

NORDIC BIOBANKS AND REGISTERS A BASIS FOR INNOVATIVE RESEARCH ON HEALTH AND WELFARE

POLICY PAPER 2/2017



NordForsk



Nordic biobanks and registers
A basis for innovative research on health and welfare
POLICY PAPER 2/2017

NordForsk, Stensberggata 25, N-0170 Oslo, Norway
www.nordforsk.org
Org.nr. 971 274 255

Editor: Juni Palmgren

Illustrations: Rassco/Shutterstock
Design: Jan Neste, jnd
Printed by: O7 Group, 2017

ISSN 1504-8640



NORDIC BIOBANKS AND REGISTERS A BASIS FOR INNOVATIVE RESEARCH ON HEALTH AND WELFARE

POLICY PAPER 2/2017

NORDFORSK /JUNI PALMGREN

CONTENTS

SUMMARY	4
WORK TO DATE	10
National initiatives: Denmark, Finland, Iceland, Norway, Sweden	11
Joint Nordic activity	13
Status on legislation and ethics	14
VISION AND NEXT STEPS	16
Harmonised legislation and ethics in the Nordic region following new EU regulations	18
Development of a secure federated Nordic Commons for data sharing and tool development	19
REFERENCES	20

PREFACE

NordForsk is an organisation under the Nordic Council of Ministers that provides funding for and facilitates Nordic research and research infrastructure cooperation in all fields of research when this adds value to activities being conducted in the Nordic region. Priority is given to thorough analysis as a basis for funding research that is deemed to have considerable potential for knowledge-based progress in the long term.

Health and welfare research is an area recognised by national policy makers and research funders as having particular Nordic added value. The Nordic countries possess unique population-based registers and biobanks that provide an unparalleled resource for research if properly utilised.

The shared practice of issuing personal identification numbers to each citizen also gives the Nordic countries a superlative basis for carrying out longitudinal research and combining register data - across borders as well. Although the Nordic countries have similar registers in each country, the great potential lies in the combination of register information into larger data sets to allow studies of rare outcomes and diseases. The combined Nordic population base is around 26 million which provides a solid foundation for multiple types of research of high international scientific value, and will also, as indicated above, lead to great benefits for society at large. The Nordic countries can thus play a pivotal role in unravelling complex relationships related to health and well-being in societies and individuals, thereby contributing to a knowledge base with global implications.

The Nordic "goldmine" of data resources remains underexplored, however, largely due to cumbersome legal, ethical, organisational, and technical constraints on cross-border sharing of data. To take advantage of the full potential of the registers in Nordic research cooperation, these barriers must be overcome.

This report emphasises registers and biobanks as research infrastructures for innovative research on health and welfare. The report has been drawn up in response to the request of the Nordic Committee of Senior Officials for Education & Research (ÅK-U) within the Nordic Council of Ministers to NordForsk to produce an overview of current knowledge on cross-border development of research that uses Nordic registers, biobanks and clinical studies, and includes suggestions for policy implications.

NordForsk would like to offer its sincere thanks to Professor Juni Palmgren, Karolinska Institutet who has written this review.

Oslo, February 2017



Gunnel Gustafsson
Director of NordForsk

SUMMARY





SUMMARY

The report describes a knowledge base for cross-border development of research that uses Nordic registers, biobanks and clinical studies, and offers suggestions for policy implications. Separate reports are provided on the Nordic Trial Alliance (NTA) (1), the Nordic eScience Action Plan 2.0 (2) and Open Access to research data from a Nordic perspective (3).

This report focuses on registers and biobanks as research infrastructures for innovative research on health and welfare. The Nordic countries have very similar and unique healthcare and welfare systems. The personal identification number (PIN) for each citizen makes it possible to carry out longitudinal research and research based on a combination of health registers (e.g. healthcare data, biobanks, register on the prevalence of different diseases and causes of death) and social registers (e.g. education, employment, migration, gender representation in democratic decision-making). In contrast to the rest of the world, the Nordic countries have very long time series at the population level, considered to be a unique "goldmine" for research. The proposed longitudinal data infrastructure is particularly well suited to studying changes in the Nordic welfare model over time and for setting up a unique basis for personalised medicine/precision medicine that could guide medical practice in real time, including social and behavioural aspects.

