1 Prospective registration and reporting of clinical trials of all interventions	74
9.1.1 Registration	
9.1.2 Summary results	
9.1.3 Full report	
9.2 Public upload of depersonalised (or anonymised) individual participant data after the report of the trial	78
9.3 Illustrations of the proposed processes	80
9.4 Harmonised legislation in the Nordic countries controlling the registration and transparency process	89
<b>10. Future aspects</b>	<b>91</b>
<b>11. Appendices</b>	<b>92</b>
11.1 Appendix 1 – Project plan for the Nordic Trial Alliance Working Group on Transparency and Registration	94
11.2 Appendix 2 – Examples of participant information and consent regarding data sharing	98
11.3 Appendix 3 – Proposal for explanation on transparent data handling in clinical trials	98
<b>12. References</b>	<b>102</b>

# Preface

Patients and societies depend on physicians and other health-care professionals regarding health and disease. Physicians and other health-care professionals depend on results of clinical research described in guidelines, systematic reviews, overviews, and study reports on randomised clinical trials, and observational studies. Authors of guidelines depend on systematic reviews, from reports on randomised clinical trials, and observational studies. Authors of systematic reviews and overviews depend on randomised clinical trials and observational studies. Randomised clinical trials have a central role in the assessment of the benefits and harms of health-care interventions, but observational studies must also be used to assess the harms of health-care interventions. Accordingly, clinical research results from randomised clinical trials and observational studies should be free of error and open for scrutiny. The only way to secure that randomised clinical trials and observational studies are correctly analysed and reported is to allow access to the individual participant data being used in the study. Moreover, such individual patient data also allow the performance of meta-analyses which provide more statistical power and allow for assessment of intervention effects in subgroups of patients, e.g., age, sex, according to disease severity, etc.

Many stakeholders in clinical research have been requesting increased transparency regarding clinical research data for decades. In spite of this, evolution of transparency has been slow. Since the year 2000, more and more clinical researchers, medical journal editors, pharmaceutical and medical devices companies, national and regional governments, charitable foundations, and regulatory agencies have emphasised the need for improved transparency regarding clinical research data.

As part of the Nordic Trial Alliance's (NTA) initiative to increase Nordic collaboration and competitiveness in clinical trials, as outlined by the Nordic Council of Ministers and NordForsk, NTA's Working Group on Transparency and Registration was formed in 2013 (see Appendix 1 on p. 94). The present report represents work conducted by the NTA Working Group from January 2014 to March 2015. In this report, we describe transparency and registration of clinical research data; map and develop 'best practices' for public, prospective registration and public reporting of clinical trials of all interventions; and map and develop 'best practices' for public upload of depersonalised individual participant data after the publication of reports of a clinical trial. Our recommendations represent our attempts to balance the interests of the public; the patients; the trial participants; the trial investigators; the regulatory authorities; and the pharmaceutical, medical devices, and biotechnology industries. By making the Nordic region a leading force in transparency and trial registration, we will consolidate and expand the trustworthiness of clinical research conducted in the Nordic countries. Hereby, we can increase Nordic collaboration and competitiveness in clinical trials in a global context.

We surmise that we have been able to formulate some clear recommendations. However, we are not able to change the applicable legislation or the practices of the stakeholders. Here we need the concerted efforts of academic investigators and their institutions and organisations; politicians; and public officers as well as civil servants. All these bodies need to formulate clear laws, regulations, and guidelines so that the public and patients can achieve the transparency that they deserve. Such laws and regulations must specify that lack of transparency and trial registration is a serious offense and that attempts to re-identify depersonalised (or anonymised) individual participant data are a breach of law, with severe consequences for those responsible. If such legislation is harmoniously adopted by the Nordic countries, and such legislation is followed by clinical researchers and investigators from all backgrounds, the Nordic countries could take the global lead in being the place to conduct trustworthy clinical trials.

Our NTA Working Group on Transparency and Registration consists of representatives from all Nordic countries with different professional backgrounds and experiences. As chair, I thank them all for their hard work and constructive participation in the process of formulating this report. I also warmly thank the academic secretaries, Maria Skoog and Jenna Maria Saarimäki, The Copenhagen Trial Unit, who worked hard with drafting and amending the report according to our suggestions. I also thank Managing Editor Dimitrinka Nikolova, The Cochrane Hepato-Biliary Group, for copy editing.



*Christian Gluud, M.D., Dr. Med. Sci.  
Chair, Nordic Trial Alliance Working Group on Transparency and Registration  
March, 2015*

**Niels Bohr, Open letter to the United Nations, Copenhagen, June 9th, 1950:**

“I turn to the United Nations with these considerations in the hope that they may contribute to the search for a realistic approach to the grave and urgent problems confronting humanity. The arguments presented suggest that every initiative from any side towards the removal of obstacles for free mutual information and intercourse would be of the greatest importance in breaking the present deadlock and encouraging others to take steps in the same direction. The efforts of all supporters of international co-operation, individuals as well as nations, will be needed to create in all countries an opinion to voice, with ever increasing clarity and strength, the demand for an open world.”

# The Nordic Trial Alliance Working Group on Transparency and Registration

## Members

### Denmark:

Maria Skoog, Dr.Med.Sci., Research Associate, The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen.

ms@ctu.dk / +45 35 45 71 65

Jenna Maria Saarimäki, Pharmaceutical Master Student at the University of Copenhagen and The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen.

zrm925@alumni.ku.dk

Christian Gluud, M.D., Dr.Med.Sci., Head of Department, The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen.

cgluud@ctu.dk / + 45 40 40 11 82

### Finland

Mika Scheinin, Professor of Pharmacology, University of Turku, Turku and Turku University Hospital.

mschein@utu.fi / + 35 84 05 01 47 62

### Iceland

Kristján Erlendsson, M.D., Specialist in Internal Medicine, Allergy and Clinical Immunology, Landspítali University Hospital of Iceland, Senior Advisor on Science and Education, Ministry of Welfare, Associate Professor, Associate Dean of Medical Education University of Iceland, Chair of the Icelandic Bioethics Committee, Reykjavik.

krerlend@landspitali.is / + 35 48 24 56 62

### Norway

Steinar Aamdal, M.D., Ph.D., Director of Section for Clinical Cancer Research and Resource Development, and Professor of Oncology, Oslo University Hospital, Oslo.

steinar.aamdal@medisin.uio.no / +47 90 13 86 75

Valentina Cabral Iversen, Ph.D., Associate Professor at St. Olavs University Hospital, Trondheim.

valentina.c.iversen@stolav.no / +47 92 60 75 02

Siv Mørkved, Physiotherapist, Ph.D., Research Director at St. Olavs Hospital, Trondheim, and Professor of Applied Clinical Research at the Norwegian University of Science and Technology, Trondheim

siv.morkved@stolav.no / + 47 97 14 64 90

### Sweden

Maria Englund, Director of Karolinska Trial Alliance, Karolinska University Hospital, Stockholm.

maria.a.englund@karolinska.se / + 46 (0)7 01 68 49 53

Eva-Carin Jacobsson, Clinical Trial Assistant at Karolinska Trial Alliance, Karolinska University Hospital, Stockholm.

eva-carin.jacobsson@karolinska.se

# Conflicts of Interest

Mika Scheinin owns stock and is board member in Clinical Research Services Turku Ltd., a private contract research organisation that carries out phase I-II clinical trials for several Finnish and international pharmaceutical companies. He has received travel support and speaker's fees from Orion Corporation and Pharma Industry Finland. He owns stock in the Swiss drug discovery company Santhera Pharmaceuticals AG. He is listed as inventor on four patents.

Christian Gluud is the Coordinating Editor of the Cochrane Hepato-Biliary Group.

Kristján Erlendsson, Steinar Aamdal, Valentina Cabral Iversen, Siv Mørkved, Maria Englund, Eva-Carin Jacobsson, Maria Skoog, and Jenna Maria Saarimäki have no known conflicts of interest associated with this publication.

There has been no significant financial support for this work that could have influenced its outcome.

# Abbreviations

<b>Anonymisation</b>	<p>A process rendering data in a form which does not identify the individuals and where identification through combination with other data is not likely to take place, i.e., the origin is not identifiable.</p>
<b>Anonymised data</b>	<p>Anonymised data are data from which personally identifiable fields have been removed. These fields include, but are not limited to name, personal ID number, address, telephone number, etc. For anonymised data, there are no legal means by which one can re-identify the data, i.e., there is no key kept by, e.g., a national data archive or other ways to connect such data with an identifiable subject.</p> <p>According to The International Organization for Standardization (ISO) Technical Specification from 2008 “anonymisation” is defined as a “process that removes the association between the identifying data set and the data subject”.</p> <p>According to the European Parliament Resolution, Recital 23, anonymised data are not covered by the data protection of the regulation: “The principles of data protection should apply to any information concerning an identified or identifiable natural person. To determine whether a person is identifiable, account should be taken of all the means reasonably likely to be used either by the controller or by any other person to identify or single out the individual directly or indirectly. To ascertain whether means are reasonably likely to be used to identify the individual, account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration both available technology at the time of the processing and technological development. The principles of data protection should therefore not apply to anonymous data, which is information that does not relate to an identified or identifiable natural person. This Regulation does therefore not concern the processing of such anonymous data, including for statistical and research purposes.”</p> <p>Please also see anonymised individual participant data and depersonalised individual participant data.</p>
<b>Anonymised individual participant data</b>	<p>Anonymised individual participant data are individual records from which personally identifiable fields have been removed. These fields include, but are not limited to name, personal ID number, address, telephone number etc. According to The International Organization for Standardization (ISO) Technical Specification from 2008 “anonymisation” is defined as a “process that removes the association between the identifying data set and the data subject”. For anonymised individual participant data there are no legal means by which one can re-identify the data, e.g., via a key kept securely by, e.g., a national data archive.</p> <p>Please also see depersonalised individual participant data.</p>
<b>BMJ</b>	<p>British Medical Journal.</p>

<b>ClinicalTrials.gov</b>	A registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.
<b>CONSORT</b>	Consolidated Standards of Reporting Trials.
<b>CRISTin</b>	Current Research Information System In Norway.
<b>CRF</b>	Clinical Research Form/ Case Report Form.
<b>CRO</b>	Clinical Research Organisation.
<b>CSR</b>	Clinical Study Report.
<b>Data</b>	Outcomes and information such as demographics, clinical variables, and responses recorded or collected within a clinical research project, necessary to document and support research findings, i.e., the data on which summary statistics and tables are based. Usually this definition does not include laboratory notebooks, preliminary analyses, communications with colleagues, or physical objects, such as x-ray images or laboratory specimens.
<b>DG</b>	Directorate General.
<b>DMP</b>	Data Management Plan.
<b>Depersonalised data</b>	Depersonalised data are data from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive. Please also see anonymised individual participant data as well as depersonalised individual participant data; deidentifiable individual participant data; and pseudonymous individual participant data. In this report, depersonalised data, deidentifiable data, and pseudonymous data mean the same.
<b>Depersonalised individual participant data</b>	Depersonalised individual participant data are individual records from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised individual participant data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive. Please also see anonymised individual participant data as well as de-identifiable individual participant data and pseudonymous individual participant data.
<b>Deidentifiable data</b>	Deidentifiable data are data from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive. Please also see anonymised individual participant data as well as depersonalised individual participant data and pseudonymous individual participant data. In this report, depersonalised data, deidentifiable data, and pseudonymous data mean the same.

<b>Deidentifiable individual participant data</b>	Deidentifiable individual participant data are individual records from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised individual participant data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive. Please also see anonymised individual participant data as well as depersonalised individual participant data and pseudonymous individual participant data.
<b>DOI</b>	Digital object identifier.
<b>DIPD</b>	Depersonalised individual participant data.
<b>DHMA</b>	Danish Health and Medicines Authority.
<b>ECRIN</b>	European Clinical Research Infrastructure Network.
<b>End of study</b>	Last data collection point/visit for the last participant or at a later point in time as defined in the trial protocol.
<b>EUDAMED</b>	European Databank on Medical Devices.
<b>EU-CTR</b>	EU Clinical Trials Register.
<b>EudraCT</b>	European Union Drug Regulating Authorities Clinical Trials.
<b>FDA</b>	Food and Drug Administration, USA.
<b>FDAAA 801</b>	Section 801 of the US Food and Drug Amendment Act of 2007.
<b>FDAAA 2007</b>	The US Food and Drug Amendment Act of 2007.
<b>EFPIA</b>	European Federation of Pharmaceutical Industries and Associations.
<b>ICH-GCP</b>	International Conference on Harmonisation-Good Clinical Practice Guidelines.
<b>ICF</b>	Informed Consent Form.
<b>ICMJE</b>	International Committee of Medical Journal Editors.
<b>ID</b>	Identity or Identifier.
<b>IOM</b>	Institute of Medicine, USA.
<b>IPD</b>	Individual participant data.
<b>ISRCTN</b>	The International Standard Randomised Controlled Trial Number Register.
<b>MRC</b>	Medical Research Council, UK.
<b>Metadata</b>	Data about data, e.g., explanations of units, rows, and columns.
<b>MPA</b>	Medical Products Agency.
<b>NCT</b>	Clinicaltrials.gov registry number for a clinical trial.
<b>NIH</b>	National Institutes of Health, USA.
<b>OECD</b>	The Organisation for Economic Co-operation and Development
<b>Pharmacovigilance (PV)</b>	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

<b>Personal data</b>	Data which relate to an individual who can be identified from those data. Such data may be used to identify that person directly or indirectly through association with other data or information.
<b>PLoS</b>	Public Library of Science.
<b>Protocol</b>	Protocol defines the objective(s), design, methodology, statistical considerations, and the organisation of a clinical trial.
<b>Pseudonymised data</b>	<p>Pseudonymous data are data from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive.</p> <p>According to the European Parliament Resolution, Article 4, 2a, pseudonymised data mean personal data that cannot be attributed to a specific data subject without the use of additional information, as long as such additional information is kept separately and subject to technical and organisational measures to ensure non-attribution.</p> <p>Please also see anonymised individual participant data as well as depersonalised individual participant data. In this report, depersonalised data, deidentifiable data, and pseudonymous data mean the same.</p>
<b>Pseudonymous individual participant data</b>	<p>Pseudonymous individual participant data are individual records from which personally identifiable fields have been removed or depersonalised. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised individual participant data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive.</p> <p>Please also see anonymised individual participant data as well as depersonalised individual participant data and deidentifiable individual participant data.</p>
<b>PRS</b>	Protocol Registration System.
<b>PURE</b>	Capital Region of Denmark's research registration system.
<b>REC</b>	Research Ethics Committee.
<b>Register of clinical trials</b>	A clinical trials register is the formal record of an internationally agreed minimum amount of information about a clinical trial. This record is usually stored in and managed using a database.
<b>Registry of clinical trials</b>	A clinical trials registry is the entity that houses the register, and is responsible for ensuring the completeness and accuracy of the information it contains, and that the registered information is used to inform healthcare decision-making. A clinical trials registry is more than its database.
<b>Registration</b>	Registration of a trial prior to enrolling participants to a publicly accessible clinical trials register.
<b>Reporting</b>	A scientific process addressing the efficacy and safety of an intervention and giving details about the design, methods and results of a clinical trial.
<b>SND</b>	Swedish National Data Service.
<b>Raw data</b>	Is a term for data collected from a source. Raw data has not been subjected to processing or any other manipulation, and are also referred to as primary data.

<b>Source data</b>	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
<b>Transparency</b>	<p>A process with openness and communication, so that it is easy for others to understand and see what has been done as well as what was intended. All information in the EU clinical trials database submitted in the clinical trial application and during the assessment procedure shall be in principle publicly accessible, unless the confidentiality of the information can be justified on the basis of any of the below listed grounds:</p> <ul style="list-style-type: none"> <li>• Protection of commercially confidential information;</li> <li>• Protection of personal data;</li> <li>• Protection of confidential communication between the Member States in relation to the preparation of the assessment report;</li> <li>• Ensuring effective supervision of the conduct of clinical trial by Member States.</li> </ul>
<b>Trial</b>	Any investigation in relation to humans with the objective of ascertaining the safety and/or efficacy of an intervention, and which fulfils any of the following conditions: (a) the assignment of the participant to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice; (b) the decision to prescribe the intervention is taken together with the decision to include the participant in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the participant.
<b>WHO</b>	World Health Organisation.
<b>WMA</b>	World Medical Association.



# 1. Executive summary





# 1. Executive summary

With this report we want to raise awareness of inadequate clinical trial registration and the consequences thereof. We also want to describe the present attitudes and working practices towards clinical research registration and transparency in the Nordic countries and to suggest ways to improve the situation. We also want to identify possibilities to minimise requests for multiple registration and reporting, and to work for an increase in the quality of the registered information and data. By establishing understanding on why registration and transparent reporting, both retrospective and prospective, are required, we hope to be able to lay the foundation for Nordic registration and reporting of clinical research of the highest international standard. Our ambition is to make clinical research conducted in the Nordic region the most trusted clinical research in the world. When patients and their relatives start asking: 'Are any of the positive trials conducted in the Nordic countries? What is the difference in treatment results between trials conducted in the Nordic countries and in other parts of the world?', investments from all over the world can be expected.

Transparency of clinical research should become a global must as it will benefit both patients and health-care providers. We review some of the recent positive developments enhancing and promoting transparency regarding clinical research such as The Cochrane Collaboration's support for prospective registration of clinical trials in 2004, the World Health Organisation's (WHO) guidelines on trial registration, The US Food and Drug Administration Amendment Act of 2007 (FDAAA), the AllTrials campaign in 2013, the Institute of Medicine (IOM) report in 2014 for responsible sharing of clinical trial data, the BioMedBridges recommendations, and the new European Union (EU) Regulation (No 536/2014) on clinical trials on medicinal products for human use.

Furthermore, we describe current national information from the Nordic research community (web searches, personal communications, and our own experiences) on procedures and norms for registration and transparency, to offer better understanding on how this is executed today.. We also requested comments on and attitudes towards registration and transparency from different stakeholders: patient organisations, investigators, and representatives of the pharmaceutical, biotechnology and medical devices industries. Generally, there is a positive attitude towards registration and transparency regarding clinical research.

Pharmaceutical and medical device industries and academic researchers and institutions will need to prepare themselves to meet the new developments of and demands for improved transparency of clinical research and the movement towards data sharing. This entails a large responsibility – which shall not be placed on a single responsible person, unit, or country, but it shall rather be a joint effort from the clinical research community.

Registration serves to build knowledge and availability of ongoing research, to prevent selective reporting and publication bias, and to prevent unnecessary duplication of research. We recommend:

- registration of all clinical trials irrespective of type of intervention, phase, or disease or condition before inclusion of the first participant, including the full protocol, in one of the primary registries approved by the WHO or in the ClinicalTrials.gov registry.
- expansion of the current WHO-defined 20 items of registration to include a monitoring plan, a statistical analysis plan, a data management plan, safety reporting procedures, and conflicts of interest.
- making trial registration a condition for ethical approval.
- better compliance with study reporting practices according to the CONSORT statement.
- making full clinical trial reports and the analysed data sets supporting the results available at the same time.
- public upload of depersonalised (or in exceptional cases anonymised) individual participant data (i.e., the analysed data set as well as essential source or raw data) after publication of the full report of the trial.
- setting up a Nordic transparency council to become a central, trusted public party for keeping the identification key for depersonalised data sets as well as to grant waivers to the general requirement to upload trial results within 12 months as well as the requirement to upload depersonalised individual participant data.
- creation of harmonised legislation in the Nordic countries requiring the posting of a summary of the study results at the site of registration. The legislation should be developed in close collaboration with all stakeholders.
- introduction of harmonised legislation in the Nordic countries in collaboration or as individual nations to govern the suggested steps of trial registration and increased transparency for both investigator-initiated and industry-initiated clinical research.
- legal definition of attempts to re-identify depersonalised or anonymised data as an unlawful act.

## 2. Background

2.1.4

-Type application/soap+xml

Length: 3932

Version: 1.0"?>

soap:encodingStyle="

xmlns="http://192.168.1.100/soap"

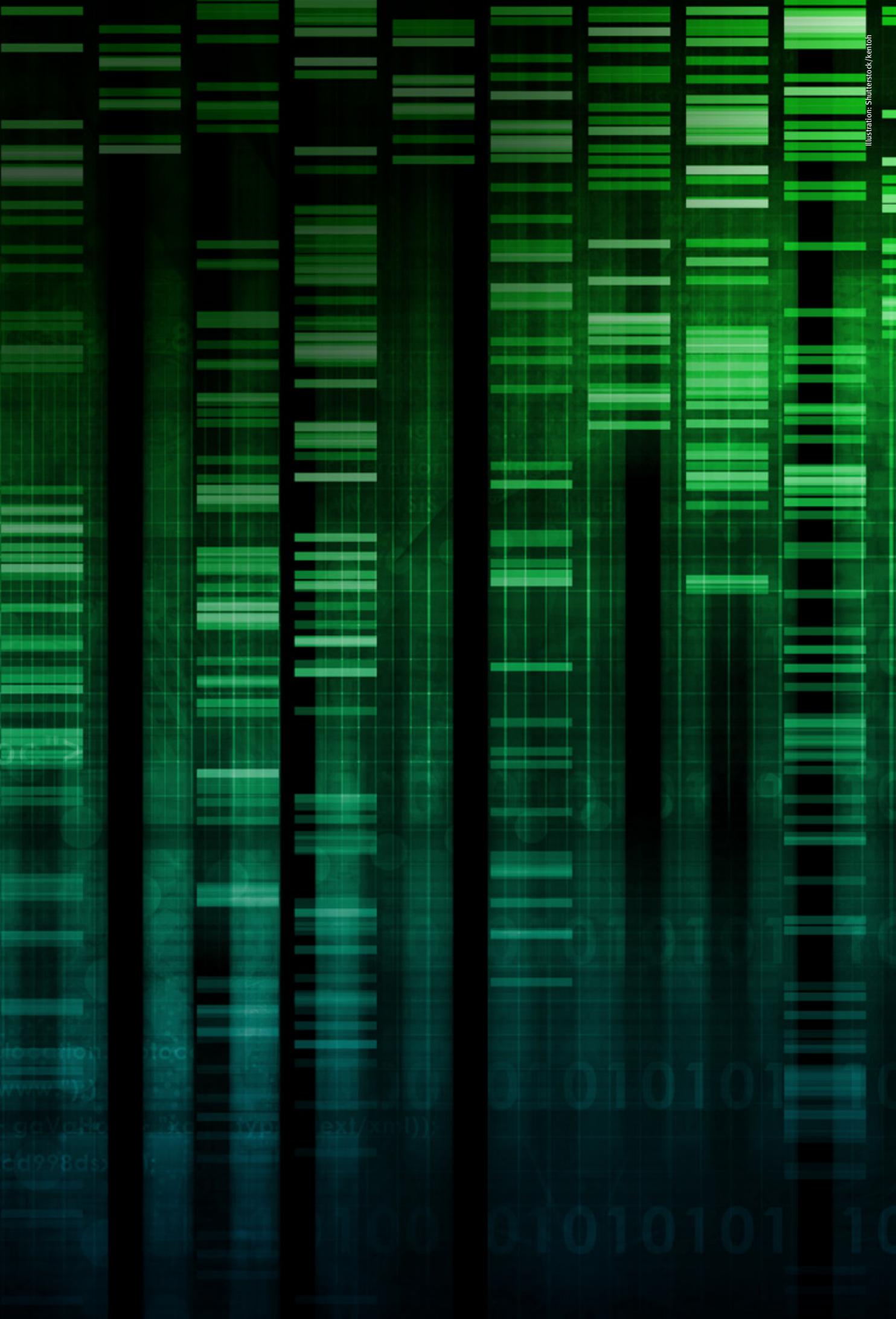
<SecurityArray>

<Password /m:Password>

</SecurityArray>

</Body>

</Envelope>



## 2. Background

Clinical trials are investigations designed to assess the benefits and harms of healthcare interventions. Decisions about healthcare should be based on systematic reviews of all available, relevant evidence in order to be as accurate and valid as possible. Failure to register and report all clinical trials and their results – especially neutral results or harmful effects – means that all relevant evidence is not available.<sup>1</sup> Further impacting the availability of evidence is the lack of registration and reporting of trials conducted prior to the norm of registration that stems from 2004 and the lack of compliance with registering after 2004. Consequently, decisions about healthcare may be based on incomplete, wrong, or biased information. To be able to summarise the evidence on the effectiveness and safety of healthcare interventions, we need to know what trials were launched, how they were conducted, and what their findings were.<sup>2;3</sup>

Inadequate registration of trial protocols, results, and data are feeding the publication bias; results often suffer from selective reporting, in that positive results are more likely to be published more often and more easily while neutral or negative findings are suppressed.<sup>1;3;4</sup> The growing competition within academic environments increases the pressure to produce publishable results, and this pressure results in bias in what gets reported.<sup>5</sup> Thus, when evaluating the evidence, publication bias and other types of bias make interventions look better than they are.<sup>6-8</sup>

As stated by Lemmens and Telfer in the American Journal of Law & Medicine, “A meaningful realisation of the right to health is only possible if healthcare decisions, both at the individual and at the systems level, are built on well-governed and publicly accountable health information systems.”<sup>9</sup>

Systematic reviews of intervention trials summarise the results from randomised clinical trials.<sup>10</sup> Meta-analysis is the main statistical method used in systematic reviews to analyse pooled results of trials.<sup>11;12</sup> Some claim that results of systematic reviews should only be considered observational evidence and hence only hypothesis-generating, and should primarily serve the purpose of designing future randomised clinical trials.<sup>13-16</sup> Other researchers consider systematic reviews with meta-analysis the highest level of evidence to assess the effects of healthcare interventions.<sup>10-12</sup> Studies have, during recent years, clearly shown that results of systematic reviews with meta-analyses of trials are more reliable than the results of a single large trial.<sup>17-22</sup> IntHout and colleagues quantified the error rates for evaluations based on single, conventionally powered trials (80% or 90% power) compared to evaluations based on the random-effects meta-analysis of a series of smaller trials.<sup>21</sup> When a treatment was assumed to have no effect and heterogeneity was present, the error rates for a single trial were increased more than 10-fold above the nominal rate, even for low heterogeneity. Conversely, the error rates for meta-analyses on a series of trials with less power were correct.<sup>21</sup> When selective publication was present, the error rates were always increased, but they still tended to be higher for a single trial than for a series of trials.<sup>21</sup> It also appears intuitively evident that inclusion of all available data from all randomised clinical trials ever conducted shall be treated as a higher level of evidence compared to the data from only a single trial.<sup>10;23-25</sup> Systematic reviews with meta-analyses cannot be conducted with the same scientific cogency as randomised clinical trials with pre-defined high-quality methodology, addressing an *a priori* and quantitatively hypothesised intervention effect.<sup>25;26</sup> Systematic review authors will often know some of the randomised clinical trials before they have prepared their protocol for the systematic review, and hence, the review methodology could be partly data driven.<sup>26</sup> Understanding the inherent methodological limitations of systematic reviews would certainly lead to minimisation of these methodological limitations and optimisation of the review methodology.<sup>26</sup>

The WHO states: “The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility”.<sup>27</sup> Supported by the World Medical Association’s statement of principles for medical research involving human participants, the Declaration of Helsinki, in its latest 2013 revision, states that every investigator running a clinical trial should register the trial and report its results.<sup>2</sup> Even though trial registration has been a requirement – as a prerequisite for publishing the results in a scientific journal – from the International Committee of Medical Journal Editors (ICMJE) since 2005,<sup>28</sup> still, 10 years later, substantially more than one third of all trials conducted have not reported study results after 6 years.<sup>29-32</sup> Nor do most trials subject to mandatory reporting according to FDAAA regulations report their results within a year of completion.<sup>33</sup> The EU has now made it mandatory to report summary data on all clinical drug trials conducted in the community into a public database, including main efficacy and safety results,<sup>34</sup> but not individual participant data. In addition, another summary report understandable to laypersons must be published. It must include the following elements: 1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers); 2. Name and contact details of the sponsor; 3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it); 4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria); 5. Investigational medicinal products used; 6. Description of adverse reactions and their frequency; 7. Overall results of the clinical trial; 8. Comments on the outcome of the clinical trial; 9. Indication if follow-up clinical trials are foreseen; 10. Indication where additional information could be found.<sup>34</sup> It is currently expected that the full implementation of the reporting requirements of the Regulation will start in 2016 or 2017, six months after the new European Clinical Trials database becomes operational.