Importantly, in recent years national policy makers and research funding agencies in the Nordic countries have gained experience and have expanded their efforts to utilise registers and biobanks for research on societal challenges. When these national efforts are coordinated, the population base of the Nordic region, comprising about 26 million people, will serve as a solid basis for multiple types of inquiry. The Nordic countries can play a pivotal role in unravelling complex relationships relating to the health and wellbeing of societies and individuals, thus paving the way for a knowledge base with global implications.

However, the Nordic "goldmine" of registers and biobanks remains underexplored, largely due to cumbersome organisational and funding procedures as well as legal, ethical and technical constraints on cross-border sharing of data. This issue was summarised in the Nordic Council of Ministers (NCM) report "Reinforced Nordic collaboration on data resources - Challenges from six perspectives" (Sandberg 2012 (8)). Although understanding of the challenges has greatly improved, important difficulties remain. This report gives an overview of key reports, analyses, pilot studies and various forms of development activity on registers and biobanks that have been carried out over recent years by NordForsk, the Nordic Council of Ministers and others actors.

In light of the new European General Data Protection Regulation (GDPR) (May 2016) and the new *European Regulation on Clinical Trials on Medicinal Products for Human Use* (April 2015), political will and decisions are needed to harmonise the interpretation of legislation, policies and safeguards for using personal data in research in the Nordic region. In April 2016 the League of European Research Universities (LERU) warned that the freedom of EU member states to set up their own legislation might restrict and fragment the conditions for carrying out scientific research within the EU. This is also true for the Nordic countries.

Of particular interest for Nordic alignment are the requirements concerning individual consent and ethical review as well as the processing of data from biological materials stored in biobanks. There is a general lack of knowledge in the research community about how ethical matters are considered in the Nordic countries, and how the national ethics committees at country level operate and what is needed to obtain an approval. Currently there are differences across the Nordic countries in the requirements for ethical review of cross-border research. These differences need to be reviewed at the highest political level, and harmonisation of national laws, regulations and procedures should be attempted before the Regulation on Clinical Trials and the GDPR enter into force in spring 2017 and 2018, respectively. A report from the Nordic Trial Alliance describes a simplified procedure based on mutual recognition of ethical review across the Nordic region as one option for cross-border clinical trials. Mutual recognition is advocated more broadly than for clinical trials by Ludvigsson et al. (2015 (36)). A letter dated 18 April 2016 from the Royal Norwegian Ministry of Health and Care Services and the Ministry of Social Affairs and Health in Finland calls for a joint Nordic effort to revise the ethical review process in the Nordic countries.

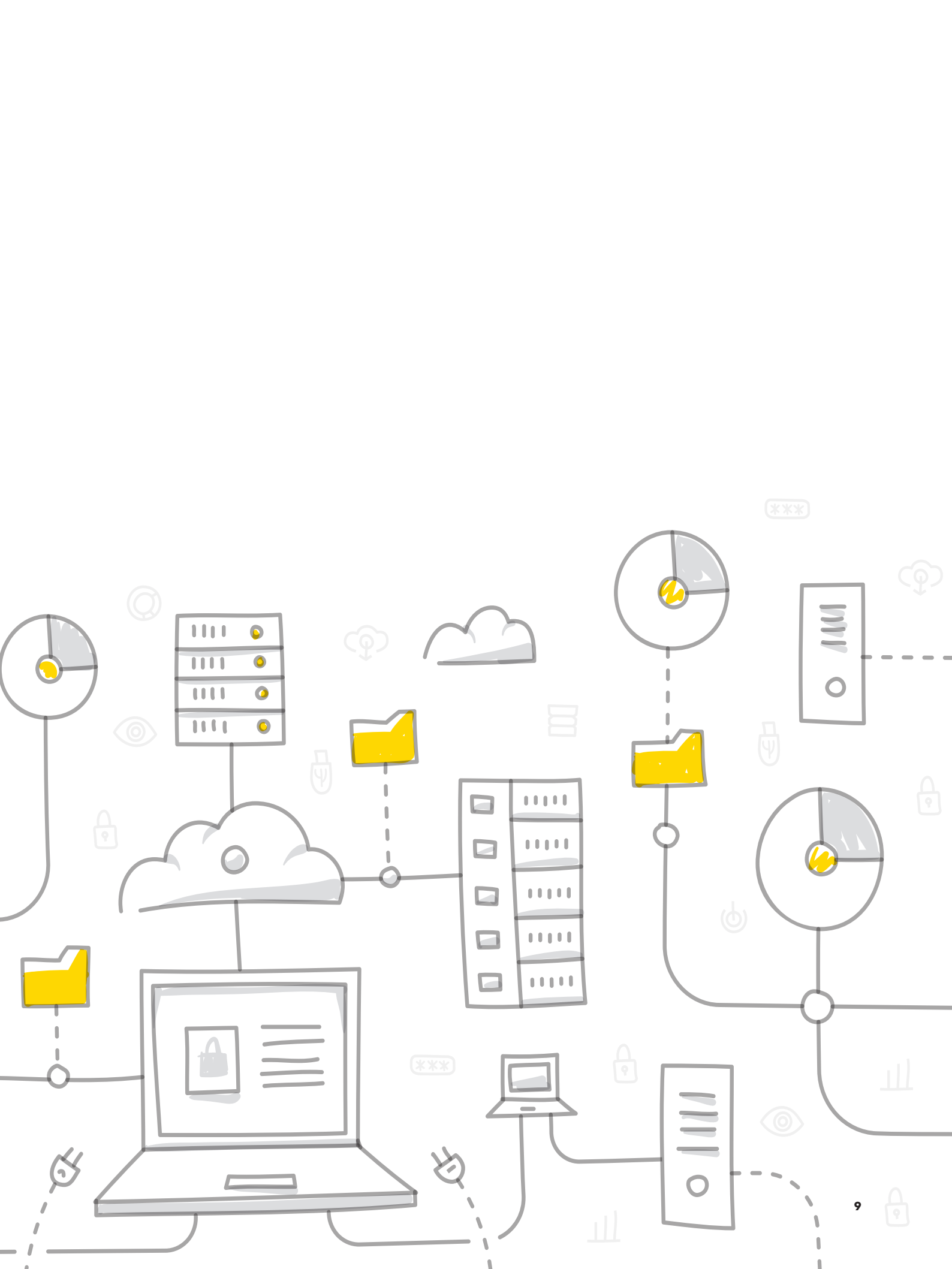
Parallel to harmonising legal and ethical procedures, safe technical solutions for distributed documentation, storage and analyses of sensitive personal data are needed, preferably in the form of a coherent Nordic platform. An ambitious long-term goal could be a *Nordic Commons*, i.e. "A shared virtual space where scientists can work with the digital objects of biomedical research. This is a system that will allow investigators to find, manage, share, use and reuse data, software, metadata and workflows." A *Nordic Commons* is in line with the Nordic eScience Action Plan 2.0, and with the visions of the Nordic eInfrastructure Collaboration (NeIC) and the Nordic Information for Action eScience Center (NIASC). It further aligns with the US National Institutes of Health concept of *The Commons*, work carried out by the Danish Ministry of Health and the recent initiative on a Medical Research Map for Finland, including the Finnish SITRA-based project Isaacus. A *Nordic Commons* would build on an open access policy and transparency.