There are several recent positive examples of international initiatives enhancing and promoting transparency regarding clinical research.

**The Ottawa Group** consists of more than 100 individuals and organisations worldwide who have signed the Ottawa Statement,<sup>35</sup> issued in the autumn of 2005, a consensus document aiming at the implementation of global trial registration. 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.

From the Ottawa Group stems the **IMPACT** (IMProving Access to Clinical Trial data) **initiative**.<sup>36</sup> It aims to define methodologies and develop standards for public disclosure of data of clinical trials, and thus, contribute to the implementation of the Ottawa Statement that calls for public disclosure of participant level data.

**The Cochrane Collaboration**, formed in 1993, is a not-for-profit organisation working as a global independent network of health-care practitioners, researchers, patient advocates, and others from over 120 countries.<sup>37</sup> 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 healthcare. The Cochrane Collaboration conducts systematic reviews of randomised clinical trials of health-care interventions and publishes them online in The Cochrane Library. Its mission is to provide accessible, credible information to support informed decision-making.

The **U.K. Medical Research Council’s** (MRC) policy on research data sharing, published in November 2011,<sup>38</sup> builds on the principles developed by the Organisation for Economic Co-operation and Development (OECD)<sup>39</sup> and applies to all MRC-funded research. Valuable data arising from MRC-funded

research are to be made available to the scientific community in a timely and responsible manner with as few restrictions as possible. The purpose is to maximise the value of the data for research and for eventual patient and public benefit. This policy and guidance were drafted specifically for the population health sciences and population and patient cohorts, but the requirements also readily apply to clinical trials.

The policy specifies the responsibility of the study director or unit director to meet the data sharing requirements for his/her studies. The policy also links to technical guidance for data managers on how to manage data and on available data standards. The policy details, among other issues, that: i) Data-sharing agreements shall be in place before data can be shared. Such agreements must prohibit any attempt to identify study participants from the released data or otherwise breach confidentiality and make unapproved contact with study participants; ii) Data preparation and transfer is the Director's or Principal Investigator's responsibility. They shall ensure that measures are in place to protect the confidentiality of study participants and the security of data sets when they are shared with, or analysed on behalf of, new users, and that practices comply with legal and regulatory requirements, MRC policies and relevant best practice; iii) Studies must document data transfers and ensure that the data and accompanying documentation (metadata) are prepared to the agreed standards.

The **U.S. National Institutes of Health (NIH)** Data Sharing Policy and Implementation Guidance is online and was last updated on March 5, 2003.<sup>40</sup> In NIH's view, all data should be considered for data sharing. Data should be made as widely and freely available as possible while safeguarding the privacy of participants, and protecting confidential and proprietary data. To facilitate data sharing, investigators submitting a research application requesting \$500,000 or more of direct costs in any single year to the NIH on or after October 1, 2003 are expected to include a plan for sharing final research data for research purposes, or state why data sharing is not possible. The policy specifies that the value of data often depends on their timeliness, thus data sharing should occur in a timely fashion. Furthermore, the initial investigators may benefit from first and continuing use of data but not from prolonged exclusive use. The NIH expects the timely release and sharing of data to be no later than the acceptance for publication of the main findings from the final dataset. The NIH recognizes that it takes time and money to prepare data for sharing. Thus, applicants can request funds for data sharing and archiving in their grant application.

The policy details: i) Researchers who seek access to individual level data are typically required to enter into a data-sharing agreement; ii) The procedures adopted to share data while protecting privacy should be individually tailored to the specific dataset; iii) Investigators may use different methods to reduce the risk of subject identification. One possible approach is to withhold some part of the data. Another approach is to statistically alter the data in ways that will not compromise secondary analyses but will protect the identities of individual participants. Alternatively, an investigator may restrict access to the data at a controlled site, sometimes referred to as a data enclave. Some investigators may employ hybrid methods, such as releasing a highly redacted dataset for general use but providing access to more sensitive data with stricter controls through a data enclave; iv) Small Business Innovation Research (SBIR) applicants are also to address data sharing in their applications, but under the Small Business Act, SBIR grantees may withhold their data for 4 years after the end of the award.

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

**The AllTrials campaign** was launched in January 2013 and calls for all past and present clinical trials to be registered and their results reported.<sup>41</sup> The initiative comes from the Bad Science website, the British Medical Journal, Centre for Evidence-based Medicine, The Cochrane Collaboration, The James Lind Initiative, *PLoS*, and the Sense About Science charitable trust, and is being led in the U.S. by Dartmouth College's Geisel School of Medicine and the Dartmouth Institute for Health Policy & Clinical Practice. The current global focus of the AllTrials campaign stresses that all clinical trials, interventional and non-interventional, must be registered and reported, and that this will involve regulators and registries, clinical trial funders, universities and institutes, professional and learned societies and medical journals, patients and researchers, and stipulates thoughts about what needs to be done to achieve these goals.

**The European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA)** as well as **the Biotechnology Industry Organization (BIO)** have released documents signalling their support for sharing clinical trial data.<sup>42;43</sup>

In the U.S., the companies Medtronic and Johnson & Johnson partnered with Yale University Open Data Access (YODA). Medtronic agreed to release all clinical trial data on one of their products widely used in spine surgery, rBMP2, for reanalysis.<sup>44</sup> Johnson & Johnson transferred authority to YODA for making decisions on data requests for all Janssen pharmaceutical trials.<sup>45</sup>

Other moves of the pharmaceutical industry towards greater transparency encompass **ClinicalStudyDataRequest.com**. This site is a multisponsor web system for requesting clinical trial data, launched in January 2014 by GlaxoSmithKline (GSK). Thus far, GSK, Astellas, Bayer, Boehringer Ingelheim, Eli Lilly, Novartis, Roche, Sanofi, Takeda, UCB, and ViiV Healthcare have agreed to release data through the website. According to the 2015 Institute of Medicine (IOM) report entitled 'Sharing Clinical Trial Data – Maximizing Benefits, Minimizing Risks'<sup>46</sup> "the web request system is based on GSK's Clinical Study Requests, which provides de-identified individual participant data from trials on medicines that had received regulatory approval (in any country) or whose development had been terminated. As with the earlier system, ClinicalStudyDataRequest.com requires investigators to submit a research proposal to an independent review panel before access to the requested data is granted. A review panel (1) assesses whether the research proposal has a valid "scientific rationale and relevance to medical science or patient care" and (2) considers the requesters' qualifications (e.g., statistical expertise) and potential conflicts of interest.<sup>47</sup> Once the review panel has accepted a data request and investigators have signed a data sharing agreement, access to individual participant data, analysable data sets, and supporting or metadata documents – including the study protocol, statistical analysis plan, clinical study report, blank annotated case record form, and data specifications – is granted through a password-protected secure Internet connection. Data are not downloadable. Finally, investigators who analyse shared data are required to post their analysis plan publicly, and after the study is completed, to post summary results and seek publication in a peer-reviewed journal.<sup>48</sup>

Recently, the **Institute of Medicine (IOM)**, the health arm of the U.S. National Academy of Sciences, assembled a committee with interdisciplinary expertise and a wide range of backgrounds, the Committee on Strategies for Responsible Sharing of Clinical Trial Data.<sup>49</sup> The IOM wanted to investigate how data from clinical trials might best be shared, and they published a report as a framework for discussion. In the report, they state that "the data sharing movement has gained substantial momentum during the last decade, in both the clinical trial and larger scientific communities." Moreover, "a cultural change has occurred in which the conversation around data sharing has moved from whether it should happen to how it can be carried out".

In the 2015 IOM report entitled ‘Sharing Clinical Trial Data – Maximizing Benefits, Minimizing Risks’,<sup>46</sup> the committee behind the report analyses how key stakeholders (including participants, sponsors, regulators, investigators, research institutions, journals, and professional societies) assess the benefits, risks, and challenges of data sharing, and concludes that all stakeholders have roles and responsibilities in responsible sharing of clinical trial data. The report presents four major recommendations designed to maximise the benefits and minimise the risks associated with data sharing:

- “Recommendation 1: Stakeholders in clinical trials should foster a culture in which data sharing is the expected norm and should commit to responsible strategies aimed at maximizing the benefits, minimizing the risks, and overcoming the challenges of sharing clinical trial data for all parties.
- Recommendation 2: Sponsors and investigators should share the various types of clinical trial data no later than the times specified in this report (e.g., the full analysable data set with metadata no later than 18 months after study completion – with specified exceptions for trials intended to support a regulatory application – and the analytic data set supporting publication results no later than 6 months after publication).
- Recommendation 3: Holders of clinical trial data should mitigate the risks and enhance the benefits of sharing sensitive clinical trial data by implementing operational strategies that include employing data use agreements, designating an independent review panel, including members of the lay public in governance, and making access to clinical trial data transparent.
- Recommendation 4: The sponsors of this study should take the lead, together with or via a trusted impartial organization(s), to convene a multistakeholder body with global reach and broad representation to address, in an ongoing process, the key infrastructure, technological, sustainability, and workforce challenges associated with the sharing of clinical trial data.”

The 2015 IOM report goes on to define what type of data one should share and when one should share these data.<sup>46</sup>

Regarding what to share, the Institute of Medicine report draws the following conclusions:

- For most trials sharing raw data would be overly burdensome and impractical; on a case-by-case basis, however, it would be beneficial to share raw data in response to reasonable requests.
- The risks of sharing individual participant data are significant and need to be mitigated in most cases through appropriate controls. In certain circumstances, the risks or burdens may be so great that sharing is not feasible or requires enhanced privacy protections.
- Sharing the analysable data set would benefit science and public health by allowing reanalysis, meta-analysis, and scientific discovery through hypothesis generation.
- The clinical trial protocol, statistical analysis plan, amendments, and other metadata (see Box) need to be shared along with the analysable data set so that secondary investigators can plan and carry out analyses rigorously and efficiently.
- It is beneficial to share the analytic data set and appropriate metadata supporting published results.
- Sharing the complete clinical study report (CSR) will benefit science and public health by allowing a better understanding of regulatory decisions and facilitating use of the analysable data set.
- CSRs may contain sensitive information, including participant identifiers and commercially confidential information. The risks of sharing CSRs are significant and may need to be mitigated in most cases through appropriate controls.

- Sponsors and principal investigators will decide, on a case-by-case basis, whether they will share data from clinical trials initiated before the recommendations in this report are implemented. They are strongly urged to do so for major and significant clinical trials whose findings influence decisions about clinical care.

**Box on metadata in clinical trials mainly according to the Institute of Medicine report<sup>46</sup>**

- Data sharing plan.
- Clinical trial registration number and data set (available through World Health Organization [WHO] registries).
- Full trial protocol (e.g., all outcomes, study structure), including first version, all amendments, and final version.
- Manual of operations describing how a trial is conducted (e.g., assay method) and standard operating procedures, including names of parties involved, specifically
  - names of persons on the clinical trial team, trial sponsor team, data management team, and data analysis team; and
  - names of members of the steering committee, Clinical Events Committee (CEC, which adjudicates outcomes), and Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), as well as committee charters.
- Details of study execution (e.g., participant flow, deviations from protocol).
- Case report templates describing what measurements will be made and at what time points during the trial, as defined in the protocol.
- Informed consent templates describing what participants agreed to, what hypotheses were included, and for what additional purposes participants' data may be used.
- Full statistical analysis plan (SAP), which includes all amendments and all documentation for additional work processes (including codes, software, and audit of the statistical workflow).
- Analytic code describing the clinical and statistical choices made during the clinical trial.
- Any raw data of central importance to interpretation of the clinical trial results (e.g., a phase II randomised clinical trial in stroke patients uses magnetic resonance imaging (MRI) of the brain for the assessment of the primary or secondary outcome. Then depersonalised MRIs should be uploaded).
- Software program used to make the analysable data sets.
- Detailed instructions on how to download and use the data set.

Regarding when to share, the IOM report draws the following conclusions:

- Once a clinical trial has been completed, a moratorium before the trial data are shared is generally appropriate to allow the trialists who have planned the trial and generated the data to complete their analyses.
- It is reasonable to expect clinical trial data that will not be part of a regulatory application to be available for sharing no later than 18 months after study completion.
- It is beneficial to allow a 'quiet period' while a product or indication is undergoing development for a regulatory application during which the full analyzable data set and metadata need not be shared unless the data are published.
- If a product will continue to be developed by the sponsor or if it is transitioned or licensed to a new sponsor that is pursuing development and approval, it is appropriate to share the post-regulatory data package 30 days after regulatory approval of the product or 18 months after study completion, whichever occurs latest.

- If a sponsor will not be seeking regulatory approval of the new indication for a marketed product for which a trial was intended to be part of a regulatory submission, it is appropriate to share the post-regulatory data package 18 months after the decision has been made definitively to abandon the indication.
- Investigators can help uphold public trust in clinical trials and adhere to current best practices and legal standards by explaining to trial participants what data will be shared with them and with other interested parties and when as part of the informed consent process; and as appropriate, making individual participants' own data collected during the course of a trial available to them following study completion and data analysis.

**Case examples: timeline for sharing clinical trial data, copied from the Institute of Medicine report<sup>46</sup>**

**Case 1. Trial not for regulatory application**

University X conducts a comparative effectiveness trial that is not intended for regulatory approval. The trial starts January 1, 2015, and includes secondary outcomes that are 5 years out, with study completion anticipated January 1, 2020. On July 1, 2018, University X publishes a paper on early outcomes. It should then release the post-publication data package by December 1, 2018. The remainder of the data that constitute the full data package should be released by July 1, 2021.

**Case 2. Regulatory application—approval**

Sponsor Y runs a trial on a drug intended for regulatory approval. The trial is completed on July 1, 2014. Because this is a regulatory trial, the post-regulatory data package should be released 18 months after study completion (December 31, 2015) or 30 days after approval, whichever is later, if the product is approved, or 18 months after product abandonment if the product is abandoned. Sponsor Y publishes an article on the primary outcome of the trial on February 1, 2015. As recommended by the committee, the investigators should then release the post-publication data package no later than August 1, 2015 (6 months after publication). The product is approved on March 1, 2016. The remainder of the data that constitute the postregulatory data package should be released by April 1, 2016.

**Case 3. Regulatory application—abandonment**

Sponsor Z runs a trial on a drug intended for regulatory approval. The trial is completed on July 1, 2014. Because this is a regulatory trial, the post-regulatory data package should be released 18 months after study completion (December 31, 2015) or 30 days after approval, whichever is later, if the product is approved, or 18 months after product abandonment if the product is abandoned. Although results of the initial phase 2 trial ending on July 1, 2014, are encouraging, final analyses of the phase 3 trials reveal new safety issues, and the product is abandoned on August 31, 2017. Sponsor Z publishes an article on December 1, 2017. Sponsor Z should then release the post-publication data package before June 1, 2018. The remainder of the data that constitute the post-regulatory data package should be released by February 28, 2019.

The main leap of transparency could be considered to constitute the publishing of clinical trial data and the sharing of depersonalised participant-level data.<sup>50</sup> Some pharmaceutical companies like Johnson & Johnson, GSK, Eli Lilly, Boehringer Ingelheim, and Bristol-Myers Squibb have already announced to release different amounts of clinical trial data.<sup>51</sup> These initiatives are very welcomed by the authors of this report. However, we question whether these initiatives are sufficient to fully re-establish the trust in the results of clinical trials. First, the companies still play a major role as custodians of the data. Second, there are as a general rule a number of requirements one has to fulfil before one can get access to the data. We find that representatives of the public would be more appropriate in both the roles, both as custodians of the data and as gate keepers.

The AllTrials campaign is putting more pressure on companies and academic trialists to commit to clinical trial transparency. The British Medical Journal (BMJ) has announced that “from January 2013, trials of drugs and medical devices will be considered for publication only if the authors commit to making the relevant anonymised participant level data available on reasonable request”.<sup>52</sup> They also many other journals have adopted this policy. The Cochrane Collaboration is a partner of the AllTrials campaign and supports the free access to all data from all clinical trials.<sup>53</sup> The need for data sharing has also been recognised by a variety of international organisations, research funders, and other bodies, including the OECD, WHO, U.S. NIH, the Bill and Melinda Gates Foundation, the Hewlett Foundation, the U.S. Congress, the European Commission, the European Ombudsman, medical journal editors, the U.K. MRC, the Wellcome Trust, and BioMedBridges.<sup>54</sup>

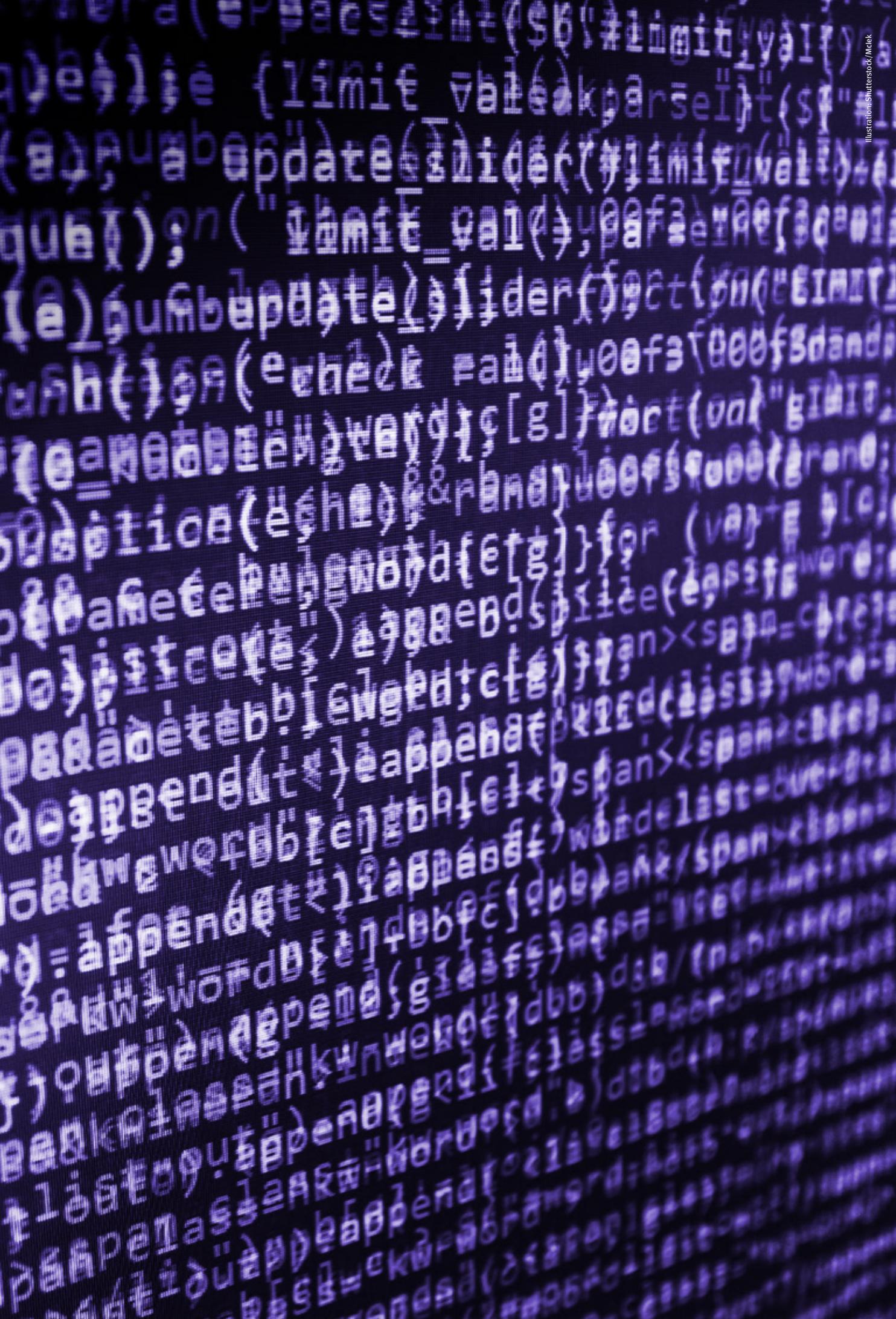
**The BioMedBridges**, constituting of the EU biomedical sciences research infrastructures, have published a position paper on data management and sharing wherein they are supporting the notion that public funders should encourage Open Access to data from their funded research. Also they recognise the importance of having appropriate safekeeping mechanisms in place to secure access under certain conditions for sensitive data or data restricted by intellectual property protection.<sup>55</sup>

Worldwide there is a big momentum in the field of transparency. The Nordic countries need to come up with a unified and active voice in order to be able to influence future data sharing policies and to protect their interests as a strong research region within Europe as well as gain from the profits of transparency worldwide.

Currently, there are actions on securing open access to research results within the Nordic countries. Research institutions are to an increasing extent providing regional and national research registries for ongoing and previously conducted research, but the aim is not to be a trial registry but to give access to the institutions’ research results, mainly in the format of scientific publications. Open access policies are being drafted, considered, and implemented. The current policies mostly concern the publication of results, and discussions regarding open access to participant-level research data are still in their infancy.

Furthermore, the Nordic countries are now facing an opportunity to unify or harmonise their practices and take benefit of each other’s already functioning solutions while implementing the new EU Regulation on clinical research on pharmaceuticals (No. 536/2014) and the upcoming reform of EU’s data protection legislation; the technological progress, such as social networks and cloud computing, and globalisation have profoundly changed the way trial data are collected, accessed and used. In addition, the 27 EU Member States have implemented the 1995 data protection rules (Directive 95/46/EC) differently, resulting in divergences in enforcement. A single EU law on data protection will abolish the current fragmentation and costly administrative burdens. A draft of the EU Regulation on data protection is currently under discussion.

### 3. Introduction to transparency



### 3. Introduction to transparency

The AllTrials cooperation defines four levels of information in clinical trial registration and reporting:<sup>56</sup>

- (1) Registration: knowledge that a trial is ongoing or has been conducted.
- (2) Summary of results: a brief summary of the trial results.
- (3) Full report: full details of the trial methods and results.
- (4) Data: depersonalised or anonymised individual participant data from the trial.

#### Knowledge that a trial is ongoing or has been conducted

This is the initial registration of a trial that is to be undertaken prior to enrolling participants and in a publicly accessible clinical trial registration site. For this purpose, there are several worldwide registries that are acknowledged by the ICMJE or the WHO as to be sufficient in terms of registered information, according to the WHO 20-items registration data set (see Table 1). It is stated the registries shall be independent of for-profit interests.<sup>57</sup> Retrospective registration of already conducted trials is also vital, or else information and results and data from past trials will be lost for the global community.

The most commonly used register within the Nordics is [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). [ClinicalTrials.gov](http://ClinicalTrials.gov) allows registration of both interventional and non-interventional studies, and for clinical trials of medicinal products, the EU Clinical Trials Register has been an option since 2011.

The AllTrials campaign stipulates that trials that for whatever reason have not been prospectively registered shall be retrospectively registered. This is particularly important for a trial that evaluates the benefits and harms of interventions that still are in use within our healthcare systems.