The time is ripe for coordinated policy support at the highest political level to organise and fund research on the Nordic welfare model in a changing society, coupled with a modern Nordic infrastructure for research data. A concrete, coherent Nordic implementation plan, with a timeline and responsible actors, is called for. An *urgent first step* involves Nordic legislation and ethical review following the EU General Data Protection Regulation and the EU Clinical Trials Regulation. A *second, longer-term step* involves technical data and tool-sharing solutions, preferably through the notion of a *Nordic Commons*. The Nordic countries should also tap into the ongoing discussions on Open Science and data sharing in the context of the European Open Science Cloud, where the Nordic region can play a key role and lead the way forward.

This report has been updated until autumn 2016.

WORK TO DATE





WORK TO DATE

As stated in the Könberg report (4), the Nordic region is a goldmine for population-based research because of access to stored data on individuals in administrative registers of personal information, and biobanks. This information has been collected over a long time, and often covers the entire Nordic population. The similarities between the health and welfare systems in the Nordic countries, and the use of the personal identification number (PIN), (augmented by the coordination number for the newly arrived), create a good basis for comparative studies and analyses in the Nordic region. Together, the Nordic region has 26 million inhabitants, which comprises an adequate population base for studies of both complex and rare phenomena.

The NOS-M White Paper on Medical Research 2014 (5) emphasises that the Nordic countries have extraordinary resources and infrastructures for medical research that have attracted international collaborations and funding for years. Closer cooperation can promote even better results. The Nordic registers and biobanks provide a good example and starting point for what can be achieved. The Nordic region can help to solve emerging, complex societal and healthcare issues as well as improve health standards and quality of life across the globe.

The reports from the NORIA-net on registers and biobanks 2014 (6) and from the conference on "Joint Nordic Focus on Research Infrastructures – Looking to the Future" (7), organised during the Swedish chairmanship of the Nordic Council of Ministers in 2013, build on six challenges for Nordic data-sharing in research: political, organisational, legal, ethical, financial and technical. These six challenges were initially summarised in the NCM report by Sandberg 2012 (8).

Through a coordinated longitudinal life course perspective on a large enough population, deep penetration and review of the Nordic welfare model has potential bearing far beyond the Nordic region *per se*. The Nordic owners of the national population and health registers, the national statistical institutes (NSI) and the health data authorities such as the national boards for health and welfare play a pivotal role in this context. Focus areas for the research include mobility, immigration and integration, unemployment, social and health inequality, education, the healthcare system, the ageing population, youth and children, etc.

The most challenging and potentially most rewarding activity in the health and welfare sciences today lies at the intersection between the molecular, medical, social and behavioural sciences. A big challenge is how molecular advances can become instrumental in guiding medical practice in real time. The concept of *personalised medicine/precision medicine* has the potential to dramatically change the clinical focus and improve early diagnoses, prevention of disease, and the efficacy and safety of patient treatment. Reduced healthcare expenditure and minimal use of unnecessary and inefficient treatments and drugs are the expected results. From a social and behavioural perspective it is important that citizens are informed and included in the transition process.

The notion of precision medicine was launched in the US in January 2015, and the US National Institutes of Health (NIH) has been given responsibility for directing the implementation. In February 2016 the Banbury Conference (9), with participants from the Nordic countries and from NIH and Cold Spring Harbor in the US, concluded that the existing resources for population-wide longitudinal research in the Nordic countries gives the region great potential to be a forerunner in the development of tools for personalised medicine.

Cross-border access to data and harmonisation of procedures are critical. A statement from the ESF Forward Look on Personalised Medicine for the European Citizen [10] presents a series of recommendations under the headings data handling, models and decision-making processes, interdisciplinarity, infrastructure and resources. Personalised medicine is not only expected to be a scientific and technological challenge but will also present a number of new ethical and legislative questions related to the use of personal data and prioritisation. It will require close cross-disciplinary interactions between clinicians in different areas of specialisation, including bio-scientists and technologists. In particular, computational biology, bioinformatics and biostatistics will become increasingly central to all aspects of health care.

National initiatives

Significant initiatives and progress have already been made at the national level in coordinating resources for research based on personal data in registers and biobanks. Some of these are described below. Preparation for this report has revealed a lack of knowledge within the Nordic countries about initiatives taken at the national level. Appropriate communication channels are needed for mutual exchange of knowledge at the Nordic level.

DENMARK

- In Denmark the Danish National Biobank at Statens Serum Institut gives scientists a comprehensive overview of and access to millions of biological samples in Denmark's healthcare system for the first time (11). In addition, these can be linked with information from the nationwide health registers through an access interface with the Danish Health Data Authority. The Danish biobank opened in 2012 with contributions from Denmark's Ministry of Science, Innovation and Higher Education, Novo Nordisk and the Lundbeck Foundation, totalling roughly EUR 20 million. Work is going on to revise the governance model for access to data from the Danish National Biobank, the purpose of which is to ensure a balance between improving the scientific utilisation of data originating from biological samples, while maintaining individual data integrity.
- In late 2013 the Danish Ministry of Health established a national forum consisting of key stakeholders, with the aim of improving the scientific and clinical impact of Danish healthcare data. Under the heading "Strategisk Alliance for Register og Sundhedsdata" (STARS*) the forum supports the Ministry of Health in developing a strategy for access to health data, thereby improving the scientific and clinical return from these.
- In 2016 the Ministry of Health launched a feasibility study concerning a national initiative for personalised medicine, the purpose of which is to investigate the scientific and clinical, technical, ethical and economic implications of a major initiative on personalised medicine. The goal is to present different scenarios that would enable personalised medicine to become an integrated part of the Danish healthcare system.

FINLAND

- The Isaacus project in Finland, a “welfare service operator” project started in 2016, is run jointly by several ministries and government agencies (12). The project is named after Isaacus Rothovius, who initiated population registration in Finland 1658, over 200 years before Statistics Finland was founded. Key tools for the project are legislation for reuse of welfare data and digital tools for data integration. The project complements the Open Science and Research Initiative (ATT) of the Ministry of Education and Culture of Finland for the promotion of research information availability and an Open Science platform for the years 2014–2017 (13).

ICELAND

- The Icelandic population is the most genotyped population in the world, with deCODE Genetics covering over half of the population in terms of high density SNP genotyping and 25 000 whole genome sequences. Genealogy is available on the whole Icelandic population and extensive phenotype data is linked to the genomic database.

NORWAY

- The Health&Care21 Strategy was developed by the universities, hospitals, municipalities, private sector, government agencies and users in 2014. The Norwegian government established the Health&Care21 Committee in 2014 and launched its follow-up plan of the Health&Care21 Strategy in 2015. Health data and clinical research are two of ten prioritised areas in the strategy and action plan (14) (15).
- The Ministry of Health and Care Services has established an expert working group with a mandate to explore and suggest measures to facilitate easier access to and linkages between health data and other types of data sources for various purposes and user groups. The work will be completed in June 2017.
- The Ministry of Health and Care Services is in the process of reviewing the national regulations on health registries, including regulations on medical quality registries and population cohort studies and biobanks. A national strategy for the implementation of personalised medicine was launched in June 2016 by the Norwegian Directorate of Health (16). The Research Council of Norway (RCN) has financed several research infrastructure projects relevant for research on personalised medicine, including BIG data MEDical and the National Consortium for Sequencing and Personalized Medicine.
- In early 2015 the Research Council of Norway initiated a dialogue with national actors on how to improve management of the Norwegian data sets for health research as part of their follow-up of the Health&Care21 Strategy and an initiative from the Health&Care21 Committee. Two research infrastructure initiatives financed by RCN, Biobank Norway (17), the Norwegian BBMRI-ERIC node, and “Health Registries for Research” (18) will explore measures to improve access to health data and metadata across the Norwegian health registries.