**Table 1. WHO 20-items Trial Registration Data Set<sup>58</sup>**

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

## Reporting a brief summary of the trial results

All trial results need to be reported to the regulatory authorities within a year after completion of the trial. Generally, these summary reports of outcomes are not publicly available. Most trial results are made publicly available at the summary level through publication in a peer-reviewed international journal. Due to hard publication competition and selective bias mechanisms of authors, and in particular for trials with negative or inconclusive results, many trials do not get published in international journals.<sup>1</sup> An alternative here is to report on a summary level through publicly accessible clinical trial registration sites, where the trial was registered. Since there is no peer review of this information, other quality assurance systems should be in place.

## Reporting of full details about the trial methods and results

Full reports compile the methods, the statistical analysis plan, the results of all predefined outcomes including adverse events, and the trial conclusions. These reports usually follow ICH-GCP guidelines<sup>59</sup> and are produced for regulatory and medical industry licensing purposes. Equivalent publications, usually complying with the 20 items of the CONSORT statement,<sup>60</sup> can be found in peer-reviewed international journals. These reports or publications of clinical trial results shall be made publicly available as soon as possible after completion of the trial. Personal information of any kind regarding trial participants shall not be included in the publicly available reports, for example any narrative descriptions of adverse events should only be obtainable to researchers upon request, and even then privacy must be respected.

## Individual participant data from the trial

All participant-level data collected in a trial are seldom reported, and thus, the data remain unavailable to outside researchers and the public. This could be data in fully analysable data sets, data from a clinical study report (CSRs), but also the individual participant data in a depersonalised or in exceptional cases in an anonymised form (see Table 2 for types and description of data).

In 2012, the UK Information Commissioner's office published a code of practice for anonymisation: managing data protection risk that is stipulating how to address the issue of anonymisation also including examples and case studies.<sup>61</sup> Depersonalisation or anonymisation processes are not to be taken lightly because they may often be shown to be incomplete or unsuccessful. The Information Commissioner's office view is that where an organisation collects personal data through a re-identification process without the individuals' knowledge or consent, it is obtaining personal data unlawfully.<sup>61</sup> Sharing of depersonalised individual participant data is to be considered vital for independent reanalysis of trial results and for meta-analysis in systematic reviews. Such depersonalised individual participant data may furthermore serve to answer questions beyond the original trial hypotheses and inspire additional research to develop new preventive methods, diagnostic tools, and therapies. The BioMedBridges, constituting the EU's biomedical sciences research infrastructures, has published a position paper on data management and sharing wherein they recommend that proposals for publicly funded research should have a data management plan describing specific resources and activities concerning deposition of data in long-term archives.<sup>55</sup>

Anonymised data may have limited value in the long run, if linking to health registries or direct contact to trial participants later becomes of urgent interest, and the preference should therefore be depersonalised or deidentified or pseudonymised data, where a trusted public party can be the governor of the key for identification. Such urgent interests could, e.g., arise if late serious adverse events seem to occur in connection with an intervention.<sup>62</sup> In such situations, access to individual personal data can determine which interventions should be allowed to stay on the market and which products need to be urgently removed.

**Table 2. Description of types of data.**

<b>Raw data</b>	Such data may or may not be valuable in public databases. In case source data or raw data are central to the interpretation of the results of a clinical trial, then such data ought to be uploaded.
<b>Analysed data</b>	Such data or data sets ought always to be uploaded.
<b>Personalised data</b>	Must never be uploaded to protect the confidentiality of trial participants.
<b>Depersonalised individual participant data</b>	Depersonalised individual participant data are individual records from which personally identifiable fields have been removed. These fields include but are not limited to name, personal ID number, address, telephone number, etc. Such data look like anonymised individual participant data, but should it be required to link the data with the person from whom the data originated, this would be possible via a key kept securely by, e.g., a national data archive.
<b>Deidentified individual participant data</b>	Same as depersonalised individual participant data.
<b>Pseudonymised individual participant data</b>	Same as depersonalised individual participant data.
<b>Anonymised individual participant data</b>	Should only be uploaded in exceptional cases where the risk of identification is substantial.

#### 4. International policies and regulations impacting the future of transparency





## 4. International policies and regulations impacting the future of transparency

### 4.1 The Declaration of Helsinki

The Nuremberg Code from 1947 was the first international collection of research ethics principles for human experimentation, the “code of trial conduct”.<sup>63</sup> The ten points of the Code comprise principles such as informed consent and absence of coercion, properly formulated scientific experimentation, and beneficence towards participants.<sup>63</sup> But it is the continuous work and update of the Declaration of Helsinki that sets the current standards for trial conduct.

The Declaration of Helsinki, the Ethical Principles for Medical Research Involving Human Subjects, was first developed by the WMA in 1964.<sup>2</sup> The latest revision (the ninth, since its inception) stems from the 64<sup>th</sup> General Assembly, October 2013 and stipulates that researchers, authors, sponsors, editors, and publishers all alike have ethical obligations with regard to the publication of the results of research.<sup>2</sup> The Declaration request to make results public and all authors to be accountable for the completeness and accuracy of the reporting. Furthermore: “Authors should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available.....Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.”

### 4.2 The Food and Drug Administration Amendments Act of 2007

The Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law 110-85 (signed by President Bush on September 27, 2007) was designed, in part, to improve transparency of clinical research.<sup>64</sup> It contains a section on 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 investigation. Generally it concerns trials with pharmaceuticals and medical 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 participant.<sup>65</sup>

FDAAA 2007 also requires submission of certain results data. In order to implement registration of results data, ClinicalTrials.gov launched a clinical trial results database in 2008. The results must be reported within 12 months of the trial 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 prespecified 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 in the ClinicalTrials.gov database.<sup>66</sup>

The ClinicalTrials.gov requires summary information of the trial results without providing individual participant data. ‘Participant flow’ describes the flow of participants throughout all trial stages (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. All anticipated and unanticipated adverse events also must be included when submitting the results of a study.<sup>67</sup>

### 4.3 The European Clinical Research Infrastructures Network (ECRIN)

ECRIN is integrating clinical research in Europe by connecting and coordinating national centres and networks. ECRIN's Scientific Board has the obligation to evaluate all protocols submitted to ECRIN before operational support and management of the multinational clinical trials is possible.<sup>68</sup> ECRIN requires high methodological quality and its acceptance criteria for access to services include requirements for clinical trial transparency:<sup>69</sup>

– *“Commitment to register the trial in a public register before inclusion of the first participant, for example on [www.clinicaltrials.gov](http://www.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.”<sup>69</sup>*

### 4.4 European Medicines Agency

The European Medicines Agency (EMA) assesses safety and efficacy of drugs in Europe. Access to clinical trial reports is given on request as a part of EMA's access-to-documents policy from 2010.<sup>70</sup> In October 2014, the Agency adopted a policy on publication and access to clinical trial data, wherein both on-screen availability (for any user) and downloadable clinical reports (for identified users) are outlined.<sup>71</sup> Furthermore, the Agency states that “the Agency acknowledges that in limited circumstances the clinical reports could contain commercially confidential information, and could, therefore, be subject to redaction prior to publication. Where redaction of commercially confidential information is proposed by the applicant/market authorisation holder, a consultation with the applicant/market authorisation holder will be undertaken, following scrutiny by the Agency of the proposed redaction, including the justification provided by the applicant/market authorisation holder, as to whether the definition of commercially confidential information applies”. Currently, there is no access to source data or raw data, but this topic will be further discussed and subject to public consultation.

The policy will be implemented in two phases:

1. The publication of clinical study data will be restricted to the clinical study reports only.
2. Later on, the Agency will review various aspects of access to individual participant data, in particular, how to submit such data for the purpose of scientific reviews, how to provide access to such data and what are the conditions that need to be fulfilled for accessing the data.

EMA will set the policy into force by a stepwise approach. In January 2015, it became valid for clinical data contained in marketing authorisation applications submitted under the centralised procedure, i.e., any new marketing authorisation applications. In June 2015, the policy will also apply to clinical data contained in extension of indication applications and line extension applications. For all other post-authorisation procedures, the valid date will be decided later in 2015. Thus, the new policy does not apply to clinical data held by the EMA for applications submitted before 1 January 2015 nor to clinical data held by the Agency for non-centrally authorised products. Access to such data can be requested in accordance with the Regulation (EC) no. 1049/2001 regarding public access to European Parliament, Council and Commission documents.

Furthermore, the policy will be revised no later than 18 months after it has come into effect in order to take into account and review the attained experience.

In September 2014, the oversight and responsibility of the EMA was about to be moved from the Directorate General (DG) Health and Consumers to DG Enterprise and Industry. This created concerns of conflicts of interest since DG Enterprise and Industry's mandate is to promote business, and this move was seen to possibly put patients' safety at risk. In November 2014, the new EU Commission was forced by the EU Parliament to let EMA stay in DG Health and Consumers, but the Commission announced that EMA in the future will be guided by both DG Health and Consumers and DG Enterprise and Industry. The full consequences of this move are still unknown.

#### **4.5 Horizon 2020**

Horizon 2020 is the EU's Research and Innovation funding program (2014-2020) for research, technology, and the environment. The Commission is "leading by example" with its approach to open access in Horizon 2020 and the pilot program on open access to and re-use of research data generated in the data pilot (see below).<sup>72</sup> The Commission highlights that one way to enhance economic performance and improve capacity to compete through knowledge is to provide wide, fair, sustainable, and easy access to publicly funded research. The defined roads for open access are 'green open access' (self-archiving with immediate or delayed open access) and 'gold open access' (publisher is providing immediate open access).

The open research data pilot is an innovation of Horizon 2020 and has been running since 2008.<sup>73</sup> It applies to two types of data: "The data that include associated metadata, needed to validate the results presented in scientific publications as soon as possible" and "other data that also include associated metadata, as specified and within the deadlines laid down in a data management plan (DMP)." Projects participating in this pilot are required to deposit their data, if possible, to a data repository, 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 on a voluntary basis as 'opt in' and will receive the same kind of support as the other projects. Projects are, however, allowed to 'opt out' from the pilot in cases of conflict with obligations to protect results, confidentiality, or data security and with rules to protect personal data.

## 4.6 Regulation on clinical trials on medicinal products for human use

On the 16<sup>th</sup> of June 2014, the new EU Regulation (Regulation (EU) No 536/2014) on clinical trials on medicinal products for human use entered into force,<sup>34</sup> and will be fully applied no earlier than 28<sup>th</sup> May 2016 but at the latest six months after the new information systems (the EU Portal and the EU Clinical Trials Database) are operational. According to the new Regulation, the Agency shall set up and maintain in collaboration with the Member States and the Commission a user-friendly EU portal at the Union level where information about planned and conducted clinical trials must be registered. The Agency shall also establish a new publicly accessible EU clinical trials database.<sup>74</sup>

The new Regulation highlights that the information from clinical study reports of trials should not be reflected as commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed or the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the decision on the authorisation of a clinical trial, information on substantial modifications of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.<sup>34</sup> The regulation requires that before the trial has begun, it must be registered in a publicly accessible WHO-accepted register. 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. The items required in this Summary of Results are listed in Annex IV of the Regulation.<sup>34</sup> Also to be included is another summary of the results that is understandable to a layperson. This layperson summary shall contain information on the following: 1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers). 2. Name and contact details of the sponsor. 3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial, and an explanation of the reasons for conducting it). 4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria). 5. Investigational medicinal products used. 6. Description of adverse reactions and their frequency. 7. Overall results of the clinical trial. 8. Comments on the outcome of the clinical trial. 9. Indication whether follow-up clinical trials are foreseen. 10. Indication where additional information may be found.<sup>34</sup> Once a decision on marketing authorization has been granted, the procedure for marketing authorization has been completed, or the application has been withdrawn, full clinical study reports must be made publicly available in 30 days after the above-mentioned milestones. If the sponsor is not able to fulfil these requirements, penalties will be imposed for non-compliance.<sup>74</sup>

All information submitted to the EU portal will be stored in the EU database. The database shall be publicly available unless confidentiality is needed on any of the following matters:<sup>34</sup>

- *Protecting personal data in accordance with Regulation (EC) No 45/2001.*
- *Protecting commercially confidential information, in particular through taking into account the status of the marketing authorization for the medical product, unless there is an overriding public interest in disclosure.*
- *Protecting confidential communication between Member States in relation to the preparation of the assessment report.*
- *Ensuring effective supervision of the conduct of a clinical trial by Member States.*

## 4.7 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 12<sup>th</sup> March, 2014, the EU Parliament voted on and approved the principles of the new EU Regulation (Proposal (EU) 2012/0011 (COD)) for data protection which will update the existing legal principles set in 1995.<sup>75</sup> To become law, the proposed Regulation has to be adopted by the Council of Ministers using the 'ordinary legislative procedure' (co-decision). This Regulation is expected to be adopted in 2015 and then have a two-year enforcement period, with an aim to have better control over people's (patients') personal data. In the future, this regulation will also have an impact on the protection of individual research participant data, consequently affecting the use of data collected in clinical trials.<sup>76</sup>

The European Parliament's committee on Civil Liberties, Justice and Home Affairs (LIBE) has proposed amendments to the articles 81 and 83 in order to tighten the rules that protect personal data.<sup>77</sup> If accepted, these amendments would prohibit or even make it impossible to use depersonalised (or deidentified or pseudonymised) data or identifiable personal data concerning health without specific consent from the participant. Much research involving health-related personal data would become illegal and unfeasible. The suggested amendments are aimed at protecting the privacy of research participants, but such protection is better achieved by strict governance framework by national and/or international laws, such as within the project approval by an independent ethics committee. Discussions and deliberations on this topic are still ongoing.



## 5. Arguments in favour of and against transparency





## 5. Arguments in favour of and against transparency

### 5.1 Arguments in favour

#### i. Participant safety regarding benefits and harms of interventions

The safety of the trial participants and ethical treatment should have priority above all other considerations on clinical research.<sup>78-80</sup> Potential trial participants need to be informed about the trial and need to know the results of other relevant ongoing and completed trials before signing an informed consent. This will only be achieved through greater transparency of methods, results, and data. The transparency should be irrespective of trial phase or whether the intervention is approved for marketing or not. Potential trial participants today seek their own information, and better and more informative registries are an advantage. Furthermore, the potential participants need to know the results of relevant systematic reviews of all conducted clinical trials before they are able to decide on their own participation in a clinical trial. Such systematic reviews inform best on benefits and harms through meta-analyses of individual participant data.

### **Benefits of accessing depersonalised individual participant data in meta-analysis of randomised clinical trials**

Treatment decisions in medicine, whether at the patient or policy level, should consider all relevant healthcare technologies potentially capable of delivering the benefits being sought. Such informed decision-making on the use of competing treatments requires evidence of relative effects from randomised clinical trials included in meta-analyses of systematic reviews.

The appeal of including individual participant data in a meta-analysis is that the statistical heterogeneity is likely to be reduced; individual participant data may also allow subgroup effects to be estimated which in turn could guide more 'personalised' treatment decisions. The use of individual participant data, alone or in combination with aggregate data, has been shown to improve inference in meta-analyses where the outcome of interest is binary (dichotomous) by aiding convergence, and by providing unbiased treatment-covariate interactions (which would otherwise be affected by ecological bias).<sup>81;82</sup> For continuous outcomes, individual participant data are likely to produce more precise estimates of treatment effects, even in the absence of treatment-covariate interactions.<sup>81;83</sup> Individual participant data meta-analysis seems an advantageous methodological approach when subgroup analyses are hypothesized to be clinically relevant. Analysing data of individual participants makes use of a much richer dataset and has greater statistical power than conventional meta-analysis.<sup>84;85</sup> Furthermore, individual participant data meta-analysis allows adjustment of covariates that are known to be important. Such analyses will also enable one to explore clinical, methodological, and statistical heterogeneity more robustly. Individual participant data meta-analysis is an attractive method to answer a clinical question on intervention effects, as such analysis consistently has more power to detect interactions between risk groups.<sup>86</sup> Hence, individual participant data meta-analyses should be regarded as more ethically correct, as they can reduce the need for randomisation of participants in clinical trials. Moreover, this could also lead to less economical waste in conducting clinical trials that only answer parts of the many pertinent questions one may have.

Individual participant data give better utilisation of trial data 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.). Individual participant data 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 trial participants. However, when doing meta-analysis from aggregated trial data, there should also be access to individual participant data coming from all of the included trials. Statistical analyses should be carried out on individual participant data from all trials as meta-analyses of individual participant data coming from a selection of trials is not very useful.<sup>87</sup>

**An example:** In a systematic review of vitamin D supplementation for prevention of mortality in adults conducted by Bjelakovic et al.,<sup>88</sup> it was noted that having access to the individual participant data would have helped to analyse the results gained in this meta-analysis. In the review process, 159 randomised clinical trials were identified. Mortality was reported in 94 trials and nine trials reported mortality but did not report in which specific treatment group the mortality occurred. This is the first issue where analysing individual participant data would have helped to identify the possible effect of vitamin D on mortality. Moreover, the review authors could not identify the importance of daily doses of vitamin D<sub>3</sub>, the influence of sex and age of the participants, the influence of vitamin D insufficiency, dietary habits, sun exposure, or influence of the latitude on the globe. All of these different effects of vitamin D in subgroups would have been easier to identify in the meta-analysis if the individual participant data from the included trials could have been accessed.<sup>88</sup>

The review assessed aggregate data on mortality in randomised clinical trials assessing vitamin D<sub>3</sub> versus placebo or no intervention. Vitamin D<sub>3</sub> was tested in 38 trials.<sup>88</sup> Overall, vitamin D<sub>3</sub> significantly decreased mortality (RR 0.94 (95% CI 0.91 to 0.98); P = 0.002; I<sup>2</sup> = 0%; 75,927 participants; 38 trials). Vitamin D<sub>3</sub> had no statistically significant effect on mortality in the trials that included women only (RR 0.93 (95% CI 0.84 to 1.03); P = 0.16; I<sup>2</sup> = 22%; 53,062 participants; 19 trials). Vitamin D<sub>3</sub> significantly decreased mortality in the trials including both men and women (RR 0.94 (95% CI 0.89 to 0.99); P = 0.01; I<sup>2</sup> = 0%; 22,865 participants; 19 trials). The difference between the estimate of the effect of vitamin D<sub>3</sub> on mortality in the trials including only women and the trials including both men and women or only men was not statistically significant by the test of interaction (Chi<sup>2</sup> = 0.03; P = 0.87). This leaves us with the open questions: does vitamin D<sub>3</sub> affect mortality in women only?; men only?; or in both sexes? This is the second issue where analysing individual participant data would have helped to identify the effect of vitamin D<sub>3</sub> on mortality in different patient groups.

## ii. Knowledge sharing

Registration of trials would enable better communication between researchers and enhance the development of scientific knowledge. Consequently, the volume of productive research could increase, and redundant trials could be avoided.<sup>89</sup> Researchers need all the available evidence on conducted trials regarding methods, results, and data before initiating further trials in order to prevent unnecessary methodological errors, duplication, and risk of causing needless harm to participants. Especially, registration of phase I trials and publication of the results of all clinical trials are essential steps to take to decrease much of the current redundancy, waste, and unnecessary harm.<sup>90-94</sup>

## iii. Research ethical standards

Increased transparency and better quality of trial protocols and trial registration would fulfil ethical standards. The Declaration of Helsinki is stating that investigators conducting research on humans should, prior to initiation of the trial, register the trial and afterwards publish the results of the study. Also, a moral contract between participants and researchers demands transparency regarding clinical research protocols, results, and data. Participants might put themselves at risk when joining a trial in order to improve clinical knowledge, and the absence of full disclosure of both methods and data is disrespectful towards these participants.<sup>95</sup> Furthermore, as a citizen receiving benefits of the healthcare system and demanding better treatments, one should also share the obligation to support the advancement of health-care practices by providing data for research and allow for such data to be shared and used to obtain best possible evidence.

## iv. Ownership

Lack of full disclosure of all trial data represents expropriation of trial participant data. One major reason for people to participate in clinical trials is to advance scientific knowledge, and hence, selection through editing of which data to be published or otherwise reported represents unlawful expropriation. Investigators or industry may own intellectual property related to interventions and should have the opportunity to protect such intellectual property through patenting. Hence, industry or investigators cannot own the results and data from a clinical trial, and they cannot decide when to report or what to report. Participants, investigators, and industry produce the data and the results in collaboration, and therefore, co-ownership can therefore only be achieved through transparent sharing of all data. Access to information about clinical trials, which is a crucial tool for development of pharmaceuticals and medical devices, ought to be recognised as a fundamental component of the right to health.<sup>9</sup>

### **Example from Karolinska Institutet (KI)<sup>96</sup>**

Ultimately, KI is responsible for all research conducted at the university and is the legal 'owner' of the raw or primary data. 'Läraryndantaget' (the teachers' exception) gives researchers at Swedish universities and higher education facilities the right to their own results, but not their own raw data.

## v. Reporting bias

Full transparency would decrease reporting bias. Historically, ‘positive’ clinical trial results are more likely 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 endurance or own bias. As a result, the published clinical trials cannot be considered as representative of the total output of clinical research.<sup>89;97</sup> This leads to major waste in clinical research since efforts and information are hidden and get lost, and this leads to harm for the patients since interventions that might not be as effective as it seems to be from available evidence, end up to be marketed and used.<sup>90-94</sup>

### **Potential consequences of lack of transparency**

In the first phase 1 clinical trial of TGN1412, an anti-CD28 antibody, the results were disastrous.<sup>98</sup> Within 12 to 16 hours after infusion, the healthy volunteers became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. According to present EU legislation, this trial does not need to be registered in a public database, nor are there requirements that the results would need to be reported. Chief Editor J. Drazen from The New England Journal of Medicine asked “would the data have become public knowledge if the volunteers had not been admitted to a public hospital?”<sup>99</sup>

## vi. Healthcare and cost effectiveness

Transparent registration of trial data would lead to improved pharmacovigilance and to an improved balance in assessing the true benefits and the true harms of medical interventions. Secondary analyses and independent verification of original findings are possible with full transparency of data and results in more trustworthy research, and consequently more trustworthy medical interventions. Clinical decision-making on medicines, devices, and all other medical interventions would be able to be improved, and it would lower the amount of unnecessary drugs and other interventions prescribed to patients. In turn, it would also make decisions on reimbursement in healthcare more cost-effective.

### **Paroxetine example from Chan et al.<sup>100</sup>**

Type of biased dissemination: Selective reporting of four positive post-hoc outcomes and suppression of four negative protocol-specified outcomes in highly cited published report of a trial of children with depression. Two trials and two observational extension studies showing increased harm (e.g., suicidal ideation) and poor efficacy in children were not reported. Systematic review showed that balance between risk and benefit no longer favoured the drug when unreported trials were included.

Effects: In 2002, about 900 000 prescriptions (costing \$55 million) were dispensed to children with mood disorders in the USA for a drug with potential harm and poor evidence of efficacy.

## vii. Utilisation

Full transparency of research methods and the data collected can generate and stimulate new uses of such data. In that way, data can benefit more research and generate hypotheses outside its original collection aim. Still a lot of collected data, as well as unused biological material, are kept by investigators and are never used for more than the primary aim of collection.

### **Example from Denmark**

For studies granted funding from The Research Council for Independent Research, there is an obligation to hand over datasets to the Danish National Archives. Within the archive, there are 931 studies classified under health, and in the 2013 statistics, 76 studies were handed out for secondary research purposes. Furthermore, the initiative by the European Federation of Pharmaceutical Industries and Associations (EFPIA) of a gateway for available clinical trial data (running since January 2014) has been facing an increasing request for trial data (personal communication Anders Larsen at meeting in Pharma, Denmark).

## viii. Increased public trust in clinical trial data and in sharing such data

Due to a large number of scandals in which major pharmaceutical companies have been involved,<sup>101;102</sup> the trustworthiness of the pharmaceutical industry and those connected to it is low.

## 5.2 Arguments against

### i. Participant safety regarding risk of re-identification of depersonalised data

Making depersonalised individual participant data available may give rise to the possibility of identifying participants. The fear of being recognised might be relevant in countries with small populations (for example in Iceland) or in trials containing only few patients (trials with rare diseases or involving orphan drugs).<sup>95;103</sup> Such possibilities must be properly prevented via depersonalisation of data which must be required in every ethical code of conduct.

#### **Example from Iceland**

Extensive discussion on how to protect the identity of research participants has taken place especially since the initiation of large scale genetic studies around 1995. The development of a special method to depersonalize the National Personal Identification Number (PIN) has been a technical success and no leak has occurred and nobody has been harmed up to date. This method (software) is authorized by the Data Protection Agency (DPA) and the coding system is based on two keys, one kept by the DPA and the other by the research company, Decode Genetics. An intense discussion is now ongoing on the necessity to find, investigate and advise on treatment and prevention the individuals of the group of 2400 women with BRCA2. With a 13-fold risk of developing breast cancer and an average of 12 year shortening of life expectancy, the pressure is mounting on doing just that. It can be done using together those two keys, and methods are being sought that will combine this necessary task with the rights of participants to know, the duty of the health-care professional to inform and at the same time to honour the wishes of those few who do not want to know, with the permission of the DPA and the Bioethics Committee.

### ii. Knowledge sharing

Transparency regarding trial methods and trial data has raised concerns that ‘your research idea’, ‘your protocol’, and ‘your data’ are being stolen and mined by others. All time and efforts spent in collecting study data can falsely give a sense of ‘my data’; hence, by publishing depersonalised individual participant data one can feel losing potential subsequent hypotheses and interesting results from data mining. Moreover, it can lead to the unintended consequence of discouraging the production of time-consuming data. Furthermore, there are concerns that it may hamper the chances for getting trial results published, and this could impair benefits to industry and academia. This concern seems to be unfounded and is dealt with in depth in Chapter 6.

### iii. Research ethical standards

Current ethical standards only demand sharing of prespecified registered items and summary results. Full protocol registration prior to initiating the trial might generate more challenges and burdens for investigators when there is a need for protocol amendments during a trial. Furthermore, it places demands on the registries to have accessible version control. Most registries are moving towards accommodating summary results for a registered trial. To accommodate large data sets would require electronic data space, extensive quality control of data and metadata, control of depersonalisation or anonymisation, and a legal unit authorised to keep the identification for future use, and it will need security of future readability via file formats.