SWEDEN

- In 2013, the Swedish Government gave the Swedish Research Council the task of enhancing access to and utilisation of register data in research, and the Swedish Research Council is in the process of aligning Swedish cohorts and other researcher-collected data into national resources. The web portal “Register-forskning.se” (19) is under construction, and will serve as a common national entry point. Statistics Sweden, the Swedish National Board of Health and Welfare, the county councils and the Swedish biobank infrastructure contribute to the national effort. A metadata framework for register and research metadata was launched in mid-2016. The Register Data Council, with representation at the highest institutional level from key stakeholders, is overseeing the Swedish coordination effort.
- The Swedish Research Council commissioned Robert Erikson, Stockholm University, to create a knowledge base on how to coordinate Swedish longitudinal data material based on questionnaires, clinical studies and register material. The report was filed in 2014 (20) and is now the basis for an important reorganisation of funding to such national infrastructure projects.

- The Swedish Government commissioned Bengt Westerberg to lead a comprehensive investigation into the Swedish legal and ethical framework for register-based research (21). A report of the findings was presented in 2014.
- 2015-2016: Through the Swedish National Infrastructure for Computing (SNIC), a platform is being set up for secure data handling of molecular data – with a possible interface with register data.

Joint Nordic activity

NordForsk, the Nordic Council of Ministers (NCM) and other actors have initiated and supported a large number of Nordic policy groups, networks, pilot projects and surveys for research and research infrastructure related to the domain of health and welfare. Some of these are part of the NCM programme *Sustainable Nordic Welfare*, but many fall within the framework of NordForsk.

These efforts include the *NORIA-net on Health and Welfare 2009–2011* (22), *NORIA-net in Sports Science 2010–2011* (23), *NORIA-net on Registers and Biobanks 2011–2014* (24), the *Nordic Biobank Network 2011–2015* (25) with the *Nordic biobank-based pilot study on colorectal cancer 2012–2015* (26), the *Nordic Trial Alliance* (NTA) 2013–2015 (27), the *Nordic High-Level Expert Group on Research Infrastructures 2014–2018* (28), the pilot for a *Nordic platform on sensitive data, Tryggve 2014* (29) set up by the *Nordic e-Infrastructure Collaboration* (NeIC) (30), the *Nordic Microdata Access Network, NordMAN 2015–2018* (31), the pilot on *Nordic Clinical Quality Registers 2015–2016* (32) and support for networking and surveys on Nordic coordination of European research activities. The purpose and results of these efforts are briefly described below.

The NORIA-net on Health and Welfare focused on how Nordic research funding organisations, including NordForsk, could support and strengthen the Nordic position in research on socioeconomic health inequality and effective public health interventions. The main outcome has been the Nordic Programme on Health and Welfare (33) and the first call "Distribution of health and welfare". The *NORIA-net in Sports Science* evaluated sports science in the Nordic region in order to identify strengths and weaknesses, and the underlying causes of these. The *NORIA-net on Registers and Biobanks* focused on strengthening Nordic research on health and welfare with considerable policy impact at national and Nordic levels and with relevance for the Nordic Programme on Health and Welfare (33).

The *Nordic Biobank Network*, formerly BBMRI.Nordic, has been an important player in the implementation of the European ESFRI BBMRI-ERIC and has been instrumental for e.g. the *Nordic biobank-based pilot study on colorectal cancer*, which illustrates what can be achieved through Nordic cooperation. Colorectal cancer (CRC) is considered sufficiently uncommon to require a joint Nordic approach in order to obtain sufficient statistical power to identify risk factors and biomarkers for early diagnosis and tailored treatment. In the first phases of the Nordic Biobank Network pilot study on colorectal cancer 2012–2015, the formal and practical logistical basis of performing such studies was established. Using linkages between the cancer registries, multi-generation registries, population registries and biobanks in the Nordic countries, a study base for assessing the importance of heredity and environment on the aetiology of colorectal cancer was established. The CRC pilot identified a large number of different biobanks in Sweden, Denmark, Finland, Norway, Estonia and Iceland that have stated that the biobanked samples and data are accessible and that requests for samples and data will be welcomed. In total, these biobanks have reported that they store samples from approximately 30 000 CRC patients. Importantly, the study encountered complexities and time-consuming processes which are believed to explain why very few joint Nordic studies that exploit biobanks and registry infrastructures exist, in spite of the potential goldmine these represent for diseases that are not common.

The *Nordic Trial Alliance* (NTA) is a pilot project funded by the Nordic Council of Ministers and NordForsk in 2014–2016, with a possible extension beyond 2016. It is based on established national networks for clinical research, with the aim of enhancing Nordic cooperation on clinical multi-centre trials and to make it easier in general to carry out clinical research in the Nordic region. Greater coordination is required if Nordic clinical research is to maintain its strong foothold and international position. Nordic collaboration is needed between companies, hospitals and universities to achieve this goal. NTA announced a pilot call for Nordic clinical studies that showed the need for funding for joint Nordic studies and the potential that lies in combining clinical and register data. NTA has also worked on targeting mutual recognition of ethical review permission for Nordic studies.

Tryggve is a project to establish a Nordic platform for collaboration on sensitive data, funded by the *Nordic e-Infrastructure Collaboration* (NeIC) and the European ESFRI ELIXIR nodes in Denmark, Finland, Norway and Sweden. The approach is to utilise and connect existing capacities and services in the Nordic countries. The NeIC is a distributed organisation consisting of technical experts from academic high-performance computing centres across the Nordic countries. The NeIC is administered by NordForsk and funded by national research funding agencies and NordForsk.

The *Nordic Microdata Access Network*, NordMAN, set up by the directors general of the Nordic national statistical institutes (NSI) was launched in autumn 2015. It is funded by the NSIs and NordForsk to coordinate delivery of register data to Nordic research projects, while at the same time developing a joint framework for metadata (data that describes or defines other data).

In addition to policy groups, networks, pilot projects and surveys, two larger research initiatives have been started, funded through Nordic common pot initiatives: *the Nordic Programme on Health and Welfare* 2014–2018 (33) and *the Nordic Centre of Excellence in Health-related eSciences* (NIASC) 2014–2018 (34). These are briefly described below.

The Nordic Programme on Health and Welfare is a cooperative effort between the Academy of Finland, the Danish Research Council for Independent Research | Medical Sciences, the Icelandic Centre for Research (Rannis), the Research Council of Norway, the Swedish Research Council for Health, Working Life and Welfare (FORTE), the Swedish Research Council and NordForsk. The programme, which runs from 2014 to 2018, will cover 11 larger research projects in 2016 with plans for expansion in 2017, with plans for expansion. The programme defines health and welfare in a broad perspective. Welfare in this context entails not only welfare and unemployment benefits, but also education and the labour market. The overall purpose is to generate knowledge on the effect of demographic, social, environmental and biological factors on human health and the challenges this implies for human welfare, and to translate this new knowledge into practical solutions in healthcare and welfare systems. Several projects targeting Nordic register data have been funded.

The Nordic Information for Action eScience Center (NIASC) has common pot funding from the Research Council of Norway, the Academy of Finland, the Swedish Research Council and NordForsk through the NordForsk-based *Nordic eScience Globalisation Initiative* (NeGI). NIASC aims to develop Open Source IT tools and support that allow easier tracking of Nordic biobank samples and data and enhance the capability to use data from national health registers and biobanks in the healthcare sector. NIASC does not develop biomarker-based risk prediction algorithms by itself, but is dependent on other projects to develop them. An example is the joint Nordic biobank-based pilot study on colorectal cancer (CRC) (26).

Status on legislation and ethics

Marjut Salokannel has been commissioned by NordForsk to review the state of the current legislation for research based on registers and biobanks and clinical studies in the Nordic countries. Salokannel (35) states that with regard to *primary processing* of health data, i.e. processing of primary health data which is based on consent, including clinical research and research using biological materials, the situation in the Nordic countries is very similar. A review by an ethics board is required in all Nordic countries. Some national differences exist with regard to the scope of consent and the details of *ethical* review process. For example, Finland does not require ethical review for research utilising biological materials and data.