#### iv. Ownership

Full transparency might put a competitive advantage at risk. By publishing full study protocols and individual participant data, both industry and academia can face the possibility of release of commercially sensitive information which could break intellectual property rights for their interventions.<sup>97</sup> Possible loss of market exclusivity and competitive advantage are concerns.<sup>104</sup> By forcing full transparency of study protocols, we may create a problem with ‘superficial protocols’ used for publication where valuable information is left out in order to protect valuable knowledge (e.g., methods which cannot be patented). The same argument stands for the full transparency of depersonalised data, where datasets can be edited to leave out potential harmful information or potentially profitable data to be used for further data mining.

The competitive advantage should be considered as very important, as it is the driver behind much of the developments in the past as well as in the future. However, neither industry nor academia should be allowed to take ownership of data which trial participants have offered in order to advance knowledge.<sup>46</sup>

#### v. Reporting bias

There is an extensive flow of electronic information, and journals are known to publish also badly performed, badly analysed, and otherwise faulty research.<sup>105</sup> Increasing the pressure on the journals might not necessarily provide better reported studies or fully reported studies. The work burden is heavily increased and may lead to poorly performed and badly reported research.

##### **Potential consequences of transparency**

A recent study, investigating the impact of inclusion of industry trial result registries as source for systematic reviews, showed that as many as 89% (133 of 150) of the reviews did not include data from trial result registries.<sup>106</sup> It was only for 17% (23 of 133) of these trials where additional data could be found in result registries, and inclusion of these data (6 of 133) of the trials. There were two changes in results from statistically non-significant to significant, to the disadvantage of the test drug for both harm and primary outcome; there was one change from statistically significant to non-significant regarding harm, to the benefit of the test drug; there were inconsistencies between the data reported in the trial result registry and that included originally in the systematic review in 7 cases (both primary outcomes and harm).

## vi. Healthcare and cost effectiveness

Major reasons for people to participate in clinical trials are to advance clinical knowledge and to improve future healthcare. If the advancement is not perceived to be for the better, for example less efficacy and more harm is demonstrated, trust in the healthcare system and/or the research system might be damaged. Secondary analyses and independent verification of original findings can be confusing in terms of which of the reports is true or false, or in terms of the conclusion that an intervention neither has benefits nor harms. Also, badly performed secondary analyses may do more harm than good, and the far-reaching consequences and resources spent on defending one against such bad analyses, and the negative media attention it can bring are not to be neglected. Errors of such a character can paralyse the healthcare industry, and the negative consequences ought to be weighed against the consequences of the impossibility to control whether the primary analyses were badly conducted or fraudulently reported. In contrast, if badly performed secondary analyses appear, then full transparency makes it easier and more convincing to rebut such analyses.

Generating data into a format that is sufficient and readable by the public costs money and is time consuming. However, this can be considered as a small cost compared to the total price of developing a new intervention. Controlling the production of expensive research is a necessary part of the clinical research endeavour, and forcing complete disclosure might increase risks in making industrial R&D economically unstable.<sup>95:97:104</sup>

## vii. Utilisation of data

Transparency can raise fears of patient-level information being used for purposes a research participant has not consented to (for example if the data collected from a clinical trial are used later on for developing another intervention). Making use of the data would be problematic if the participant's own ideology or religion does not agree with the new use. Concerns also include whether valid 'informed consent' can be obtained if the research question is not specified to the participant.

Such concerns are real and should be dealt with during the informed consent process. According to the 2015 IOM report, the informed consent process provides an opportunity to obtain the participants' approval for the planned data sharing and the potential future data sharing.<sup>46</sup>

6. Does publication of trial protocols or trial results in registers impede journal publications?





## 6. Does publication of trial protocols or trial results in registers impede journal publications?

Concerns have been expressed that the demand for more transparency may obstruct the possibility for later publication of trial results. According to the International Committee of Medical Journal Editors (ICMJE) (the 'Vancouver Group') this concern is ungrounded.<sup>107</sup>

The ICMJE encompasses 14 official members of the ICMJE (representing the following journals: *Annals of Internal Medicine*, *British Medical Journal*, *Canadian Medical Association Journal*, *Chinese Medical Journal*, *Ethiopian Journal of Health Sciences*, *JAMA (Journal of the American Medical Association)*, *Nederlands Tijdschrift voor Geneeskunde*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *Revista Medica de Chile*, *The Lancet*, *PLoS (Public Library of Science)*, *Tidsskrift for Den Norske Lægeforening*, and *Ugeskrift for Læger*). However, several thousands of journals follow the principles developed by the ICMJE.

In a 2014 report, the ICMJE acknowledges that the FDA Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII) mandates the posting of summary results data for trials, subject to the requirements of Section 801 of the FDAAA 801 in ClinicalTrials.gov. Thus, the ICMJE will not consider result data posted in tabular format as required by ClinicalTrials.gov for prior publication.

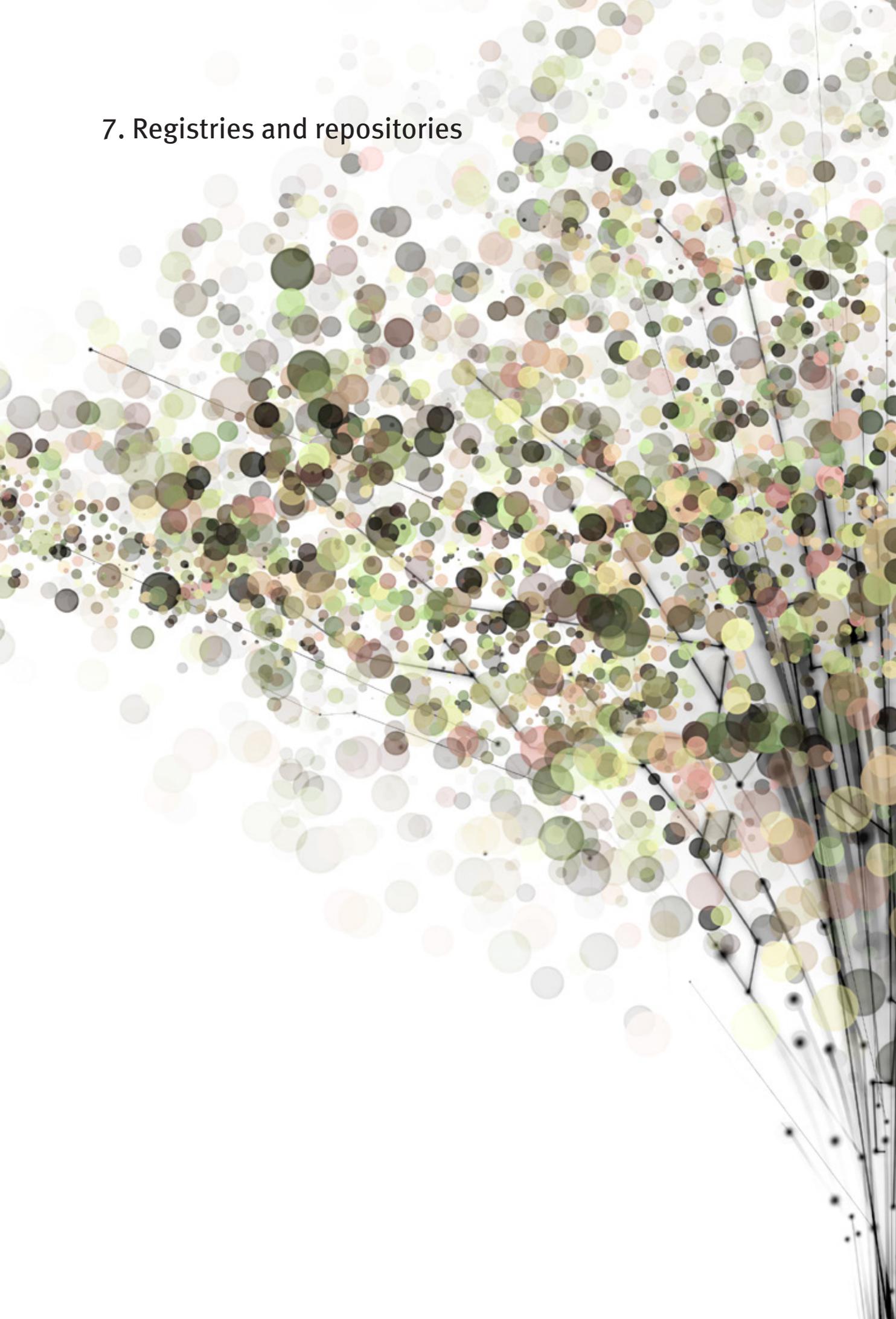
Furthermore, the ICMJE anticipates that the climate for reporting results of registered trials will change dramatically over the coming years, and the ICMJE may need to amend its recommendations as additional agencies institute other mandates related to results reporting. The ICMJE believes that data sharing has the potential to maximise the contributions of trial participants for the benefit of society. The ICMJE believes that sharing of clinical trial data is an integral part of the scientific endeavour by enabling verification of published trials. The ICMJE states that:

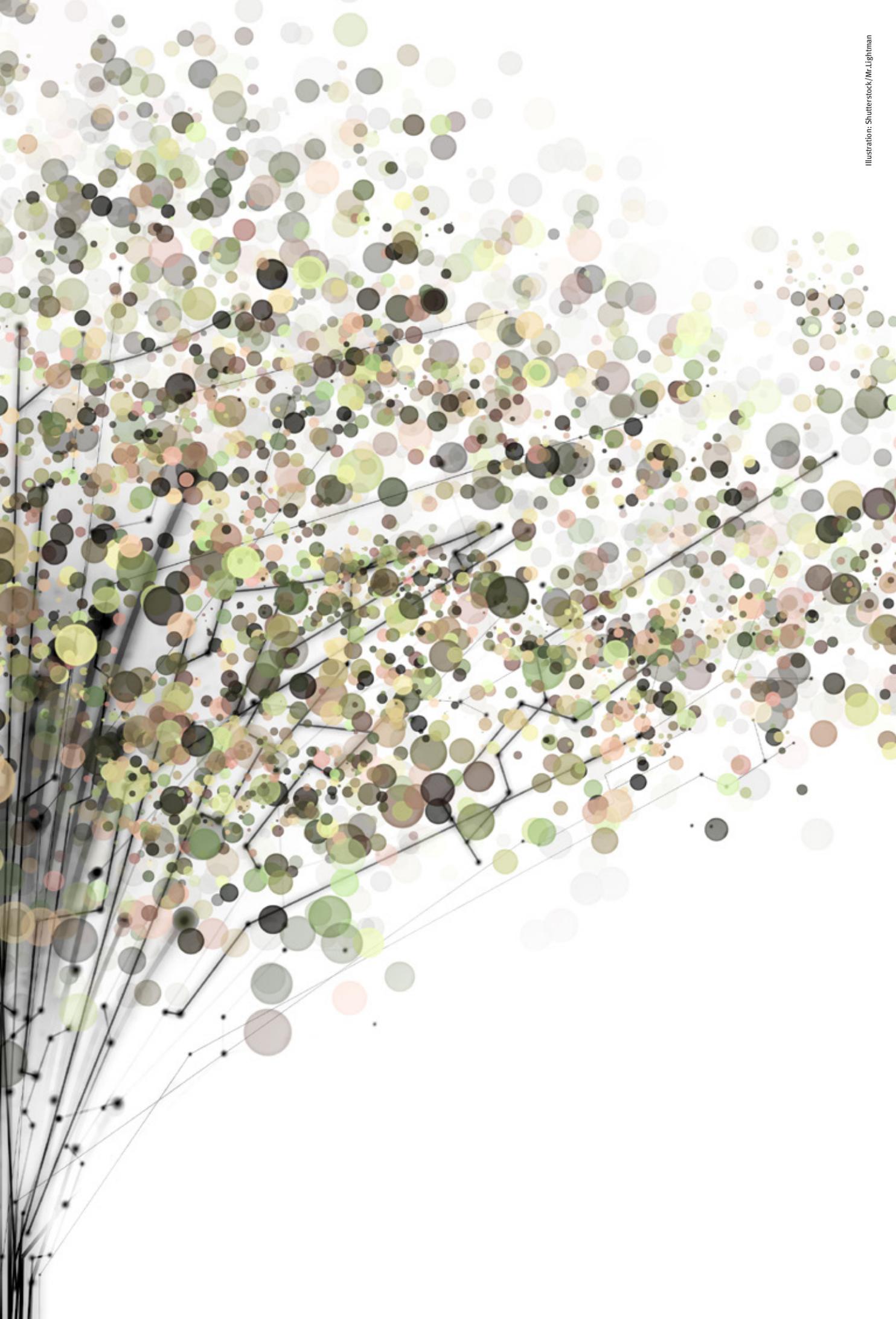
- i. Authors, their institutions, and funders have an obligation to ensure that data supporting the submission of a clinical trial for publication is in a form that can be understood and reanalysed by others.
- ii. Shareable data should include all data that underpin the published results and also data collected on all adverse events (serious and other, whether anticipated or not) until the time of the request.
- iii. Shareable data must be in a format that is readable and sufficient to allow reproduction of the original analysis. It comprises de-identified individual participant data, a data dictionary that specifies the definition of each variable, including how and when it was measured, and the statistical plan and code used to analyse the data. Further work is necessary to begin to define how the quality of shared data is to be maintained (e.g., whether data should remain with the primary investigators, a third party, each requestor, and/or others).
- iv. If journals become aware that data sharing obligations are not being met, journals may choose to investigate, to publish an expression of concern, or in certain cases to retract the publication. Additional stakeholders (e.g., granting institutions) should be encouraged to consider policies aimed at ensuring that data sharing obligation are being met.
- v. Authors and institutional review boards should ensure that the language of participant informed consent documents enables that data are de-identified and can be shared.

- vi. Authors must maintain their data in a shareable state and they should commit to sharing data upon reasonable request. Further work is necessary to plan and establish the secure, reliable and sustainable mechanism(s) by which shareable data will be made available upon reasonable request. Further work is necessary to also define what constitutes a reasonable request according to factors such as the purpose of the requester, the timing (e.g., a defined period following article publication during which authors need not share data), and others. Who is to evaluate whether requests are reasonable also requires clarification.

Some journals are even more progressive. The *BMJ* does not consider posting of protocols or results in clinical trial registries to be 'prior publication'. From January 2013, trials of drugs and medical devices will be considered for publication in the *BMJ* only if the authors commit to making the relevant depersonalised participant level data available upon reasonable request. 'Relevant data' encompass all depersonalised data on individual participants on which the analysis, results, and conclusions reported in the paper are based.

## 7. Registries and repositories





## 7. Registries and repositories

None of the available clinical trials registries currently allow for depersonalised or anonymised individual participant data to be uploaded after study end.<sup>108</sup> Some scientific journals allow for such data files to be submitted and published as supplementary material to a publication in that journal.<sup>109</sup> However, this opportunity can be a disadvantage if the journal ceases to exist, with no permanent curation of its materials, and these data may be lost for the future. Some of the big scientific journals support the uploading of depersonalised or anonymised individual participant data to electronic, publicly accessible, and sustainable repositories at the time of publication.<sup>109</sup>

There are three main electronic publicly accessible and sustainable repositories accepting submission of depersonalised or anonymised individual participant data coming from research from all fields.<sup>110</sup> A digital object identifier (DOI) is assigned to every submission in order to make the storage citable and searchable.

**Dryad** (<http://datadryad.org>) is governed by a nonprofit membership organisation and hosts research data underlying scientific and medical publications. Non-data files may also be submitted to Dryad, provided that the files are integral to the publication and can be released to a public domain. Submission fees are charged depending on institutional memberships or the publishing journal, and researchers based in low-income countries have been offered a waiver for submission fees. Any data format can be submitted, but the material needs to be in English and associated with a publication. Ten GB of material can be submitted within the fee limit, and larger data packages will incur additional charges. The collected data have been placed in custody of the public domain and all contents are free to download and reuse. Use of downloaded data from Dryad must be cited with both the original article as well as the data package. The free access is provided due to financial support from members and data submitters.

**Figshare** (<http://figshare.com>) is supported by Digital Science and allows researchers to publish all of their data in the form of publications and supporting data files. Storage space for free is unlimited for data that are made publicly available on the Figshare site, and in addition, users are offered 1 GB of free private storage space. Any file type can be uploaded as well as file sets (groups of files). Use of downloaded data is free of charge and shall be cited using the associated DOI. Figshare has launched a partnership with PLoS journals to aid the visualisation of different types of data across the PLoS journals and will host the supplemental data for all seven PLoS journals.

**ZENODO** (<https://zenodo.org>) is developed and hosted by CERN, the European Organization for Nuclear Research, and allows publications and supporting data files with data from all scientific fields. ZENODO was launched within the EU funded OpenAIRE project and is using the same cloud infrastructure as the research output from CERN, and it is a well-tested software. Furthermore, ZENODO allows communication with existing online services such as DropBox, and users can also establish communities and share material to the community members. Storage space for free is unlimited for files up to 2 GB and one may upload several files; larger single files can be submitted for a fee. ZENODO allows closed access uploads for data not supported by open access licensing in order to be inclusive. Use of downloaded data is free of charge and shall be cited using the associated DOI.

All of these repositories can facilitate the storing of depersonalised or anonymised individual participant data and meet the criteria for being electronic, publicly accessible, and sustainable repositories. Our choice is to recommend the medical community to use ZENODO as the primary data repository for the Nordic countries for the following reasons: it was launched by the EU-funded OpenAIRE project; it is funded by the EU; and the connection to CERN signals for considerable knowledge and experience in building and operating large scale digital repositories. Moreover, it is open to researchers from all over the world. Accordingly, ZENODO can become EU's gift to the global medical research community in a similar way as USA gave us PubMed.

**Table 3. Specifications of the Dryad, Figshare and ZENODO data repositories**

	<b>Dryad</b>	<b>Figshare</b>	<b>ZENODO</b>
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 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 For very large amounts of data (terabytes or above) 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	Yes	Yes
Checking of 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 uploaded for free – and larger sizes can be arranged.
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. Status of the Nordic countries



## 8. Status of the Nordic countries

### 8.1 Current national procedures for public, prospective registration, and reporting of clinical trials of all interventions

In Norway the research institutes/universities/hospitals have local registration policies for their research.

Sweden reports that commonly there is a recommendation for investigators to examine the requirements journals have for registration; pharmaceutical studies are registered via the EudraCT Database, and other studies are recommended to be registered in a WHO approved database to avoid problems when it is time for publishing. The Declaration of Helsinki is followed as well as the transparency policies of companies.

In Finland, there are no nationally defined common procedures with respect to issues of transparency, and trial registration in biomedical and clinical research. The Finnish Advisory Board on Research Integrity, in its most recent Guideline, “Responsible conduct of research and procedures for handling allegations of misconduct in Finland (2012)” states: *“The researcher complies with the standards set for scientific knowledge in planning and conducting the research, in reporting the research results and in recording the data obtained during the research.”*<sup>111</sup>

In Denmark, the Danish Code of Conduct for Research Integrity,<sup>112</sup> published in November 2014, states: *“All phases of research should be transparent. This requires openness when reporting conflicts of interests, planning of research, research methods applied, results and conclusions”*, and furthermore that *“research results should be published in an honest, transparent, and accurate manner.”*

Iceland reports that institutions generally have in place surveillance activities that document/follow published studies. However, currently there is hardly any active surveillance for follow-up of publishing practices of those granted permission to perform research projects by the Data Protection Agency and the Icelandic Ethical Review Board.

#### 8.1.1 Available registries

ClinicalTrials.gov is the most commonly used registry in all Nordic countries, and it is used for all types of interventions. The Nordic pharmaceutical industry often uses ClinicalTrials.gov for primary trial registration with or without parallel registers on their own websites.

EudraCT (European Union Drug Regulating Authorities Clinical Trials) is the European clinical trials database for pharmaceutical trials launched in the community from 1<sup>st</sup> of May 2004 and registration is mandatory for studies on medicinal products. Information from EudraCT is searchable through the EU Clinical Trial register (EU-CTR), and as of September 2011, this registry is one of the World Health Organisation’s (WHO) primary registers. The EU-CTR register is for interventional medicinal product trials only, and excludes phase I studies.

The International Standard Randomised Controlled Trial Number Register (ISRCTN) is an option for both observational studies and interventional trials that assess the efficacy of health interventions in humans. Due to the extra costs, it is not as frequently used as ClinicalTrials.gov.

The Medical Products Agencies (MPA) register studies on medical devices in their register EUDAMED. This registry is the European databank for medical devices and its use became obligatory in May 2011. This secure web-based portal is working as a central repository for information exchange between the national competent authorities and the Commission in accordance with the Medical Device Directives, but the data are not publicly available. EUDAMED has been created to strengthen the market surveillance and transparency of medical devices.<sup>113</sup>

### 8.1.2 Other public databases available in the Nordic countries

Most Nordic countries have some local or national open archives that entail research activities and facilitate Open Access publishing; however, none of these are acknowledged by the WHO as primary registers.

Sweden reports of the Swedish National Data Service (SND) housed by the University of Gothenburg. The Swedish Research Council has made the SND a national resource for co-ordination of existing and newly established databases within the social sciences, humanities, and health sciences. SND offers support to Swedish research by facilitating researchers' access to data within and outside Sweden as well as offers support for research during the whole research process. The Swedish research council has a database, VR-Proj, for approved projects and funding issues encompassing all funded projects by the council.<sup>114</sup> This database is during 2015 changed into SweCRIS.

In Denmark, public research councils and research funds all advocate a common Open Access policy; research shall be made public in an accessible archive 'online repository', such as the Capital Region of Denmark's research registration system PURE, or via a central database for Open Access journals (e.g., PubMed Central). For access to full articles in PURE, the publisher must allow parallel publication, either by an Open Access policy, or the researcher applies for this right with the publisher.

Within Norway, the national database CRIStin (Current Research Information System In Norway) is available.<sup>115</sup> CRIStin covers research from universities and university colleges as well as institutions and health trusts, and CRIStin was mandated from the Norwegian Ministry of Education and Research and the Norwegian Ministry of Health and Care Services. Furthermore, the Norwegian Department of Health has taken the initiative to collect information about all ongoing clinical trials in Norway to be published at the web site to be available for patients.<sup>116</sup> The database shall be searchable and also contain necessary contact information. Working Groups have been established with the aim of having this up and going by spring 2015.

Iceland reports of important registers, kept by the Directorate of Health (Surgeon General). Various databanks are kept at healthcare institutions, the University Hospital (Data warehouse) in addition to large research institutions such as Decode Genetics, the Icelandic Heart Association, and the Icelandic Cancer Society. Most of these are not publicly available.

Finland did not report on other public databases.

### 8.1.3 What type of research – interventional and non-interventional – is registered?

The requirements for trial registration are interpreted or suggested to apply for all human studies in most Nordic countries (such as Sweden, Norway, and Denmark), but in Finland the requirements only apply to interventional studies.

Sweden reports that non-interventional studies belong to a grey zone whether it is trials, development projects, student work, etc., and some clinical trial centres do not commonly register non-interventional studies. Pharmaceutical companies shall, similar to the corresponding provisions in clinical trials, publish the information in the summary of the study report or publication for non-interventional studies. However, the Declaration of Helsinki is followed, and accordingly, every research study involving human subjects must be registered, and this is strongly encouraged.

The pharmaceutical industry in Denmark reports that all clinical trials conducted with participants (phase I-V), whether they are interventional or non-interventional, are registered, and this commitment exceeds what is required by current law and regulations. Also academia in Denmark is most often following similar registration practices.

However, common for all Nordic countries is that when an Ethical Review Board determines that a study does not fall under its jurisdiction, in other words, is a non-interventional study, it is important to document this, to avoid problems with future publication.

#### 8.1.4 When is registration conducted?

Within all Nordic countries the requirements set by the Declaration of Helsinki and the International Committee of Medical Journal Editors (ICMJE) for trial registration are generally followed in order to avoid future problems with publication. Accordingly, trial registration is taking place before the time of enrolment of the first participant.

In Finland, Sweden, and Denmark, there are no requirements for granting authorisation by authorities, but researchers and sponsors are supposed to provide a statement referring to clinical trial registration upon application, as well as how results will become publicly available.

Iceland reports that trial registration is done with the application to the Bioethics Committee and the Data Protection Agency when applicable. Researchers are expected to send the Committee(s) reports and publications at the finish of the trial. Reports from drug trials are usually from multinational studies and reported as such. This would have to be considered a summary type of a report. It is a huge task to follow in detail whether all obligations are met, but reports of mistakes in research conduct are investigated promptly.

#### 8.1.5 What items are registered?

For all studies registered in the ClinicalTrials.gov or the EU clinical trials register, the protocol items follow the WHO standard 20 items (see Table 1), as a minimum. There are, however, concerns as to whether these two registries can be considered equal, keeping in mind the level of information registered.

ClinicalTrials.gov allows entering summary results into a template by the record holder. Denmark reports that only a minority of the registered studies, in particular the academic ones, have added summary results into the templates. This situation is similar in the other Nordic countries.

Also the EU CTR will include summary results in the near future. The final study report can be uploaded into the registry, and there is a standard for what items need to be reported as results.<sup>117</sup> The sponsor decides who the user of the account is, thus either the sponsor or the investigator can enter this information by themselves. It is believed to be the same procedure for the other Nordic countries as well.

Both the Danish Ethical Review Board and the Competent Authority state that “If results cannot be published in a scientific journal, they shall be made public elsewhere, for example on the ClinicalTrials.gov or the EU CTR”.<sup>118;119</sup>

In Iceland, any practices from the research community for uploading summary results are according to their approved research protocols. In order to seek new grants and submit new grant proposals, the researchers in Iceland need to submit progress reports to the grant keeper.

Norway reports of common practices for the research community on uploading summary results in the national CRISTin database. In Norway, research funders require at the end of a study that a final report is submitted, and the requirements of commercial sponsors depend on each sponsor individually. Also the competent authorities in Norway require annual status updates and a final report of the study, while the RECs require only a final report. The latter two are not publicly available.

Researchers receiving grants from the Swedish Research Council must either publish their results in web-based journals with open access, or they must archive the article in an openly searchable database immediately after, or within 6 months of its publication in a traditional journal. Researchers with grants in educational sciences or humanities and social sciences will have to publish parallel in an open access database within twelve months.<sup>120</sup>

### **8.1.6 The full protocol including statistical analysis plan**

It is not common in the Nordic countries to upload a full study protocol to the registers. The ClinicalTrials.gov, the EU-CTR, or the ISRCTN Register do not support files to be uploaded to their registers.

Denmark reports that for some international journals a full protocol can be attached to a publication, as a file, and it is available as electronic additional material. Also, there is the growing awareness of publishing a design article, i.e., the protocol in a digestible format, and a detailed statistical analysis plan. These are not yet common practices within the other Nordic countries.

Norway reports that it is not possible to upload a full protocol or statistics analysis plan anywhere. Only a summary of the protocol is possible to upload at ClinicalTrials.gov.

### **8.1.7 Level of help with registering study and results**

Among the Nordic countries, clinical research organisations (CRO) give support for registration but at a cost. For trials on medicinal products, the competent authorities help with EudraCT applications and subsequent amendments to it, and also the reporting of summary results.

Sweden also reports that there are support units at the university hospitals which can help investigators with trial registration.

In Finland, the university hospitals have good clinical practice units who will give help upon request.

In Denmark, support can be given by local good clinical practice units as well as a few university hospital-based research units.

In Norway, at the local level, help can be given from applied clinical research departments.

In Iceland, there is help provided for registering summary results.

### 8.1.8 Updating and quality of registered information

The ClinicalTrials.gov, the EU CTR, and the ISRCTN Register checks registered information for correctness and consistency, upon registration and during revisions. There is no information as to whether there is a quality check on any reported summary data. Sweden specifically reports that their competent authority does not quality check the register files that arrive from sponsors, investigators, or CROs before registration. The EU-CTR is updated when a trial is amended following approval of the competent authority (a substantial amendment).

Generally, the response from the Nordic countries confirms that both updating and quality control of registered information is sparsely, if at all existing, within the academia. From the Danish pharmaceutical industry, there is a statement that records are “periodically updated”.

Sweden reports that their requirements follow the International Conference on Harmonization of Good Clinical Practice (ICH-GCP) guidelines, whereas in Norway, there is no quality check of summary results uploaded to the national database CRIStin.

In Iceland, the application forms for the Ethical Review Board are being standardised including quality issues to provide some level of quality check, and all changes in research protocols have to be filed with the Ethical Review Board.

### 8.1.9 Reuse of information from registries — for what purposes?

In Sweden, new studies are checked whether they are already conducted or registered, so no double registration will be performed. In Norway, the units are using information from registers in order to account for the number of projects and doctoral degrees finalised during the year in their units. In Finland, information from registries is used occasionally for monitoring and planning of clinical research.

### 8.1.10 Governance of access to summary results

Generally, access to summary data in registries like ClinicalTrials.gov, the EU-CTR, and the ISRCTN register is not governed, but publicly available.

According to Svensk Nationell Datatjänst (SND), the level of access depends on an agreement between SND and the principal investigator. The Swedish Research Council has been appointed by the government to develop national guidelines for Open Access.<sup>121</sup> This assignment encompasses both research results as well as the underpinning data from publicly funded research. The outcome of the assignment will be reported in 2015. It is stated that these guidelines will give the researchers incentives to deposit and make their data available for others.

## **8.2 National wishes and foreseeable problems regarding registration of protocols, statistical analysis plans, and reporting of summary data**

There are a few comments from Denmark and Sweden regarding ClinicalTrials.gov, stating that it is not easy to use and could be more intuitively organised. Major flaws with ClinicalTrials.gov are that the registered information is not as detailed as it should be. Another problem is that the database is not updated as it should be, and that study results are not entered at the level that is required. Furthermore, a concern may exist as to the upload of data into the custody of a non-European body, and in particular of individual participant data, even if they are depersonalised or anonymised.

It is good that the obligation of compiling the EudraCT application for medicinal product trials is now recognised as trial registration, but are the levels of information in the EU Clinical Trials Register and ClinicalTrials.gov comparable? Denmark commented on the problematic situation with the different level of details, depending on the type of intervention. One remark from Denmark also targeted the peer-review process of journals. It could be improved, since there is too little focus on transparency with regard to the initial aim and design of the trials.

Iceland stresses that the possibilities for uploading full protocols and full statistical analysis plans could be made much better. Furthermore, there is a need for better co-operation and organisation regarding transparency, and including co-operation with other countries.

### **Reporting from Finland states that measures should be taken to:**

- i. increase researchers' awareness of the registration requirements;
- ii. improve the quality of study registration by providing guidance and technical help to researchers by institutional GCP units;
- iii. improve the quality and comprehensiveness of public registration by institutional control of the fulfilment of the registration obligation; currently, registration is far from ideal in terms of data quality and study progress and study results are seldom entered; public registration to the full extent required by international standards should enter the researchers' code of conduct, and failure to register should be considered a breach of research integrity;
- iv. increase the awareness of the general public, the press and funding agencies of the registers, and promote their use as sources of information; remove the legal obstacles of more comprehensive public registration than is now the norm.

### **Concerns were expressed from Finland that one should not:**

- i. go beyond the internationally agreed standards in trial registration and start requiring more than the ICMJE, funding agencies such as the NIH and some other important funding agencies (Howard Hughes, Wellcome Trust, etc.), drug regulatory agencies and the WMA do; this would hamper our researchers' competitiveness and international collaboration;
- ii. come up with requirements that would hurt the Nordic pharma industry or Nordic clinical CROs or clinical researchers performing commercial clinical trials by setting standards that are different from the EU and US pharma industry requirements;
- iii. or establish a Nordic register, but instead, be active in the further development of a common European register.

Norway did not report on this topic.

Consequently, there is a need for 'better' transparency, data need to be comprehensive, correct, easy to handle, and interpreted and reused correctly by others.

### 8.3 Status of Open Access

In 2014, the Swedish Research Council worked out a proposal for Open Access guidelines for scientific publications/artistic works and research data. The proposal, which also contains recommendations on what needs to be further investigated, was submitted to the Government on 15 January 2015. Following feedback from the Ministry of Education, the Swedish Research Council continues to work with the national guidelines.

In Denmark, the Ministry of Higher Education and Science announced in July 2014 a national strategy for Open Access, with a vision to create 100% free access to all research articles from Danish research institutions financed by public or private means by 2022. This can be considered a somewhat low ambition level because of the long transition period.

Denmark speaks of Open Science and promotes open access to peer-reviewed scientific articles and open access to research data; however, no policy on Open Access to data exists yet. There are initiatives from research library communities<sup>122</sup> and universities<sup>123</sup>, and there are requirements for grantees from The Research Council for Independent Research to hand over datasets to the Danish National Archive. The 2013 report of the Danish electronic research library informs that Danish research councils and universities welcome in general data sharing and a national solution to accommodate the data sharing, and also recognises the need for legal clarification concerning access to data.<sup>122</sup>

We sent letters to national patient organisations, the national medical associations and the national industry associations (pharmaceutical, biotechnology and medical devices) to seek a dialogue on the way forward with transparency and trial registration.

Both the Danish Medical Association and the Danish Association of the Pharmaceutical Industry responded very positively and supportively, and stress that the topic is already on their agendas. The Danish Medical Association policy paper further stresses the necessity for sharing data, and their joint statement with the Danish Association of the Pharmaceutical Industry encourages their members to live up to both ethical and legal requirements to ensure registration and transparency regarding clinical trials as well as non-intervention studies.

In Finland, unofficial personal discussions were carried out with representatives of the Finnish Medical Association and some patient organisations. There were no reservations to the proposed principles of increased transparency and trial registration, as long as confidentiality of trial participants is maintained. In discussions with pharmaceutical industry representatives, a concern was expressed that the Nordic countries should not pose additional requirements on data sharing compared to the rest of the world. Such added demands could reduce the attractiveness of the region in global multi-centre trials, as trial protocols, and data management and data sharing policies are written to pertain to the entire trial, and any special requirements posed by individual countries may not be possible to take into account.

In Iceland, the dialogue with the patient organisations is in its early stages, but there is an indirect measure of patient group content, as shown by the willingness to participate in research and often very close interaction by patients and patient groups with researchers and their institutions. There are plans to formalise those interactions under the lead of the Bioethics Committee. The same can indeed be said about the pharmaceutical companies, and the associations of the health-care professionals.

In Norway, letters were sent to a number of different bodies engaged in medical research. The Research Council of Norway responded, and stated that they considered implementing transparency requirements in their contracts with researchers, and asked NTA for suggestions on how to word such requirements in the contracts.

The Swedish Society of Medicine responded positively and supportive and points out that this is an important question.

## 8.4 Current national procedures for public upload of depersonalised or anonymised individual participant data after the report of the trial

In general, there are no specific policies in the Nordic countries regarding upload of depersonalised individual participant data after the report of the study, regardless whether it is an interventional or non-interventional study. This type of data can generate secondary analyses, outside the primary target for data collection, and also confirmatory analyses on the primary target using different or alternative analysis methods. Moreover, such data can become essential for systematic reviews with meta-analyses.

In Sweden, there is a commission from the Government to the Swedish Research Council to develop and manage a database over grant-funded research in Sweden (2012-02-09). This is in co-operation with Svensk Nationell Datatjänst (SND).<sup>124</sup> The goal is to take care of collected data in the best possible way and to provide the possibility for other researchers to use these data and avoid double work. The Swedish Research Council has been appointed by the government to develop national guidelines for Open Access. This assignment encompasses both research results as well as the underlying raw data from publicly funded research. The outcome of the assignment will be reported in 2015. It is stated that these guidelines will give researchers incentives for data deposition and will make their data available to others. The Data Inspection Board has determined that SND does not have the right to maintain registers containing identifiable personal data, i.e., such formats where the code key is still retained by someone. This represents a serious limitation of SND's activities.<sup>125</sup>

The Danish Code of Conduct for Research Integrity,<sup>112</sup> published in November 2014, states: "Data and primary material should be retained, stored and managed in a way that makes them available for use by other researchers. Access should be allowed to the stored primary materials and data, except when this is in conflict with contractual legal obligations or current regulations on for example ethical, confidentiality or privacy matters or intellectual property rights." Although the publication is from 2014, the recommendations already seem outdated.

The Finnish Advisory Board on Research Integrity, in its most recent guideline "Responsible conduct of research and procedures for handling allegations of misconduct in Finland (2012), states: "*The researcher complies with the standards set for scientific knowledge in planning and conducting the research, in reporting the research results and in recording the data obtained during the research.*"<sup>111</sup>

### 8.4.1 Registries/data repositories in the Nordics available for individual participant data

Sweden has reported of an open data archive under development, administered by the SND, a support organisation for Swedish research within the humanities, social science, medicine and health.

In Denmark, the national data bank – the Danish National Archive – is dedicated to the acquisition, preservation, and dissemination of machine-readable data created by researchers from the social sciences and health sciences communities. This includes individual participant-level data for long-term storage. In this way, a researcher can deliver personal data with the code key for indefinite storage by the national archive.

In Iceland, an effort is underway to register, organise, and make useful connections between the multiple databases already existing in the country; the health service databases, the research databases, etc., without physically combining them or putting them under one governance. This calls for tight regulations and use of a coding system as described earlier, defined permission processes, and active surveillance.

Iceland's new law on health research ethics also includes an article on broad consent for retention of biological samples and data, stating in Article 19: "*Broad consent for retention of materials for use in subsequent studies.* Participants' consent may be elicited to retain biological samples and health data for subsequent use in designated scientific research in the health sector. The Bioethics Committee or Health Research Ethics Committee states conditions for the use of broad consent. The committee may also decide that a renewed consent should be elicited, if deemed necessary.

Participants who have given broad consent under para. 1 shall have access to information on what research is being carried out by the principal investigator, institution or company. Participants may refuse use of their materials in specified studies, in which case their use is prohibited.

Biological samples retained under para. 1 shall be permanently stored in a biobank of scientific samples for use under the provisions of the Biobanks and Health Databanks Act.

Health data retained under para. 1 shall be permanently stored in a health databank for use under the provisions of the Biobanks and Health Databanks Act. Participants must be informed of this.

The principal investigator of a study which deposits biological samples in a biobank, or other health data in a health databank, makes an agreement with the management of the bank on arrangements for access to materials for scientific research. It shall be ensured that the use is covered by the participants' consent under para. 1 and is consistent with the Data Protection Act."

Furthermore, the initiative by EFPIA on a gateway for available clinical trial data is aimed at advancing responsible clinical trial data sharing, and came into action on 1st of January 2014.<sup>126</sup> Applications for data are reviewed by independent review groups, and the data are accessed in a secure website where analysis takes place. The results of the analyses are then downloaded, thus data are never released out of the secured environment. Simultaneous access to data from several trials from different companies can be given, all depending on the research question.

Norway, Finland, and Iceland have not reported on any type of national databases or archives that are used or are under development that could facilitate the storage and re-use of individual participant-level data.

#### 8.4.2 Governance of access to individual participant data

In all Nordic countries, personal data are governed by national laws. In Denmark, Sweden, and Finland depersonalised or pseudonymised individual participant data are considered to be personal data to which the EU data protection regulation applies, regardless of who holds the key to such data.<sup>127</sup> This is in contrast to other Member States (e.g., Austria, Germany, Greece, Ireland, Luxembourg, the Netherlands, Portugal, the UK), in which depersonalised or pseudonymised data are considered personal data for those holding the 'key' for identification, but not for those not having access to this 'key'.<sup>127</sup>

### 8.4.3 Requirements and common practices of storage, use, and quality checks of individual participant data

Sweden reports, based on interviews, that most scientists in the universities/hospitals keep their collected participant-level data locally at the unit's servers, not available to others. According to SND, the options for access are depending on an agreement between the SND and the principal investigator. SND can support researchers in uploading of individual participant data, and quality requirements are according to the ICH-GCP. Access to individual participant data from Swedish pharmaceutical companies requires contact to the company.

The Danish National Archive is used very sparsely by Danish academics; they do not report on re-usage of their stored data, but according to a personal communication, reuse was taking place in 76 of 931 health studies in 2013. Data in the Danish National Archive are accompanied by relevant metadata and also allow contact to the primary data provider to allow readability. Access to data is via a request to the Danish National Archive, and if the intention is to publish scientific or statistical results, then the owner of the data shall approve of the access.

There is no information on quality check of data at submission. From the Danish pharmaceutical companies (Leo Pharma, Novo Nordisk), researchers can apply for access to anonymised individual participant data, only after the clinical study report is listed on the corporate website.

Iceland reports that requirements or possibilities for uploading individual participant data (depersonalised) is only through permission by governing bodies (Bioethics Committee), and as needed by an approved research protocol. Help with registering individual participant data can be given at institutional, regional, or national levels. Quality checks of the individual participant data are not performed.

Norway and Finland did not report on uploading of individual participant data.

## 9. Recommendations for the Nordic countries





## 9. Recommendations for the Nordic countries

The Nordic countries' contribution to the global knowledge pool is large, considering that only about 26 million people live in the region. Looking at the number of publications on randomised clinical trials and controlled clinical trials produced per million inhabitants from 1946 to 2005, the Nordic countries are leading (ranking 1, 2, 4, 7, and 13 out of all countries).<sup>3</sup> A recent report from Germany shows that studies from the Nordic countries used in Health Technology Assessment evaluations led the ranking when population size (ranking 1-3, 6, and 9 out of 45 countries), gross domestic product (GDP)(ranking 1, 2, 5, 9, and 14 out of 45 countries), or health expenditure in billion US\$ (ranking 1, 3, 5, 12, and 13 out of 45 countries) were accounted for.<sup>128</sup> Data in this study were from 2006 to 2010. It was stressed by the authors that regardless of the size of a contribution, all countries are dependent on knowledge generated globally. This same pattern was a few years earlier also appearing when contributions to studies used in Cochrane reviews were investigated.<sup>129</sup> When adjusting for population size, the Nordic countries were within the top 10 and when adjusting for spending on research and development and the GDP, the Nordic countries were within the top 15. This pattern was evident when looking at studies within all specialities, and also when looking at complementary and alternative medicine studies. These data are striking as many rich countries showed poorer contribution to the global medical knowledge pool compared to the Nordic countries.

### 9.1 Prospective registration and reporting of clinical trials of all interventions

#### 9.1.1 Registration

Registration serves to build knowledge and availability of ongoing research, to prevent selective reporting and publication bias, and to prevent unnecessary duplication of research.

- We recommend to follow international guidelines and national requirements on trial registration.
- We recommend to register all clinical trials irrespective of the type of intervention, phase, or disease or condition; we stress that trials of all phases, from phase I to phase IV, should be registered; likewise, we recommend also to register non-interventional studies such as observational studies.
- We stress that registration ought to be done before inclusion of the first participant.
- We support retrospective registration and reporting of results in registries. The aim is to bring forward all results and all data from all trials, which will show that the research community is putting an effort to minimise waste and utilise past efforts in the best possible way.
- We recommend the use of ICMJE-suggested registries, i.e., the WHO's primary approved registries and the ClinicalTrials.gov. Registries are a good tool, as they categorise the information from the protocols, making the information searchable.
  - i. Note: there are items in ClinicalTrials.gov that are optional, such as: study start date, intervention model (single, parallel, cross over), number of arms (intervention groups), masking, allocation, study classification (safety, efficacy, bio-equivalence, etc.). Ross et al. concluded that without greater attention to reporting of all data elements, the potential for ClinicalTrials.gov to address selective publication of clinical trials will be limited.<sup>31</sup>
  - ii. The ClinicalTrials.gov is preferred as it is accepting all trials and gives more options of including free text as compared to the EU clinical trials register.

- We recommend, in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline for protocols,<sup>130</sup> expansion of the acknowledged WHO 20 items of registration to also include
  1. Monitoring plan.
  2. Statistical analysis plan (SAP).
  3. Data management plan including open access policy for publication and data (DMP).<sup>131</sup>
  4. Safety reporting.
  5. Conflicts of interest.
  
- i. The above additions can be fitted into the ClinicalTrials.gov record or files uploaded separately to data repositories with a link to it in the trial registry.
- ii. Suggested expansion puts more pressure on the researcher to have these topics in place before launch of a clinical trial. This is the way in which we can rebuild trust of the public towards clinical research, a reassurance that the existence and reporting of important safety, quality, and design features of all trials are disclosed at their inception.
- iii. Considerations for SAP and DMP should be made a stronger requirement for granting funding (e.g., by funding agencies) or demanded from the research institution prior to launch, or by the data protection agencies for the DMP.

**Table 4. Recommended trial registration data set**

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 (SAP)
23.	Data management plan (DMP) including open access policy for publication and data.
24.	Safety reporting.
25.	Conflicts of interest.

- Alongside the recommended expansion of the WHO 20 items into 25 items (Table 4), we recommend also to upload the full trial protocol. The text of the full protocol document is recommended to be uploaded at an electronic publicly accessible and sustainable repository like ZENODO.
  - i. A protocol upload to a repository will generate a DOI, for cross referencing and can be done prior to launch of the clinical trial.
  - ii. Later on, a protocol (or design) publication will generate a publication ID for cross referencing but will most likely be published some time after enrollment has been launched.
- We recommend research institutions to be the gate keepers of such practices. i.e., research institutions need to include standard operating procedures detailing the procedures to be followed in their institutional good clinical research practice guidelines. By assuring that their research is properly registered, they can take advantage of such registries in the recruitment of potential participants. If clinicians and potential participants are able to identify studies that are currently open to recruitment, there may well be increased participation in trials.
- Furthermore, we recommend a most effective way to ensure prospective registration of all trials by making registration a condition for ethical approval. Accordingly, a failure to comply with proper registration should be seen as a breach of a favourable opinion. This condition of the favourable ethical opinion shall be monitored for compliance, and the favourable opinion revoked if failure to register occurs. An example of such mechanism is already in place in the NHS Health Research Authority in the UK.<sup>132</sup>

### 9.1.2 Summary results

Posting of a summary of study results serves to inform of the main results and outcomes of the research as soon as possible and at least within a year after end of the study (defined as last data collection point or visit of the last participant, or at a later point in time as defined in the protocol). This is currently in the EU Regulation No 536/2014 on medicinal products. Our recommendation is that the same procedures must cover all clinical trials, irrespective of the intervention assessed.

- We recommend to follow international guidelines and national requirements: main outcomes shall always be reported to granting authorities within a year after the end of the study.
- We recommend main summary outcomes to be reported together with the entry of registration.
  - i. For a record on ClinicalTrials.gov subject to US law, posting of summary result is a demand. Others using this registry for free should ‘pay’ to the global community by also posting summary results.
  - ii. For a record on the EU Clinical Trials register, posting of summary results by the investigator is mandatory.

- We recommend a harmonised legislation in the Nordic countries demanding posting of summary results at the site of registration. The legislation should be developed in close collaboration with all stakeholders. Its effectiveness must be secured by broad anchoring within the research community. It has been shown that even if posting of summary result for research under U.S. law is a demand, still there is not adequate compliance, and still not after one email reminder.<sup>133</sup> Note: For trials reported in both the EU ClinicalTrials register and the ClinicalTrials.gov, results shall be entered in both places. We advocate that such double registration should become less needed in the future by common standards for transparency as well as linkage between registers.
- We recommend stronger disincentives for not complying with requirements for results reporting. Breaches should be reported to and managed by the bodies mandated to handle cases of alleged fraud and misconduct in science, according to national practice.

### 9.1.3 Full report

Posting of full reports serves to inform in detail of the research methods and results of all pre-specified outcomes. For academic research, this is usually the research results publication, and is completed at the same time as the summary results become available (i.e., within a year after the end of the study).

- We recommend to follow international guidelines on the content of full reports. EMA guidelines for full reports from industry-sponsored research<sup>134</sup>, and CONSORT statements for publications.<sup>135</sup>
- We recommend better compliance with the reporting according to the CONSORT statement,<sup>135</sup> and not to letting the specified journal dictate the content. Even for CONSORT-endorsing journals, compliance with CONSORT is not optimal.<sup>136</sup> Other materials that cannot be covered in a specific journal article shall be uploaded as supplementary data, either with the journal or in a repository, e.g., ZENODO.
- Full clinical trial reports from the industry are extensive documents and the EMA must protect the interests of patients and release all necessary information for a fair assessment of the intervention. We recommend that full clinical trial reports and the analysed data sets supporting the results (see section 9.2.1) are made available as a minimum at the time of reporting.
- Academic researchers must also live up to the same requirements, and put forward all necessary information for a fair assessment of the intervention. We recommend that the analysed data set supporting these results (see section 9.2.1) is made available in an electronic publicly accessible and sustainable repository as a minimum at the time of full reporting, e.g., in ZENODO.
- We recommend parallel upload of additional gained summary results elsewhere (and supporting source data or raw data, see section 9.2.1). For this purpose Clinicaltrials.gov. can be used if the study is registered there, otherwise we recommend that the analysed data set supporting these results is made available in an electronic publicly accessible and sustainable repository (see section 9.2.1), as a minimum at the time of full reporting.
  - i. Clinical trials are usually reported in scientific journals, regardless whether they are from academia or industry, and due to styles, preferences, and space restrictions and limitations, not all results may be reported. Perusing journal publications for such information would be time-consuming and is not productive.
- Uploading additional data to registries is especially important for additional safety data collected. Furthermore, it is vital for trials that are terminated early because these trials do not generally become published in a journal.

## 9.2 Public upload of depersonalised (or anonymised) individual participant data after the report of the trial

Public upload of depersonalised (or in exceptional cases anonymised) data serves to give access to the data supporting the reported results, and additionally, to give access to all other collected data that might not be part of a full report. Furthermore, this serves to generate secondary analyses, and optimal use and reuse of collected resources.

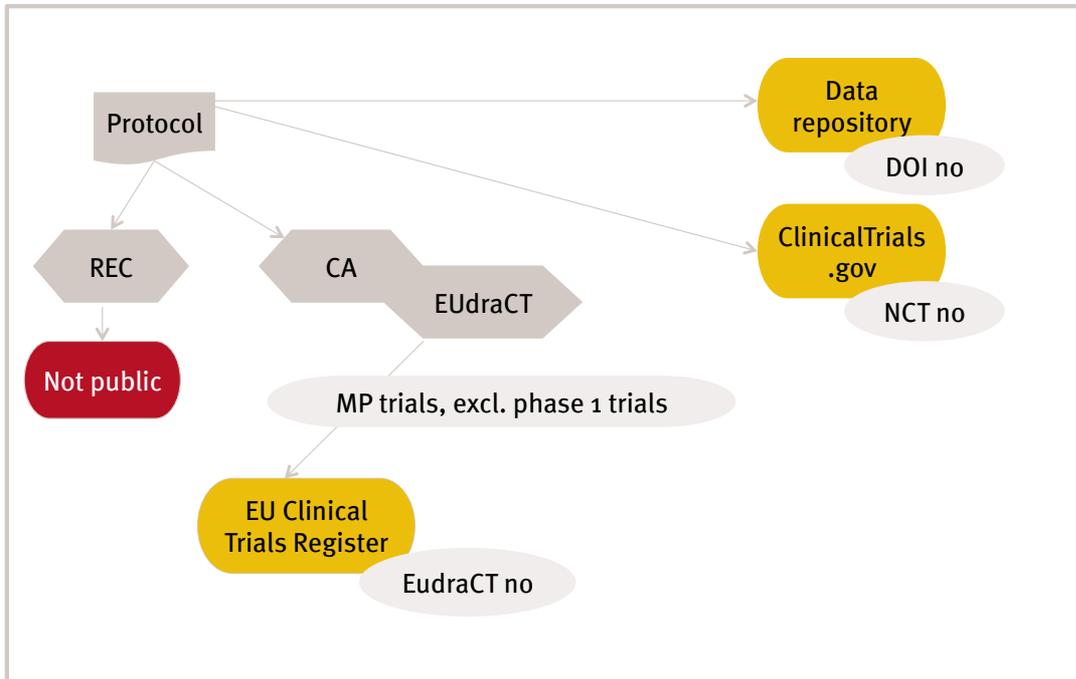
- We recommend to follow international guidelines and national requirements on the topic.
- We recommend upload of depersonalised individual participant data (i.e., the analysed data set as well as essential source data or raw data) after the full report of the trial. For this purpose electronic publicly accessible and sustainable repositories like Dryad, Figshare and ZENODO are available, supporting data from all fields of science.
  - i. Our recommendation is to use ZENODO (see Chapter 8); this platform is used by the European Commission via the OpenAIRE pilot projects, and thus, it is already a demand for Nordic research funded within Horizon 2020's data pilot.
  - ii. An upload of data to a repository will generate an ID/DOI, for cross referencing to other public trial information.
  - iii. Use of deposited data is acknowledged by referencing the ID/DOI of the data.
  - iv. We recommend that any uploaded data shall be accompanied by cross-references to registration information as well as other published material on that research. Likewise, the registry for the research shall also contain a cross-reference to the deposited data.
  - v. We recommend strong incentives and reward systems, such as full academic credit, for sharing data, using shared data, as well as giving feedback regarding re-analysis of shared data.
- We recommend following national requirements and practices for anonymisation and management of data protection risks.
- We recommend research institutions to be the gate keepers of the upload of the analysed data sets as well as essential source data or raw data. Accordingly, such institutions should establish standard operating procedures in their institutional good clinical research practice guidelines. Thus, the institutions gain advantages by having access to other collected data in a structured way.
- We recommend the Nordic countries to set up a Nordic transparency council to become a central, trusted public party for keeping the identification key for depersonalised data sets. This Nordic transparency council can also be the place to apply for waivers to the demand on uploading trial results within 12 months as well as the demand on uploading depersonalised individual participant data. The Nordic transparency council is suggested to contain three members per Nordic country, one representing academics, one industry, and one patient organisations. The cost for running the Nordic transparency council could be covered by fees paid of those applying for waivers.

- An implicit assumption is that data are machine-readable source data or raw data and analysed data sets in a time-secured, reusable format.
  - i. Note: Excel.xls is not a standard file format and does not assure compatibility between versions. Plain text data (ASCII) and Open Document Format (.ods) should be preferred.
  - ii. Considerations shall be made by the researcher/research institution regarding the quality of the collected data, the correctness of the metadata to allow understanding and readability of the dataset, and that depersonalisation or anonymisation is secured.
- We recommend that participant consent for participation in a research study should always include permission to upload of depersonalised individual participant data to an electronic, publicly accessible and sustainable repository. A suggested draft template for participant information and consent regarding data sharing is shown in Appendix 2 and 3.
- We suggest the national data protection agencies in collaboration with the ethical committees take action and strengthen their collaboration on this, and jointly look into the format and security needed for allowing research institutions to upload depersonalised individual participant data.

### 9.3 Illustrations of the proposed processes

For studies on medicinal products, medical devices, and all other interventions (surgery; physiotherapy; nurse interventions; psychology; psychiatry; rehabilitation; nutrition; ergotherapy; etc.), the flow processes of transparency is illustrated at the four levels of transparency as described in Chapter 3: Introduction to transparency.

**Figure 1a. Registration: knowledge that a clinical trial on one or more medicinal product(s) is to be initiated.**

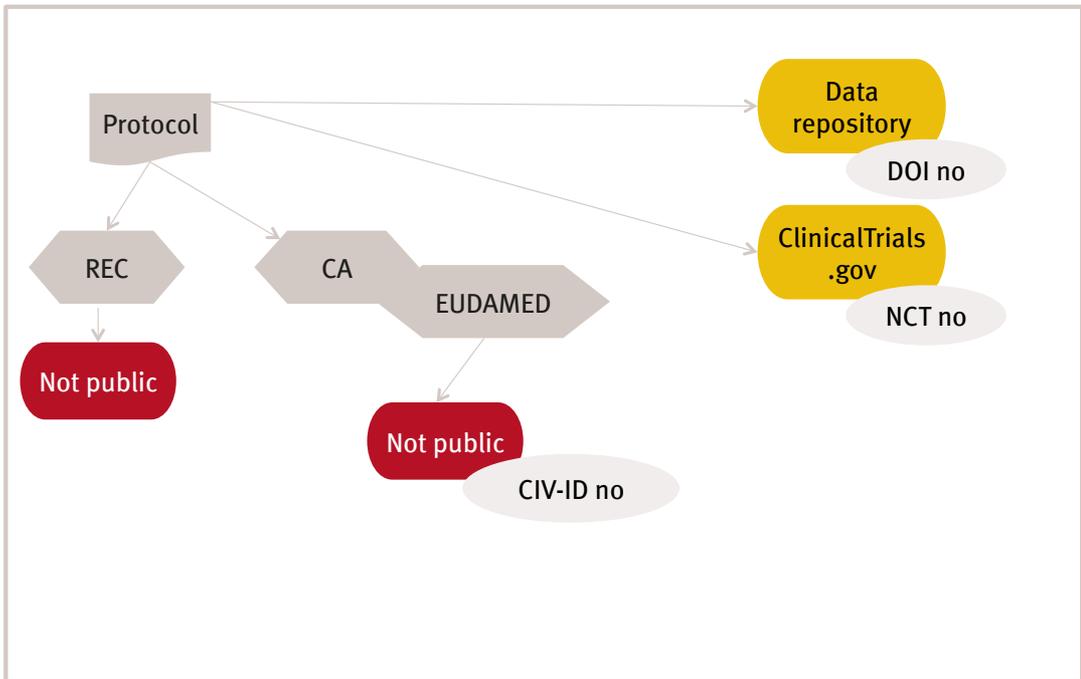


The protocol is approved by an ethical review board (REC) and the competent authorities (CA). The data protection assessment is mostly inherent in the ethical review and for some countries, it consists only of a protocol summary and the data specific procedures. The REC registers are usually not public.

The EudraCT application is a part of the application to the CA and contains selective parts of the full protocol. The approved EudraCT application is publicly available in the EU Clinical Trials Register (EU CTR) with an exception for phase I trials.

A study is registered at ClinicalTrials.gov (containing selective parts of a full protocol) prior to any participants being included. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, in addition, the full protocol text file is uploaded to an electronic, publically accessible and sustainable repository, and may contain the monitoring plan, the statistical analysis plan (SAP), the data management plan including open access policy for publication and data (DMP), the safety reporting, and the conflicts of interest. The study shall cross-reference the EudraCT number, the NCT number (from ClinicalTrials.gov), and the digital object identifier (DOI) number from the repository.

**Figure 1b. Registration: knowledge that a clinical trial on one or more medicinal device(s) is to be initiated.**

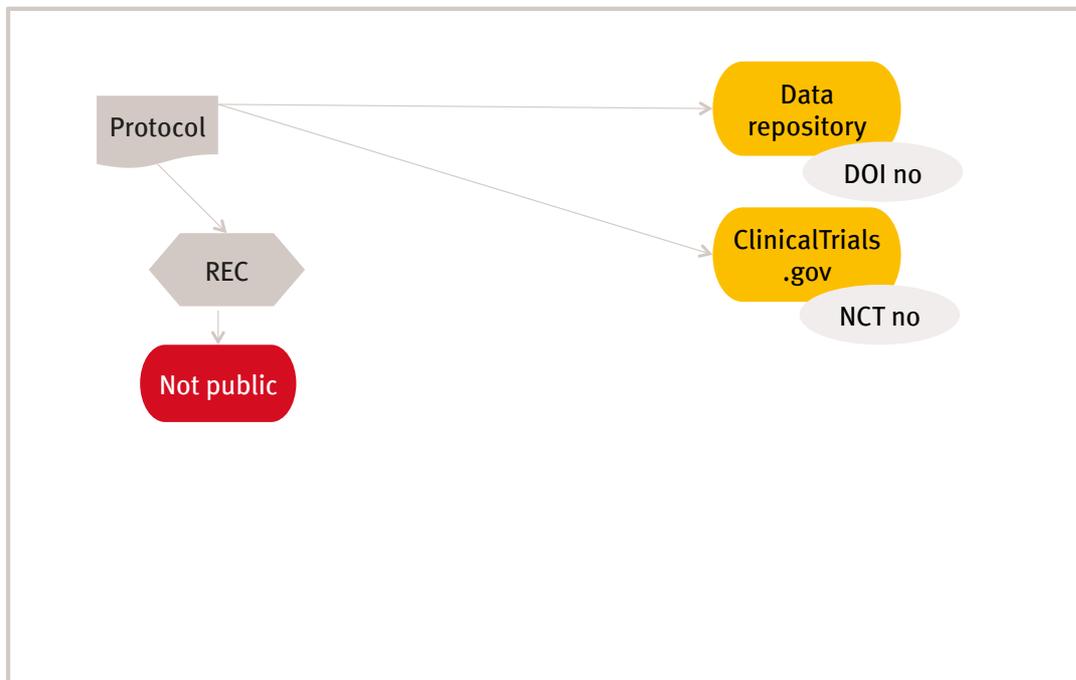


The protocol (Clinical Investigation plan) is approved by an ethical review board (REC) and the device section of the competent authorities (CA). The data protection assessment is mostly inherent in the ethical review and for some countries, it consists only of a protocol summary and the data specific procedures. The REC registers are usually not public.

The EUDAMED application is a part of the application to the CA and contains selective parts of the full protocol. The EUDAMED is usually not publicly available.

A study is publicly registered at ClinicalTrials.gov (containing selective parts of a full protocol) prior to any participants being included. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, in addition, the full protocol text file is uploaded to an electronic, publically accessible and sustainable repository, and may contain the monitoring plan, the statistical analysis plan (SAP), the data management plan including open access policy for publication and data (DMP), the safety reporting, and, the conflicts of interest. The study shall cross-reference the EUDAMED CIV-ID number (if known), the NCT number (from ClinicalTrials.gov), and the digital object identifier (DOI) number from the repository.

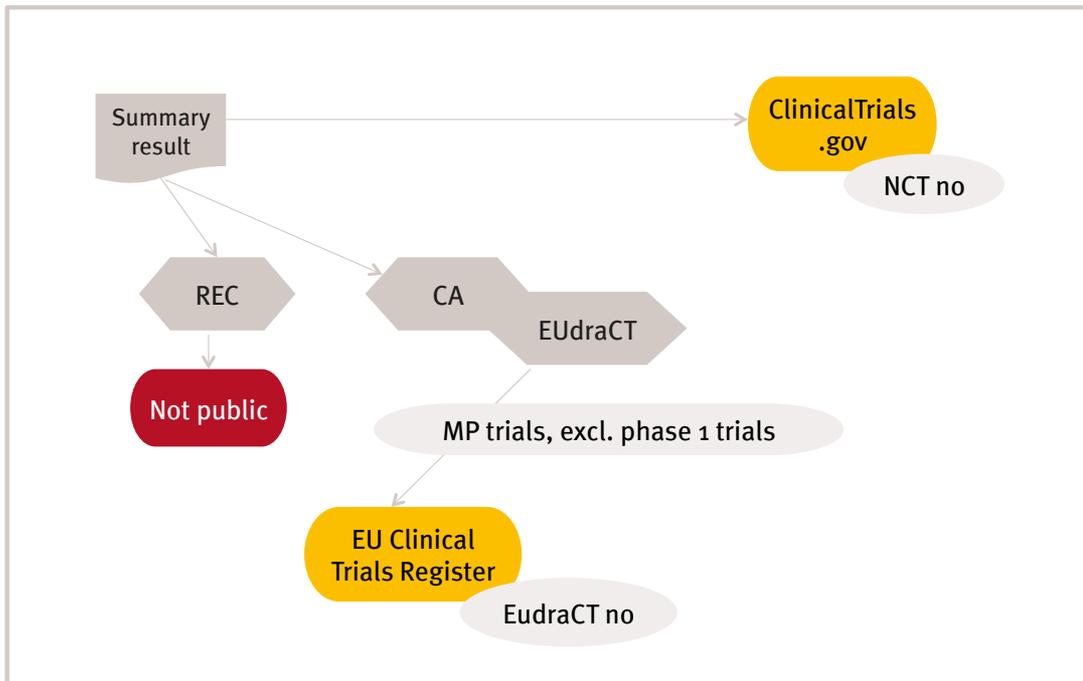
**Figure 1c. Registration: knowledge that a clinical trial on one or more other intervention(s) than medical products or devices is to be initiated.**



The protocol is approved by an ethical review board (REC). The data protection assessment is mostly inherent in the ethical review and for some countries, it consists only of a protocol summary and the data specific procedures. The REC registers are usually not public.

A study is publicly registered at ClinicalTrials.gov (containing selective parts of a full protocol) prior to any participants being included. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, in addition, the full protocol text file is uploaded to an electronic publically accessible and sustainable repository and may contain the monitoring plan, the statistical analysis plan (SAP), the data management plan including open access policy for publication and data (DMP), the safety reporting, and the conflicts of interest. The study shall cross-reference the NCT number (from ClinicalTrials.gov) and the digital object identifier (DOI) number from the repository.

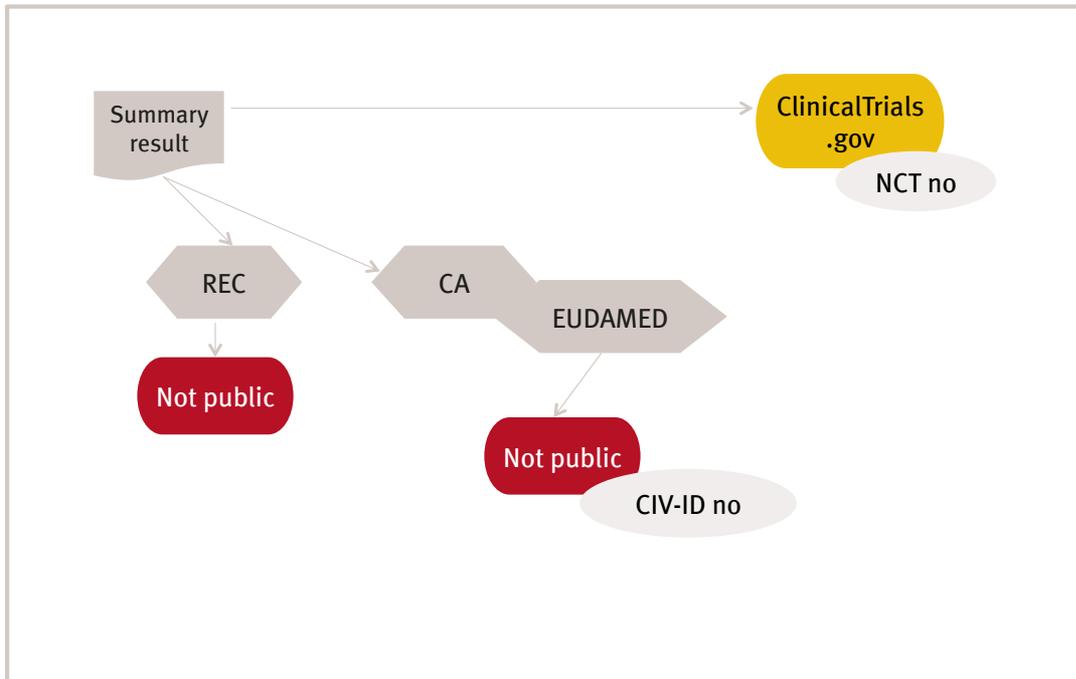
Figure 2a. Summary results: a brief summary of a medicinal product clinical trial's main results.



Summary results are reported to the ethical review board (REC) and the competent authorities (CA) no later than one year after the end of the study (last participant last visit). The REC registers are usually not public. Main summary results are displayed in the EU Clinical Trials Register (EU CTR), with an exception for phase I trials.

Additionally, main summary results are entered into ClinicalTrials.gov (as summarised in tables), as the ClinicalTrials.gov does not support uploading of files.

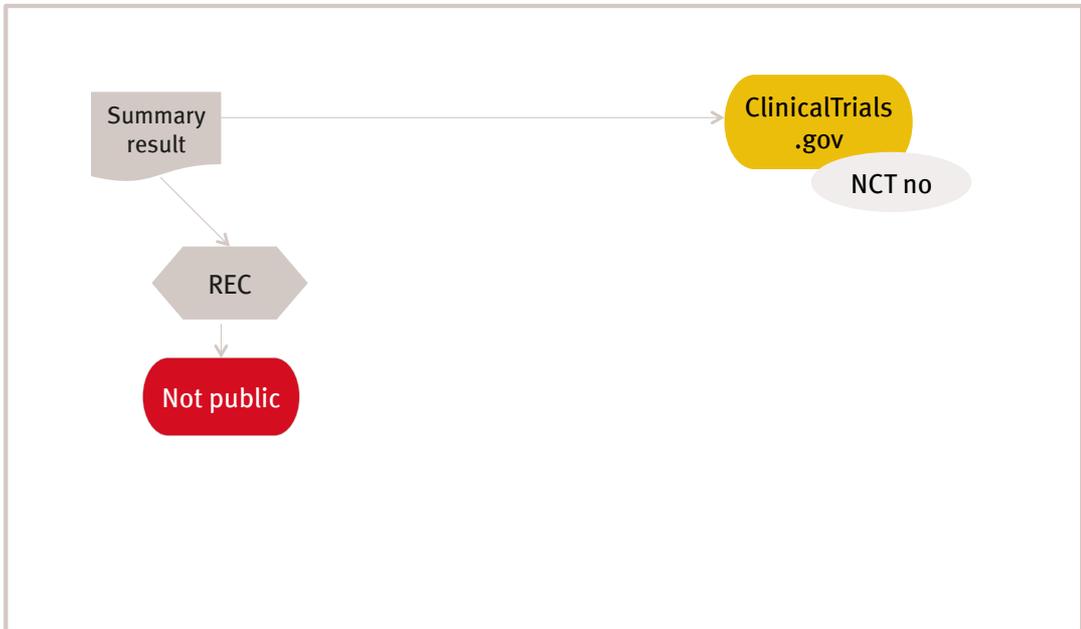
Figure 2b. Summary results: a brief summary of a medical device clinical trial's main results.



Summary results are reported to the ethical review board (REC) and the competent authorities (CA) no later than one year after the end of the study (last participant last visit). The REC registers are usually not public. The EUDAMED register is usually not publicly available.

Additionally, main summary results are entered into ClinicalTrials.gov (as summarised in tables), as the ClinicalTrials.gov does not support uploading of files.

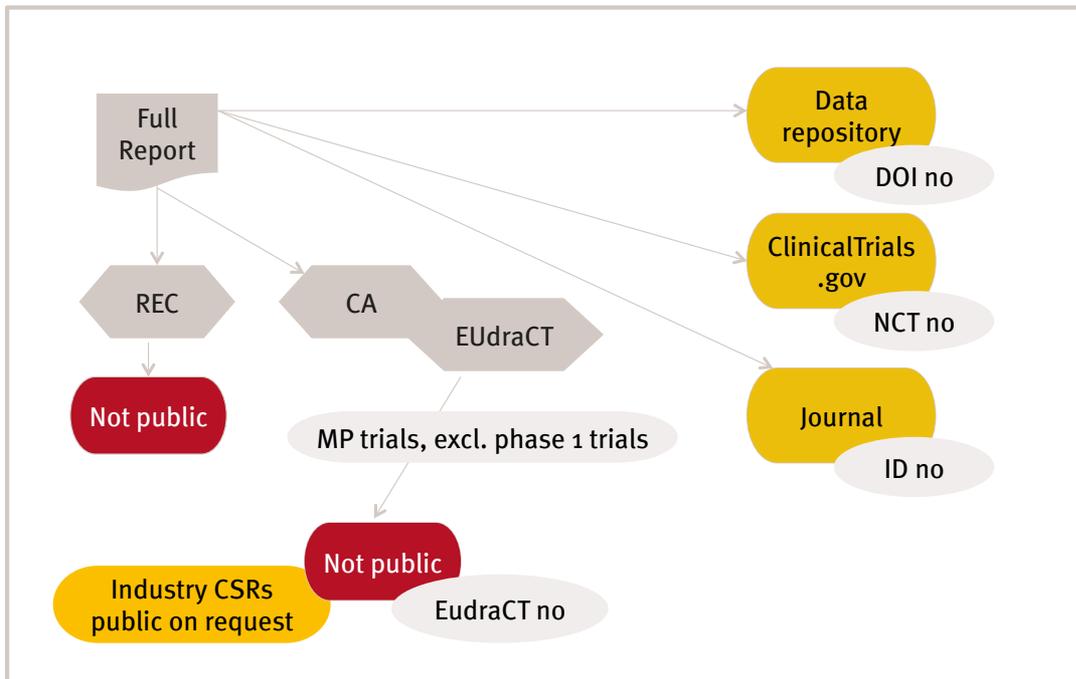
**Figure 2c. Summary results: a brief summary of a clinical trial's main results assessing all other interventions than medicinal products and medical devices.**



Summary results are reported to the ethical review board (REC) no later than one year after the end of the study (last participant last visit). The REC registers are usually not public.

Additionally, main summary results are entered into ClinicalTrials.gov (as summarised in tables), as the ClinicalTrials.gov does not support uploading of files.

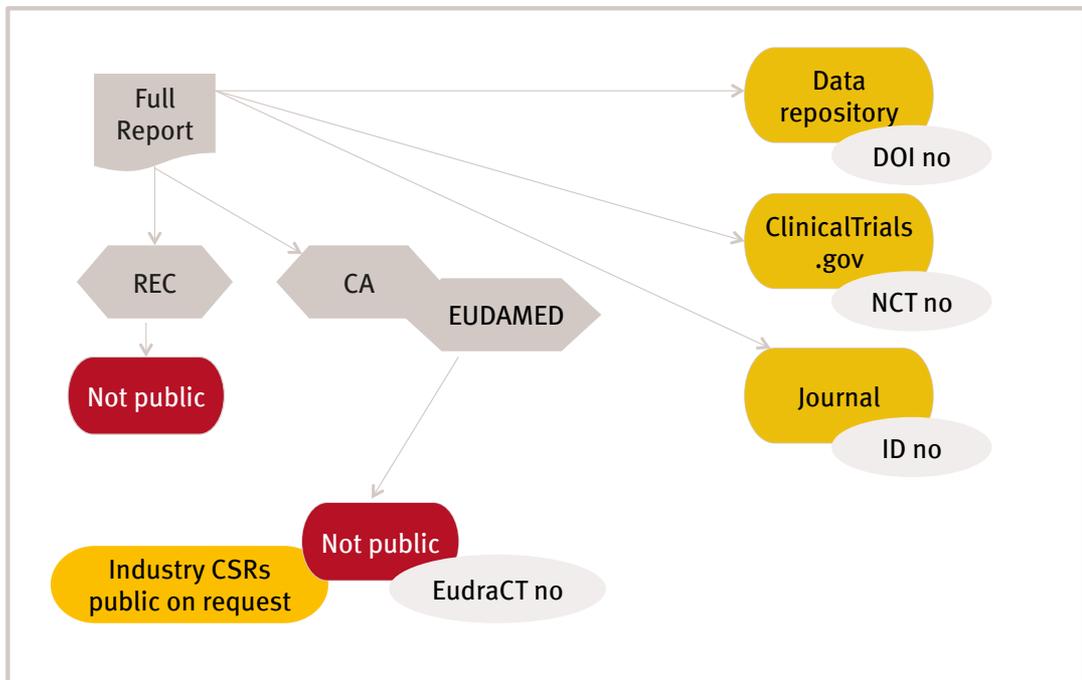
**Figure 3a. Full report: full details about a medicinal product clinical trial’s methods and outcomes.**



The full report of an academic study is typically a journal publication, and the full report of an industry study is typically a clinical study report (CSR) and a journal publication. A journal publication is usually reported one year after end of study (last participant last follow up). The full report is reported to the competent authorities (CA) and the ethical review board (REC); however, the REC usually suffice with an abbreviated CSR. The REC registers are usually not public. The EU Clinical Trials Register (EU CTR) supports displaying of text files with an exception for phase I trials. Full CSRs are usually available on request. A journal publication is made publicly available when published in a scientific journal.

Additional results that are not part of the main report are entered into ClinicalTrials.gov (as summarised in tables), at the time of the full reporting. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, the full report text file is uploaded to an electronic, publically accessible and sustainable repository. The study shall cross-reference the EudraCT number, the NCT number (from ClinicalTrials.gov), the DOI number from the repository, and the journal ID number.

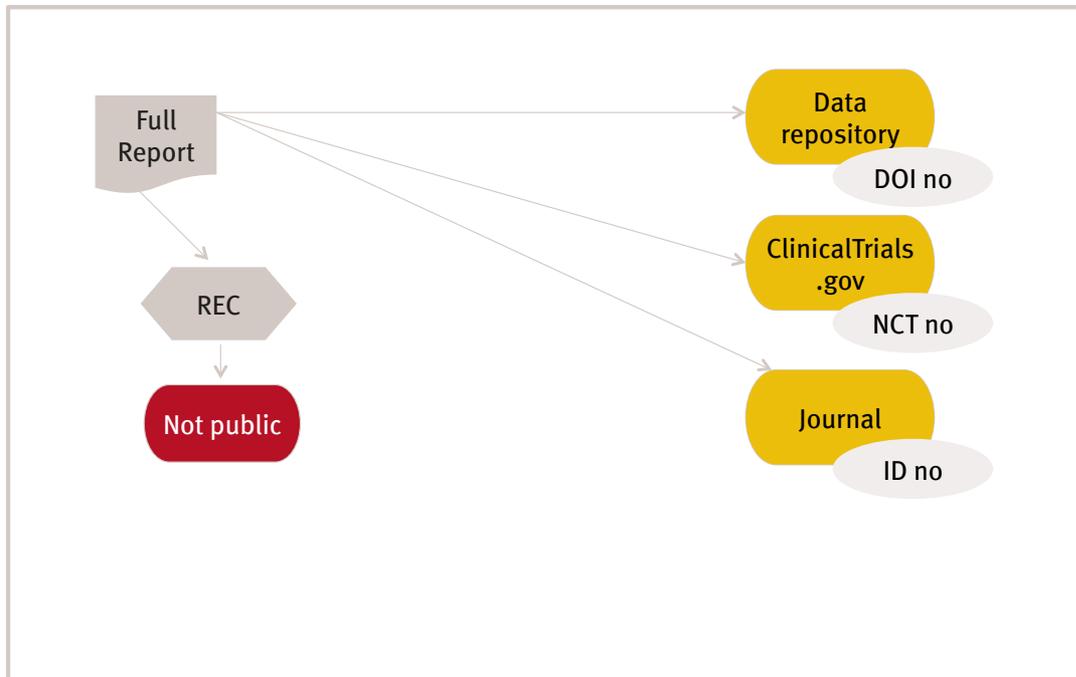
**Figure 3b. Full report: full details about a medical device clinical trial's methods and outcomes.**



The full report of an academic study is typically a journal publication, and the full report of an industry study is typically a clinical study report (CSR) and a journal publication. A journal publication is usually reported one year after the end of the study (last participant last visit). The full report is reported to the competent authorities (CA) and the ethical review board (REC); however, the REC usually suffice with an abbreviated CSR. The REC registers are usually not public. Full CSRs are usually available on request. A journal publication is made publicly available in a scientific journal.

Additional results not part of the main summary results are entered into ClinicalTrials.gov (as summarised in tables), at the time of the full reporting. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, the full report text file is uploaded to an electronic, publicly accessible and sustainable repository. The study shall cross-reference the EUDAMED CIV-ID number (if known), the NCT number (from ClinicalTrials.gov), the DOI number from the repository, and the journal ID number.

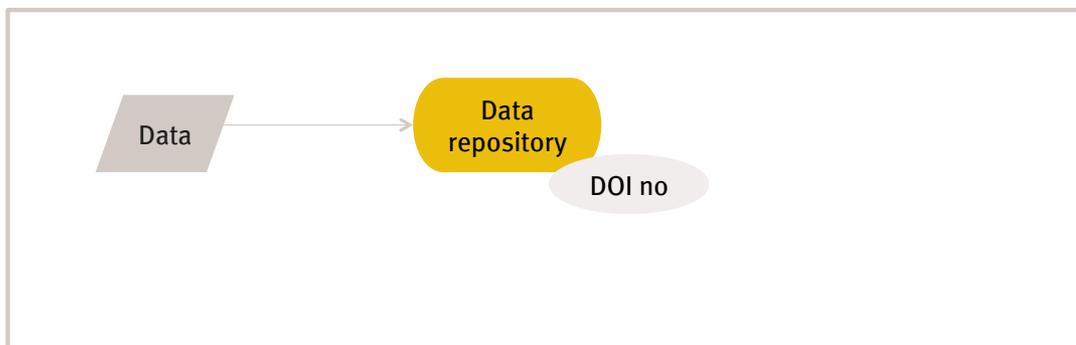
**Figure 3c. Full report: full details about a clinical trial’s methods and outcomes assessing other interventions than medicinal products and medical devices.**



The full report is typically a journal publication for academic studies and is reported to the ethical review board (REC). A journal publication is usually reported one year after the end of the study (last participant last visit). The REC registers are usually not public. A journal publication is made publicly available in a scientific journal.

Additional results not part of the main summary results are entered into ClinicalTrials.gov (as summarised in tables) at the time of the full reporting. The ClinicalTrials.gov does not support uploading of files, only linking to files via web addresses (URLs). Thus, the full report text file is uploaded to an electronic, publically accessible and sustainable repository. The study shall cross-reference the NCT number (from ClinicalTrials.gov), the DOI number from the repository, and the journal ID number.

**Figure 4. Data: individual depersonalised individual participant data from clinical trials assessing medicinal products, medical devices, and all other interventions.**



The depersonalised individual participant data (i.e., the analysed data set as well as essential source or raw data) of a clinical study are uploaded onto an electronic, publicly accessible and sustainable repository, after the summary reporting or the full reporting has been done. The study shall cross-reference the DOI number with any prior identification numbers (EudraCT number, NCT number, DOI number, and journal ID number).

#### **9.4 Harmonised legislation in the Nordic countries controlling the registration and transparency process**

We recommend that the Nordic countries in collaboration or as individual nations introduce harmonised legislation which can govern the suggested steps of registration and secure transparency for both investigator-initiated and industry-initiated clinical research. Such legislation should give precise guidelines for proper conduct and introduce appropriately severe sanctions in case the legislation is not strictly followed. All experience until now shows that too few follow the present guidelines for registration and transparency, and those who make attempts to follow the present guidelines make too many mistakes in their registration. Such legislation should declare unauthorised attempts to identify persons from depersonalised (or deidentified or pseudonymised) data or anonymised data an unlawful act and implement adequate punishments. The legislation should be developed in close collaboration with all stakeholders. The new legislation could be an inspiration for the rest of the world's countries to introduce similar legislation.



## 10. Future aspects

There are hurdles to clear in order to develop an effective data-sharing culture. We propose, in line with the IOM report, to modify and supplement trial registries to accommodate better transparency, and store and share trial data in a responsible and useful manner. Aside the technical matters, we urge a change in how we think about data. They are not one's personal property but should be viewed as a gift to the research community and, therefore, we have a responsibility to make use of this gift and turn it into profits for the giver, the trial participant. This profit should materialise as better knowledge and better interventions for diagnosis, prevention, treatment, and care.

One challenge is the task of minimising duplicate entries both within and across trial registers, and data repositories. The WHO and other major registers around the world are working together in order to share experience and technical expertise to ensure that these challenges can be overcome. The aim is to facilitate a system whereby anyone looking for trials related to a certain condition can access a one-stop search portal which will look within and across registers and provide a shortlist of potential trials and their details within seconds. Furthermore, the process of structuring trial information and data to fit a long-term global perspective is a huge task, and the value of the information and data depend on its timeliness.

As stated in our report, we find the initiatives taken by parts of the industry as very valuable steps forward. However, the whole governing structure does not seem to fulfil the requests for transparency and may therefore not provide the necessary trust. Building trust in clinical research has been a goal for us. We wish to make the Nordic region a frontrunner in re-establishing peoples' trust in clinical research. By creating harmonised laws for registration and transparency, the Nordic region could regain a leading position in ethical conduct of clinical research. In the future, when there is a new treatment, one should ask: are any of the clinical trials from the Nordic region? How large a proportion of the clinical trials is from the Nordic region? Did the Nordic clinical trials find the same intervention effects for benefits and harms as the clinical trials from other parts of the world? Through conduct of ethical clinical research, the Nordic region may regain its attractiveness to the global health industries.

We have written the present report with a focus on clinical trials assessing preventive and therapeutic interventions as well as diagnostic studies.<sup>137</sup> However, we want that similar approaches should be used for all clinical research including prognostic studies and observational studies. It is through clear planning of studies with transparent reporting of all phases that we will increase our understanding of diseases and of how to diagnose, prevent, and treat them.<sup>138-144</sup>

## 11. Appendices





# 11. Appendices

## 11.1 Appendix 1

### Project Plan for the Nordic Trial Alliance Working Group on Transparency and Registration

#### WG: Transparency and registration

##### Project plan

###### Introduction

The World Health Organization states: “The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility.”<sup>1</sup> Supported by the World Medical Association’s statement of principles for medical research involving human participants, the Declaration of Helsinki<sup>2</sup> states that every investigator running a clinical trial should register it and report its results. Current global focus of the AllTrials campaign, which is lobbying for this cause, stresses that all trials, interventional and non-interventional, must be registered and reported, and this will involve regulators and registries, clinical trial funders, universities and institutes, professional and learned societies and medical journals, patients and researchers, and their thoughts about what they will need to do to achieve this goal. Even though trial registration and reporting has been a demand from the International Committee of Medical Journal Editors (ICMJE)<sup>3</sup> since 2004, still, 9 years later, substantially more than one third of trials have not reported study results after 6 years.

Clinical trials are investigations designed to assess the effects, beneficial and harmful, of healthcare interventions. Decisions about health care should be based on systematic reviews of all evidence in order to be as accurate as possible. Failure to register and report all clinical trials and their results – especially non-efficacy results or harmful effects – means that all possible evidence is not available.<sup>4</sup> Consequently, decisions about health care may be based on incomplete, wrong, or biased information. Registration and reporting of all trials will also increase transparency for researchers and funding agencies, it will decrease the risk of unnecessary duplication, and it will also help to identify gaps in research.

There are several public platforms available for registration of trials and reporting of results. The most well-known platform is ClinicalTrials.gov; a US-based government-owned public registry and results database of publicly and privately supported clinical studies. Also the EU Clinical Trials Register for medicinal products is now a public registry, but may still be fowled with lag times and not easily digestible information. The area is fragmented, current public registries have different layouts, and there is incomplete consensus as to what elements or items must be reported. The most commonly followed are the WHO recommendations (“the 20 items”) and the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing and publication of scholarly work in medi-

1 [http://www.who.int/ictrp/trial\\_reg/en/](http://www.who.int/ictrp/trial_reg/en/)

2 <http://www.wma.net/en/30publications/10policies/b3/>

3 International Committee of Medical Journal editors’ Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journal

4 Song et al. 2010. Dissemination and publication of research findings: an updated review of related biases.

cal journals. However, for the single investigator, or even for the industry, it is time consuming to digest all this information and stumble their way through all too many different application and registration systems in order to be able to conduct your clinical trial. There is a need for more smart systems to take you faster through the administrative hurdles of a trial, amongst other through easy to use standard operating procedures (SOPs).

## **Aim**

WG will work towards raising the awareness of the hampered trial registration and reporting and towards finding possibilities to minimise double registration and reporting.

We want to improved registration and reporting of clinical studies, interventional and non interventional, by raising the homogeneity and quality of what is registered and reported for all studies. Transparency levels in clinical trial reporting encompass: 1. knowledge that the trial is being conducted; 2. required details about design, methods, and outcomes; 3. required details about results; 4. summary of results; 5. depersonalised individual patient data.

**The first part of the proposed work** will be 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 (1 and 2) and reporting of results (3 and 4), and sharing of depersonalised individual participant data (5). We will identify the main barriers to lack of reporting and transparency issues, compared to the WHO recommendations ('the 20 items') and other international guidelines.

**The second part of the work** will be aimed at developing a consensus on a common Nordic best practice and Nordic possibilities for meeting the transparency levels in order to reduce the fragmentation. Here we will liaise with the NRI initiative and seek a dialogue with the industry sector.

## **Objectives and planned deliverables**

1. Map and develop 'best practices' for public, prospective registration and reporting of clinical trials of all interventions.
2. Map and develop 'best practices' for public upload of depersonalised individual participant data after the report of the trial.

## **Added value of Nordic cooperation**

Trial registration and publication is a global concern. With a joint Nordic approach to transparency we will help our research communities tackle this issue, and at the same time give a collective aid to the global voice of transparency. Our public money is spent on research, and the primary output is data, and we can act together now, to maximize the return of investment and the research opportunities that this data can provide in the Nordic countries. A recent article by Eichler et al<sup>5</sup> supports the idea that more transparency will in particular benefit the industry as less is spent on duplication and trial errors. Depersonalised data need to be preserved for sharing and use beyond the originating research question.

---

5 Eichler HG, Pétavy F, Pignatti F, Rasi G. Access to Patient-Level Trial Data — A Boon to Drug Developers. *New Engl J Med* 2013; 369:1577-79.

Many trials are conducted jointly in the Nordic countries, where the advantages of similar healthcare systems and research cultures can aid their successful progression. To jointly develop and propose a model for best-practice transparency will benefit all and enable the individual countries to make greater impacts on both European and global level. Our research participants and other patients will be able to find ongoing and published research easier, and thereby can actively take part in the research. Our researchers will access simple and concise guidelines to achieve the transparency goals and will also benefit from the possibility to join other Nordic research projects and easier find areas where evidence is lacking. The healthcare sector will be able to take better advantage of new interventions, after being more rigorously tested at different but comparable locations, and will also find new evidence on already implemented interventions, to keep providing the best and most cost-efficient healthcare. The joint Nordic input will create added value for the individual countries and their citizens.

### **Feasibility of the project plan**

The plan will be implemented through three well-prepared Nordic meetings during 2014. By jointly agreeing on a work plan, the issues to solve, and the estimated workload we see it plausible for all to meet the deadlines scheduled. The work package leader will allocate one month for academic secretary tasks, to secure that deadlines are met and that work is kept on track. For all project participants some compensation will be allocated for the work delivered, and this is deemed necessary for the quality. This compensation will be paid to the institution of the project participant.

The involved parties have very 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 networks.

**Christian Gluud** (Denmark) is the director of the Copenhagen Trial Unit and the national coordinator of the Danish Clinical Research Infrastructures Network and is participating in the build-up of the European Clinical Research Infrastructures Network (ECRIN) since 2003. He was academic secretary for the Danish National Strategy for Health Research in 1995. He is involved in the European Communication on Research Awareness Needs (ECRAN) since its start in 2012 as well as in the Nordic Trial Alliance (NTA) since 2012.

**Kristján Erlendsson** (Iceland) is an associate professor of Medical Education at the Icelandic Medical Faculty, senior advisor on Science and Education at Landspítali – the National University Hospital of Iceland as well as to the Ministry of Welfare and has a long record within Iceland's clinical research arena, presently being the leader of the national research ethics committee. He is involved in ECRIN and NTA and member of the Board of Directors and Advisory group of Nordic Health Research and Innovation Networks (NRI).

**Mika Scheinin** (Finland) is professor of Pharmacology and director of a Clinical Trials Unit in Turku and has been active in different aspects of clinical research for 30 years. He has served as chairman of the Ethics committee of the Hospital District of Southwest Finland since 1997. He is involved in NTA and NRI.

**Siv Mørkved** (Norway) is professor of Applied Clinical Research at the Norwegian University of Science and Technology, Trondheim, and Research Director at St.Olavs Hospital, Trondheim University Hospital with large experience in randomised clinical trials and systematic reviews. She is involved in ECRIN and NTA.

**Mia Englund** (Sweden) is director of Karolinska Trial Alliance at Karolinska University Hospital. Mia has developed full-service phase I-IV trial and support units, both in Örebro and in Stockholm. She is a member of the Advisory group of Nordic Health Research and Innovation Networks (NRI).

## List of partners

### Denmark

Christian Gluud, Chair, MD., Dr. Med. Sci. Head of Department  
Copenhagen Trial Unit, Centre for Clinical Intervention Research  
Department 7812, Rigshospitalet  
Copenhagen University Hospital, Blegdamsvej 9, DK 2100 Copenhagen, Denmark  
E-mail: cgluud@ctu.dk  
Phone: + 45 35 45 71 75  
Mobile: + 45 40 40 11 82  
Fax: + 45 35 45 71 01

### Finland

Mika Scheinin, MD., Professor, Director  
Clinical Research Services Turku  
University of Turku, Itäinen Pitkätatu 4B  
FI 20014 Turku, Finland  
E-mail: mschein@utu.fi  
Phone: + 35 8 23 33 75 02  
Mobile: + 35 84 05 01 47 62

### Iceland

Kristján Erlendsson, Professor, Director  
Landspítali University Hospital, Hringbraut, 101 Reykjavík, Iceland  
E-mail: krerlend@landspitali.is  
Mobile: + 35 48 24 56 62

### Norway

Siv Mørkved, Professor, Research Director  
St. Olavs Hospital, Trondheim University Hospital, NO 7006 Trondheim, Norway  
E-mail: siv.morkved@stolav.no  
Mobile: + 47 97 14 64 90

### Sweden

Mia Englund, Director  
Karolinska Trial Alliance  
Karolinska University Hospital, M62, SE 113 62 Stockholm, Sweden  
E-mail: maria.a.englund@karolinska.se  
Phone: + 46 (0)8 51 77 82 10  
Mobile: + 46 (0)7 01 68 49 53

## 11.2 Appendix 2

### Examples for participant information and consent regarding data sharing

#### A. Template examples from Iceland

Your participation and contribution to this study includes that you: .....

- Permit, if found necessary, that you will be contacted again for requesting further information or to invite you to participate in another study. This might be done with reference to whole genome sequencing or other outcomes from your samples or information you have given in this study. This might imply that you will be informed about certain results concerning your person. Up front it is not possible to assess what impact these results might have for you, but you will be informed with reference to understanding and knowledge following from the general results of the study.

...

By participating in this study you authorize the researchers to inform you about your personal outcomes in the study. This entails that you accept that test results, data from measurements or other information emerging from this study will be linked to your name and brought to your attention.

#### B. Template example from Norway

Releasing material and data to other parties

If you agree to participate in the study, you also consent to samples and non-identifiable data being released to [Insert the agency and country. If non-identifiable data are to be sent to countries outside the EU/EEA, a detailed explanation must be provided if the country has a differing policy on data privacy and if this might have consequences for the participant's data privacy].

## 11.3 Appendix 3

### Proposal for explanation on transparent data handling in clinical trials

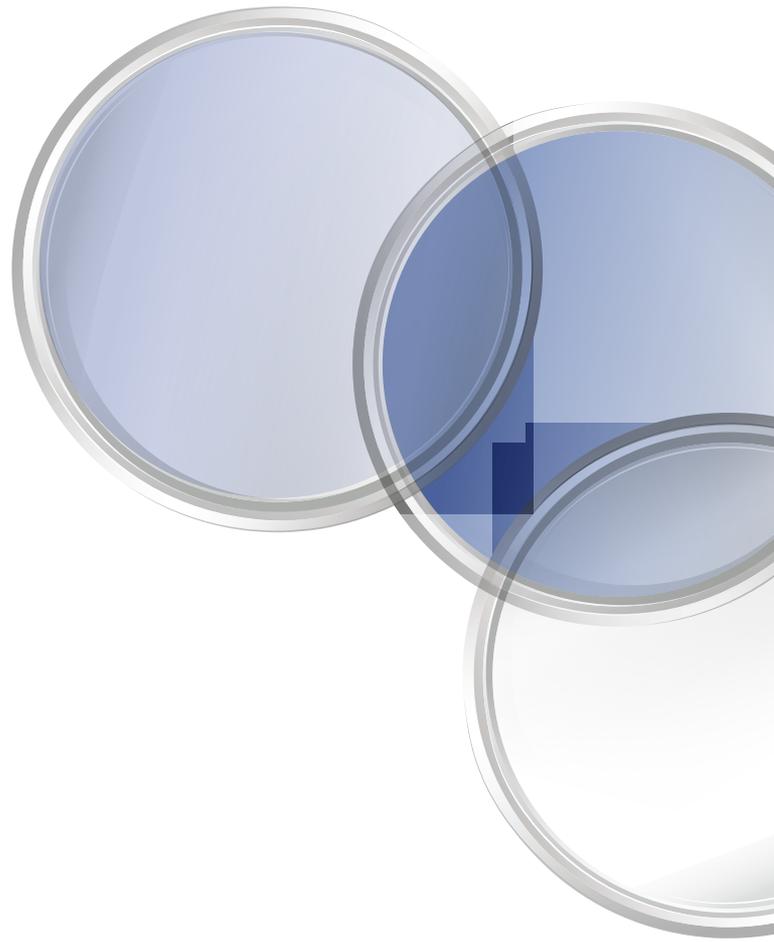
This is a proposal from the Working Group for explanation on transparent data handling in clinical trials suggested to be included in the written and verbal informed consent material.

Participation and contribution to this study includes that you consent to/ permit the depersonalised data set from the study is made publicly available for secondary analyses and for future use.

After completion of the study as described above, the data you have provided for the study will be depersonalised (pseudonymised) according to best available practices [insert name of reference document/institution used for the depersonalisation process]. In practice this means you cannot be identified through the data alone, and that all data will look like anonymised data. The data will be stored in a public repository for future use so that other researchers can use the data for reanalyses of the trial results and for inclusion into individual patient data meta-analyses. If it will be necessary for important scientific reasons in the future to identify you as the data donor, a key making this process possible will be kept in a secure national data bank [name the custodian]. Combination of the depersonalised data with the key can only occur after renewed assessment and approval from the appropriate ethics committee. These steps are taken to maximally secure your data safety and public safety.



## 12. References





## 12. References

- (1) Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess.* 2010; 14(8):iii, ix-iii,193.
- (2) World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last update: October 2013; wma net. Available from [www.wma.net/en/30publications/10policies/b3/](http://www.wma.net/en/30publications/10policies/b3/)
- (3) Gluud C, Nikolova D. Likely country of origin in publications on randomised controlled trials and controlled clinical trials during the last 60 years. *Trials.* 2007; 8:7.
- (4) Killeen S, Sourallous P, Hunter IA, Hartley JE, Grady HL. Registration rates, adequacy of registration, and a comparison of registered and published primary outcomes in randomized controlled trials published in surgery journals. *Ann Surg.* 2014; 259(1):193-196.
- (5) Fanelli D. Do pressures to publish increase scientists' bias? An empirical support from US States Data. *PLoS ONE.* 2010; 5(4):e10271.
- (6) Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ.* 2012; 344:d7202.
- (7) Savovic J, Jones HE, Altman DG, Harris RJ, Juni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med.* 2012; 157(6):429-438.
- (8) Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ.* 2008; 336(7644):601-605.
- (9) Lemmens T, Telfer C. Access to information and the right to health: the human rights case for clinical trials transparency. *Am J Law Med.* 2012; 38(1):63-112.
- (10) Higgins JPT, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* Last update: March 2011; The Cochrane Collaboration. 2011 Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
- (11) Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA.* 2014; 312(2):171-179.
- (12) Sun X, Guyatt G. Meta-analysis of randomized trials for health care interventions: one for all? *J Evid Based Med.* 2009; 2(1):53-56.
- (13) Berlin JA, Golub RM. Meta-analysis as evidence: building a better pyramid. *JAMA.* 2014; 312(6):603-605.
- (14) Hennekens CH, DeMets D. The need for large-scale randomized evidence without undue emphasis on small trials, meta-analyses, or subgroup analyses. *JAMA.* 2009; 302(21):2361-2362.
- (15) Stegenga J. Is meta-analysis the platinum standard of evidence? *Stud Hist Philos Biol Biomed Sci.* 2011; 42(4):497-507.
- (16) Borzak S, Ridker PM. Discordance between meta-analyses and large-scale randomized, controlled trials. Examples from the management of acute myocardial infarction. *Ann Intern Med.* 1995; 123(11):873-877.
- (17) Ioannidis JP, Haidich AB, Pappa M, Pantazis N, Kokori SI, Tektonidou MG, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA.* 2001; 286(7):821-830.
- (18) Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA.* 2005; 294(2):218-228.
- (19) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakaravitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003; 7(27):iii-173.
- (20) Borm GF, Lemmers O, Franssen J, Donders R. The evidence provided by a single trial is less reliable than its statistical analysis suggests. *J Clin Epidemiol.* 2009; 62(7):711-715.
- (21) Int'Hout J, Ioannidis JP, Borm GF. Obtaining evidence by a single well-powered trial or several modestly powered trials. *Stat Methods Med Res.* 2012.
- (22) Jakobsen JC, Gluud C. The necessity of randomized clinical trials. *Br J Med Res.* 2013; 3(4):1453-1468.
- (23) Clarke M, Brice A, Chalmers I. Accumulating research: a systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. *PLoS ONE.* 2014; 9(7):e102670.

- (24) Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. *BMC Med Res Methodol.* 2010; 10:90.
- (25) Jakobsen JC, Gluud C, Winkel P, Lange T, Wetterslev J. The thresholds for statistical and clinical significance - a five-step procedure for evaluation of intervention effects in randomised clinical trials. *BMC Med Res Methodol.* 2014; 14:34.
- (26) Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Med Res Methodol.* 2014; 14:120.
- (27) World Health Organisation. Trial Registration; International Clinical Trials Registry Platform (ICTRP). Last update: August 2014; who int. Available from [www.who.int/ictrp/trial\\_reg/en/](http://www.who.int/ictrp/trial_reg/en/)
- (28) De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *Lancet.* 2005; 365(9474):1827-1829.
- (29) Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med.* 2010; 153(3):158-166.
- (30) Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ.* 2013; 347:f6104.
- (31) Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM. Trial publication after registration in ClinicalTrials.gov: a cross-sectional analysis. *PLoS Med.* 2009; 6(9):e1000144.
- (32) Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ.* 2012; 344:d7292.
- (33) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ.* 2012; 344:d7373.
- (34) European Commission. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. 16 April 2014. Available from [www.eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L\\_.2014.158.01.0001.01.ENG](http://www.eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG)
- (35) Ottawa Group. Ottawa Statement on Trial Registration. Last update: August 2014; ohri.ca. Available from [www.ottawagroup.ohri.ca/](http://www.ottawagroup.ohri.ca/)
- (36) Ottawa Group. Improving access to clinical trial data initiative. Last update: November 2014; ohri.ca. Available from [www.ottawagroup.ohri.ca/disclosure.html](http://www.ottawagroup.ohri.ca/disclosure.html)
- (37) The Cochrane Collaboration. About us. Last update: October 2014; cochrane.org. Available from [www.cochrane.org/about-us](http://www.cochrane.org/about-us)
- (38) Medical Research Council. MRC Policy and Guidance on Sharing of Research Data from Population and Patient Studies. Report no. 01-00. 23 November 2011. Available from [www.mrc.ac.uk/news-events/publications/mrc-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies/](http://www.mrc.ac.uk/news-events/publications/mrc-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies/)
- (39) Organisation for Economic Co-operation and Development. OECD Principles and Guidelines for Access to Research Data from Public Funding. Report no. (00 2007 39 3 P) - No. 88180 2007. 2007. OECD Publications. Available from [www.oecd.org/sti/sci-tech/38500813.pdf](http://www.oecd.org/sti/sci-tech/38500813.pdf)
- (40) National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. Last update: March 2003; U S Department of Health and Human Services. Available from [www.grants.nih.gov/grants/policy/data\\_sharing/data\\_sharing\\_guidance.htm#fin](http://www.grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm#fin)
- (41) AllTrials Campaign. Last update: November 2014; Sense About Science. Available from [www.alltrials.net](http://www.alltrials.net)
- (42) PhRMA - Pharmaceutical Research and Manufacturers of America. EFPIA and PhRMA release joint principles for responsible clinical trial data sharing to benefit patients. Last update: 2013; pharma.org. Available from [www.phrma.org/press-release/EFPIA-and-phrma-release-joint-principles-for-responsible-clinical-trial-data-sharing-to-benefit-patients](http://www.phrma.org/press-release/EFPIA-and-phrma-release-joint-principles-for-responsible-clinical-trial-data-sharing-to-benefit-patients)
- (43) BIO - Biotechnology Industry Organization. BIO principles on clinical trial data sharing. Last update: 2014; bio.org. Available from [www.bio.org/articles/bio-principles-clinical-trial-data-sharing](http://www.bio.org/articles/bio-principles-clinical-trial-data-sharing)
- (44) Yale University. Welcome to the YODA Project. Last update: 2015; yoda.yale.edu. Available from [www.yoda.yale.edu/welcome-yoda-project](http://www.yoda.yale.edu/welcome-yoda-project)
- (45) Kumar S. Johnson & Johnson Announces Clinical Trial Data Sharing Agreement with Yale School of Medicine. Last update: 2015; jnj.com. Available from [www.jnj.com/news/all/johnson-and-johnson-announces-clinical-trial-data-sharing-agreement-with-yale-school-of-medicine](http://www.jnj.com/news/all/johnson-and-johnson-announces-clinical-trial-data-sharing-agreement-with-yale-school-of-medicine)
- (46) Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy, Institute of Medicine. *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk.* Washington, D.C.: The National Academies Press; 2015. Available from [www.nap.edu/catalog.php?record\\_id=18998](http://www.nap.edu/catalog.php?record_id=18998)

- (47) Nisen P, Rockhold F. Access to patient-level data from GlaxoSmithKline clinical trials. *N Engl J Med.* 2013; 369(5):475-478.
- (48) Hughes S, Wells K, McSorley P, Freeman A. Preparing individual patient data from clinical trials for sharing: the GlaxoSmithKline approach. *Pharm Stat.* 2014; 13(3):179-183.
- (49) Committee on Strategies for Responsible Sharing of Clinical Trial Data, Board on Health Sciences Policy, Institute of Medicine. Discussion Framework for Clinical Trial Data Sharing: Guiding Principles, Elements, and Activities. Washington, D.C.: The National Academies Press; 2014. Available from [www.nap.edu/openbook.php?record\\_id=18610](http://www.nap.edu/openbook.php?record_id=18610)
- (50) Poensgen M, Schell J, Wilson S. Transparency impact. *International Clinical Trials.* 2014;10-14.
- (51) AllTrials Campaign. Lilly commits to sharing some information from past clinical trials. Last update: June 2014; Sense About Science. Available from [www.alltrials.net/news/lilly-commits-to-sharing-some-information-from-past-clinical-trials/](http://www.alltrials.net/news/lilly-commits-to-sharing-some-information-from-past-clinical-trials/)
- (52) Godlee F, Groves T. The new BMJ policy on sharing data from drug and device trials. *BMJ.* 2012; 345:e7888.
- (53) Tudur SC, Dwan K, Altman DG, Clarke M, Riley R, Williamson PR. Sharing individual participant data from clinical trials: an opinion survey regarding the establishment of a central repository. *PLoS One.* 2014; 9(5):e97886.
- (54) The Cochrane Collaboration. Access to Data from All Trials. Last update: March 14 A.D.; cochrane.org. Available from [www.cochrane.org/organisational-policy-manual/27-access-data-all-trials](http://www.cochrane.org/organisational-policy-manual/27-access-data-all-trials)
- (55) ELIXIR, EU-OPENSOURCE, RI, ATRIS, ECRIN, INFRAFRONTIER, INSTRUCT, ERINHA, EMBRC, Euro-BioImaging, LifeWatch, AnaEE, ISBE, and MIRRI. Editors: Blomberg N, Meiners T, and Suhr S. Principles of data management and sharing at European Research Infrastructures. Report no. Version 1.0. 5 February 2014. ZENODO. Available from [www.zenodo.org/record/8304#.U\\_vFTfl\\_uT8](http://www.zenodo.org/record/8304#.U_vFTfl_uT8)
- (56) AllTrials Campaign. What AllTrials is calling for. Last update: November 2014; Sense About Science. Available from [www.alltrials.net/find-out-more/all-trials/](http://www.alltrials.net/find-out-more/all-trials/)
- (57) International Committee of Medical Journal Editors. FAQs: Clinical Trials Registration. Last update: 2014; ICMJE.org. Available from <http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/>
- (58) World Health Organisation. WHO Trial Registration Data Set (Version 1.2.1). Last update: November 2014; who.int. Available from [www.who.int/ictrp/network/trds/en/](http://www.who.int/ictrp/network/trds/en/)
- (59) International Conference on Harmonisation Guideline for International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Guideline for Good Clinical Practice E6 (R1). ICH Harmonised Tripartite Guideline. 10 June 1996. Available from [www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf)
- (60) The Consort Group. Consort statement. Last update: March 2010; [www.worldpsychiatricassociation.org](http://www.worldpsychiatricassociation.org). Cited: 2009 Apr. 7.(7th Congress in Vienna, Italy) Available from <http://www.consort-statement.org/>
- (61) Information Commissioner's Office. Anonymisation: managing data protection risk code of practice . 1 November 2012. Available from [www.ico.org.uk/media/for-organisations/documents/1061/anonymisation-code.pdf](http://www.ico.org.uk/media/for-organisations/documents/1061/anonymisation-code.pdf)
- (62) Winkel P, Hilden J, Hansen JF, Kastrup J, Kolmos HJ, Kjoller E, et al. Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10years in the CLARICOR randomised, blinded clinical trial. *Int J Cardiol.* 2015; 182C:459-465.
- (63) The Nuremberg Code (1947). *BMJ.* 1997; 313(1448).
- (64) U.S.Food and Drug Administration. FDA's Role: ClinicalTrials.gov Information. Last update: May 2013; U S Department of Health and Human Services. Available from [www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm)
- (65) National Institutes of Health. Frequently Asked Questions FDaAA - Further Resources for NIH Grantees. Last update: April 2013; U S Department of Health and Human Services. Available from [www.grants.nih.gov/clinicaltrials\\_fdaaa/faq.htm](http://www.grants.nih.gov/clinicaltrials_fdaaa/faq.htm)
- (66) ClinicalTrials.gov. Background. Last update: May 2014; US National Institute for Health. Available from [www.clinicaltrials.gov/ct2/about-site/background](http://www.clinicaltrials.gov/ct2/about-site/background)
- (67) ClinicalTrials.gov. About the Results Database. Last update: March 2014; US National Institute for Health. Available from [www.clinicaltrials.gov/ct2/about-site/results](http://www.clinicaltrials.gov/ct2/about-site/results)
- (68) European Clinical Research Infrastructure Network. General Information. Last update: November 2011; ecrin.org. Available from [www.ecrin.org/index.php?id=102](http://www.ecrin.org/index.php?id=102)
- (69) European Clinical Research Infrastructure Network. Instruction to applicants: Instructions to applicants requesting ECRIN support regarding transparency. <http://www.ecrin.org/en/knowledge-about-clinical-trials/transparency>.

- (70) European Medicines Agency. European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use). Report no. EMA/110196/2006 ; POLICY/0043. 30 November 2010. Available from [www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2010/11/WC500099473.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf)
- (71) European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. Report no. EMA/240810/2013; POLICY/0070. 2 October 2014. Available from [www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/10/WC500174796.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf)
- (72) European Commission. Towards better access to scientific information: Boosting the benefits of public investments in research. Report no. COM(2012) 401 final. 17 July 2012. Available from [www.ec.europa.eu/research/science-society/document\\_library/pdf\\_06/era-communication-towards-better-access-to-scientific-information\\_en.pdf](http://www.ec.europa.eu/research/science-society/document_library/pdf_06/era-communication-towards-better-access-to-scientific-information_en.pdf)
- (73) European Commission. Fact sheet: Open Access in Horizon 2020. Last update: December 2013; europa.eu. Available from [www.ec.europa.eu/programmes/horizon2020/sites/horizon2020/files/FactSheet\\_Open\\_Access.pdf](http://www.ec.europa.eu/programmes/horizon2020/sites/horizon2020/files/FactSheet_Open_Access.pdf)
- (74) European Parliament. Texts adopted Wednesday Apr 2, 2014. Last update: April 2014; europarl.europa.eu. Available from [www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2014-0273+0+DOC+XML+Vo//EN](http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2014-0273+0+DOC+XML+Vo//EN)
- (75) European Commission. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). Report no. 2012/0011 (COD). 25 January 2012. Available from [www.europarl.europa.eu/RegData/docs\\_autres\\_institutions/commission\\_europeenne/com/2012/0011/COM\\_COM%282012%290011\\_EN.pdf](http://www.europarl.europa.eu/RegData/docs_autres_institutions/commission_europeenne/com/2012/0011/COM_COM%282012%290011_EN.pdf)
- (76) European Parliament. Background: Q&A on EU data protection reform. 4 March 2014. Available from [www.europarl.europa.eu/pdfs/news/expert/background/20130502BKG07917/20130502BKG07917\\_en.pdf](http://www.europarl.europa.eu/pdfs/news/expert/background/20130502BKG07917/20130502BKG07917_en.pdf)
- (77) Position of non-commercial research organisations and academics. Protecting health and scientific research in the Data Protection Regulation. January 2014. Available from [www.p3g.org/news/protecting-health-and-scientific-research-data-protection-regulation-20120011cod](http://www.p3g.org/news/protecting-health-and-scientific-research-data-protection-regulation-20120011cod)
- (78) Brown T. It's time for all trials registered and reported. *Cochrane Database Syst Rev.* 2013; 4:ED000057.
- (79) Liberati A. Need to realign patient-oriented and commercial and academic research. *Lancet.* 2011; 378(9805):1777-1778.
- (80) Gøtzsche PC. We need access to all data from all clinical trials. *Cochrane Database Syst Rev.* 2011;(12):ED000035.
- (81) Saramago P, Chuang LH, Soares MO. Network meta-analysis of (individual patient) time to event data alongside (aggregate) count data. *BMC Med Res Methodol.* 2014; 14:105.
- (82) Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. *Stat Med.* 2002; 21(3):371-387.
- (83) Riley RD, Lambert PC, Staessen JA, Wang J, Gueyffier F, Thijs L, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Stat Med.* 2008; 27(11):1870-1893.
- (84) Sud S, Douketis J. ACP Journal Club. The devil is in the details...or not? A primer on individual patient data meta-analysis. *Ann Intern Med.* 2009; 151(2):J1-C3.
- (85) Clarke MJ. Individual patient data meta-analyses. *Best Pract Res Clin Obstet Gynaecol.* 2005; 19(1):47-55.
- (86) Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *J Clin Epidemiol.* 2002; 55(1):86-94.
- (87) Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ.* 2010; 340:c221.
- (88) Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev.* 2014; 1:CD007470.
- (89) Johnson RT, Dickersin K. Publication bias against negative results from clinical trials: three of the seven deadly sins. *Nat Clin Pract Neurol.* 2007; 3(11):590-591.
- (90) Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, et al. Biomedical research: increasing value, reducing waste. *Lancet.* 2014; 383(9912):101-104.
- (91) Chalmers I, Bracken MB, Djulbegovic B, Garattini S, Grant J, Gulmezoglu AM, et al. How to increase value and reduce waste when research priorities are set. *Lancet.* 2014; 383(9912):156-165.
- (92) Al-Shahi SR, Beller E, Kagan J, Hemminki E, Phillips RS, Savulescu J, et al. Increasing value and reducing waste in biomedical research regulation and management. *Lancet.* 2014; 383(9912):176-185.

- (93) Glasziou P, Altman DG, Bossuyt P, Boutron I, Clarke M, Julious S, et al. Reducing waste from incomplete or unusable reports of biomedical research. *Lancet*. 2014; 383(9913):267-276.
- (94) Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet*. 2009; 374(9683):86-89.
- (95) Association of the British Pharmaceutical Industry. Clinical Trial Transparency: Technical standards for data sharing for old, current and future clinical trials. December 2013. Available from [www.abpi.org.uk/industry-info/Documents/Clinical%20Trial%20Transparency.pdf](http://www.abpi.org.uk/industry-info/Documents/Clinical%20Trial%20Transparency.pdf)
- (96) Karolinska Institutet. Research documentation at Karolinska Institutet. June 2010. Available from [www.ki.se/sites/default/files/h9\\_handbok\\_forskningsdokumentation.pdf](http://www.ki.se/sites/default/files/h9_handbok_forskningsdokumentation.pdf)
- (97) Border P. Transparency of Clinical Trial Data. Report no. 461. 26 March 2014. The Parliamentary Office of Science and Technology. Available from [www.parliament.uk/business/publications/research/briefing-papers/POST-PN-461/transparency-of-clinical-trials-data](http://www.parliament.uk/business/publications/research/briefing-papers/POST-PN-461/transparency-of-clinical-trials-data)
- (98) Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med*. 2006; 355(10):1018-1028.
- (99) Drazen JM. Transparency for clinical trials--the TEST Act. *N Engl J Med*. 2012; 367(9):863-864.
- (100) Chan AW, Song F, Vickers A, Jefferson T, Dickersin K, Gotzsche PC, et al. Increasing value and reducing waste: addressing inaccessible research. *Lancet*. 2014; 383(9913):257-266.
- (101) Goldacre B. *Bad Science*. United Kingdom: Fourth Estate; 2008.
- (102) Gøtzsche PC. *Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare*. London: Radcliff Publishing; 2013.
- (103) Henke N, Kelsey T, and Whately H. Transparency - the most powerful driver of health care improvement? Report no. 11. 2012, Pages: 72. McKinsey & Company. Available from [www.mckinsey.com/client\\_service/healthcare\\_systems\\_and\\_services/latest\\_thinking/health\\_international/archive/issue\\_11](http://www.mckinsey.com/client_service/healthcare_systems_and_services/latest_thinking/health_international/archive/issue_11)
- (104) Grainger D. Industry Voices: Clinical trial transparency--time for some carrot as well as more stick? Last update: October 2013; FierceBiotech. Cited: 2014 Nov. 18. Available from [www.fiercebiotech.com/story/industry-voices-clinical-trial-transparency-time-some-carrot-well-more-stic/2013-10-17](http://www.fiercebiotech.com/story/industry-voices-clinical-trial-transparency-time-some-carrot-well-more-stic/2013-10-17)
- (105) Spears T. Medical journal will 'print anything'. Last update: August 2014; The StarPhoenix (Saskatoon) 2014. Available from [www2.canada.com/saskatoonstarphoenix/news/story.html?id=5f5c83ab-89d9-4fe7-a93c-f683ca3aabc3](http://www2.canada.com/saskatoonstarphoenix/news/story.html?id=5f5c83ab-89d9-4fe7-a93c-f683ca3aabc3)
- (106) Potthast R, Vervolgyi V, McGauran N, Kerekes MF, Wieseler B, Kaiser T. Impact of inclusion of industry trial results registries as an information source for systematic reviews. *PLoS One*. 2014; 9(4):e92067.
- (107) International Committee of Medical Journal Editors. Guiding Principles for the Development of Policies on Sharing Clinical Trials Data. Last update: January 2014; ICMJE org. Available from [www.icmje.org/news-and-editorials/principles\\_data\\_sharing\\_jan2014.html](http://www.icmje.org/news-and-editorials/principles_data_sharing_jan2014.html)
- (108) Saarimäki JM, Rasmussen K, Krleža-Jeric K, Sim I, Gluud C. Global registries for clinical trials, compliance with WHO standards, and possibilities for uploading anonymised individual participant data. submitted to *BMJOpen*. 2015.
- (109) PLoS. Editorial and Publishing Policies. Last update: 2014; plosone.org. Cited: 2014 Nov. 18. Available from <http://www.plosone.org/static/policies#sharing>
- (110) Saarimäki JM, Skoog M, Gluud C. Where can we safely upload our depersonalised individual participant data from clinical trials? submitted to *BMJOpen*. 2015.
- (111) Finnish Advisory Board on Research Integrity. Responsible conduct of research and procedures for handling allegations of misconduct in Finland: Guidelines of the Finnish Advisory Board on Research Integrity 2012. 14 November 2012. Available from [www.tenk.fi/sites/tenk.fi/files/HTK\\_ohje\\_2012.pdf](http://www.tenk.fi/sites/tenk.fi/files/HTK_ohje_2012.pdf)
- (112) Ministry of Higher Education and Science. The Danish Code of Conduct for Research Integrity. 5 November 2014. Available from [www.ufm.dk/publikationer/2014/filer-2014/the-danish-code-of-conduct-for-research-integrity.pdf](http://www.ufm.dk/publikationer/2014/filer-2014/the-danish-code-of-conduct-for-research-integrity.pdf)
- (113) European Commission. European Databank on Medical Devices - EUDAMED. Last update: August 2014; europa.eu. Available from [www.ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index\\_en.htm](http://www.ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm)
- (114) Vetenskapsrådets projektdatabas. Last update: January 2015; vr.se. Available from [www.vrproj.vr.se/default.asp?funk=s](http://www.vrproj.vr.se/default.asp?funk=s)
- (115) CRISStin - Current Research Information SysTem In Norway. Norges teknisk-naturvitenskapelige universitet. Cited: 17-11-2014. Available from [www.cristin.no](http://www.cristin.no)
- (116) Helsedirektoratet. Helse Norge. Last update: January 2015; helsenorge.no. Available from [www.helsenorge.no](http://www.helsenorge.no)

- (117) European Commission. List of fields contained in the 'EUDRACT' clinical trials database to be made public, in accordance with article 57(2) of Regulation (EC) NO 726/2004 and its implementing guideline 2008/C168/02. Report no. ENTR/F/2/SF D (2009) 3687. 4 February 2009. Available from [www.ec.europa.eu/health/files/eudralex/vol-10/2009\\_02\\_04\\_guideline\\_en.pdf](http://www.ec.europa.eu/health/files/eudralex/vol-10/2009_02_04_guideline_en.pdf)
- (118) Danish Health and Medicines Authority. Guideline for applications for authorisation of clinical trials of medicinal products in humans. Last update: January 2015; sundhedsstyrelsen dk. Available from [www.sundhedsstyrelsen.dk/en/medicines/regulation/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisation-of-clinical-trials-of-medicinal-products-in-humans#bilag1](http://www.sundhedsstyrelsen.dk/en/medicines/regulation/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisation-of-clinical-trials-of-medicinal-products-in-humans#bilag1)
- (119) Den Nationale Videnskabsetiske Komité. Guidelines about Notification. Last update: January 2015; cvk sum dk. Available from [www.cvk.sum.dk/english/guidelinesaboutnotification.aspx](http://www.cvk.sum.dk/english/guidelinesaboutnotification.aspx)
- (120) Vetenskapsrådet. Open Access - free accessibility to research findings. Last update: January 2015; vr se. Available from [www.vr.se/inenglish/researchfunding/applyforgrants/generalconditionsforgrantapplications/openaccess.4.44482f6612355bb5ee780003075.html](http://www.vr.se/inenglish/researchfunding/applyforgrants/generalconditionsforgrantapplications/openaccess.4.44482f6612355bb5ee780003075.html)
- (121) Svensk Nationell Datatjänst. Tillgänglighetsnivåer hos SND. Last update: December 2014; gu se. Available from [www.snd.gu.se/sv/overlamna-data/tillganglighetsnivaer](http://www.snd.gu.se/sv/overlamna-data/tillganglighetsnivaer)
- (122) Thestrup JB, Kruse F, Nondal L, Dorch B, Andersen M, Blaabjerg NJ, et al. Forvaltning af forskningsdata i Danmark. DEFF-rapport. 2013. Available from [www.deff.dk/fileadmin/user\\_upload/dokumenter/DEFF/aktuelt/Afrapporteringer/Rapport\\_Forvaltning\\_af\\_forskningsdata.pdf](http://www.deff.dk/fileadmin/user_upload/dokumenter/DEFF/aktuelt/Afrapporteringer/Rapport_Forvaltning_af_forskningsdata.pdf)
- (123) Faculty of science at University of Copenhagen. Editors: SCIENCE Research and Innovation and SCIENCE communication. White paper on dealing with research data - developing a roadmap. 23 July 2015. Available from [www.science.ku.dk/english/](http://www.science.ku.dk/english/)
- (124) Svensk Nationell Datatjänst. SND Open Data. Last update: November 2014; gu se. Available from [www.opendata.snd.gu.se/webview/?language=en](http://www.opendata.snd.gu.se/webview/?language=en)
- (125) Datainspektionen. Tillsyn enligt personuppgiftslagen (1998:204) - av Göteborgs universitet (Svensk nationell datatjänst). Last update: April 2012; datainspektionen se. Available from [www.datainspektionen.se/Documents/beslut/2012-04-23-snd.pdf](http://www.datainspektionen.se/Documents/beslut/2012-04-23-snd.pdf)
- (126) European Federation of Pharmaceutical Industries and Associations. EFPIA Clinical Trial Data Portal Gateway. Last update: 2015; efpia eu. Available from [www.transparency.efpia.eu/responsible-data-sharing/efpia-clinical-trial-data-portal-gateway](http://www.transparency.efpia.eu/responsible-data-sharing/efpia-clinical-trial-data-portal-gateway)
- (127) Salokannel M. Status of the revision of the EU data protection framework. In: Joint Nordic Registers and Biobanks - A goldmine for health and welfare research. Report no. 5. 2014, Pages: 44-56. Available from [www.nordforsk.org/no/publikasjoner/publications\\_container/joint-nordic-registers-and-biobanks-a-goldmine-for-health-and-welfare-research](http://www.nordforsk.org/no/publikasjoner/publications_container/joint-nordic-registers-and-biobanks-a-goldmine-for-health-and-welfare-research)
- (128) Herrmann KH, Wolff R, Scheibler F, Waffenschmidt S, Hemkens LG, Sauerland S, et al. All nations depend on the global knowledge pool--analysis of country of origin of studies used for health technology assessments in Germany. *PLoS ONE*. 2013; 8(3):e59213.
- (129) Wolff RF, Reinders S, Barth M, Antes G. Distribution of country of origin in studies used in Cochrane Reviews. *PLoS ONE*. 2011; 6(4):e18798.
- (130) Chan AW, Tetzlaff JM, Altman DG, Dickersin K, Moher D. SPIRIT 2013: new guidance for content of clinical trial protocols. *Lancet*. 2013; 381(9861):91-92.
- (131) European Commission. Guidelines on Data Management in Horizon 2020. Report no. Version 1.0. 11 December 2013. Available from [www.ec.europa.eu/research/participants/data/ref/h2020/grants\\_manual/hi/oa\\_pilot/h2020-hi-0a-data-mgt\\_en.pdf](http://www.ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-0a-data-mgt_en.pdf)
- (132) Groves T. Big strides in Europe towards clinical trial transparency. *BMJ*. 2014; 349:g6276.
- (133) Maruani A, Boutron I, Baron G, Ravaud P. Impact of sending email reminders of the legal requirement for posting results on ClinicalTrials.gov: cohort embedded pragmatic randomized controlled trial. *BMJ*. 2014; 349:g5579.
- (134) International Conference on Harmonisation Guideline for International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Topic E 3 Structure and Content of Clinical Study Reports. Report no. CPMP/ICH/137/95. June 1996. Available from [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002832.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002832.pdf)
- (135) The Consort Group. Consort statement. Last update: March 2010; [www.worldpsychiatricassociation.org](http://www.worldpsychiatricassociation.org). (7th Congress in Vienna, Italy) Available from [www.consort-statement.org/](http://www.consort-statement.org/)
- (136) Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database Syst Rev*. 2012; 11:MR000030.
- (137) Colli A, Fraquelli M, Casazza G, Conte D, Nikolova D, Duca P, et al. The architecture of diagnostic research: from bench to bedside--research guidelines using liver stiffness as an example. *Hepatology*. 2014; 60(1):408-418.

- (138) Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med.* 2013; 10(2):e1001380.
- (139) Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med.* 2013; 10(2):e1001381.
- (140) Hemingway H, Croft P, Perel P, Hayden JA, Abrams K, Timmis A, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ.* 2013; 346:e5595.
- (141) PLOS Medicine Editors. Observational studies: getting clear about transparency. *PLoS Med.* 2014; 11(8):e1001711.
- (142) Peat G, Riley RD, Croft P, Morley KI, Kyzas PA, Moons KG, et al. Improving the transparency of prognosis research: the role of reporting, data sharing, registration, and protocols. *PLoS Med.* 2014; 11(7):e1001671.
- (143) Thomas L, Peterson ED. The value of statistical analysis plans in observational research: defining high-quality research from the start. *JAMA.* 2012; 308(8):773-774.
- (144) Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ.* 2015; 350:g7594.

**Nordic Trial Alliance**

NordForsk, Stensberggata 25, NO-0170 Oslo

[www.nta.nordforsk.org](http://www.nta.nordforsk.org)

---