With regard to register-based research and other types of re-utilisation of data, i.e. for *secondary processing* of health data for research purposes, with the exception of patient records, none of the Nordic countries require an explicit consent from the data subject. Denmark and Norway require a prior authorisation from the national data protection authority, and Finland requires a notification to the data protection authority. Sweden requires an obligatory ethical review for all processing of sensitive data for research use.

An article by Ludvigsson et al. (36) states that handling of pseudonymised data varies between countries. For pseudonymised data, a key file (between the PIN and the serial number) is stored at the government agency responsible for data matching (applicable in Sweden, Finland, Norway, and Iceland). The key file can generally be kept for one to three years in Sweden, but can be kept for five years in Finland (thereafter, a re-approval is needed) or must be destroyed immediately upon linkage (e.g. for some studies in Iceland).

The new EU General Data Protection Regulation (GDPR) was published in the Official Journal of the European Union in May and will be applied as law in all member states on 25 May 2018. The GDPR makes it possible to process personal data for scientific research purposes without consent subject to appropriate *safeguards* for the rights and freedoms of the data subject. Those safeguards will ensure that technical and organisational measures are in place, in particular to ensure respect for the principle of data minimisation. Pseudonymisation of data can be regarded as one of those measures (Art. 89.1). Moreover, the GDPR requires that national law, which provides the basis for processing of health-related data for scientific research without consent, must be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject (Art.9.2 (j)).

In a paper in April 2016, the League of European Research Universities (LERU) (37) warns that the freedom of EU member states to set up their own legislation may restrict and fragment the conditions for carrying out scientific research within the EU. This concern is certainly true for the Nordic countries as well, and it would be important to use the two-year period until the GDPR will be enforced in May 2018 to align the legal and ethical processes for conducting research in the Nordic countries.

On 16 April 2014, the EU approved the new Regulation on Clinical Trials on Medicinal Products for Human Use. To enact changes in national legislation in European countries, a three-year transition period is foreseen (Art. 98). For the Nordic countries, this primarily concerns the ethical review of clinical trial applications. Further processing and matching of data from clinical trials requires a separate consent from the data subject and is subject to the GDPR. The possibility of harmonising consent forms and terms for reuse of data across the Nordic region should be investigated.

The report from the Nordic Trial Alliance (NTA) (38) emphasises the need for a general revision of the Nordic ethical review process for clinical research. This is reinforced in a letter dated 18 April 2016 from the Royal Norwegian Ministry of Health and Care Services and the Ministry of Social Affairs and Health in Finland calling for a joint Nordic effort (39).

The NTA report describes three alternative solutions for a Nordic ethical review process, which have been developed in collaboration with professionals of ethical review of health data for clinical trials in the Nordic countries. These alternatives are (i) a joint Nordic committee, (ii) a mutual recognition procedure and (iii) maintaining the ethical review of both national and international research at the national level. The report states that all of these suggestions for harmonisation have their pros and cons. Alternative (i) is not considered realistic within the available time frame, while the mutual recognition procedure in alternative (ii) appears attractive due to its clear purpose and simplicity. It builds on the fact that the Nordic countries share moral philosophy and moral values and states that one of the Nordic countries (e.g. the reporting country) would be responsible for the ethical review and that the other countries would automatically recognise the result of the review. The NTA report finds alternative (iii) the most realistic. However, in order for alternative (iii) to bring any benefits beyond what is currently the status today, national procedures would need to be more closely aligned. In this case, agreements may prove more difficult and time consuming in practice than the principle of mutual recognition in alternative (ii).

A mutual recognition procedure for ethical review in the Nordic countries, more broad-based than for clinical trials, has been advocated by Ludvigsson et al. (36). A focused discussion on the scope and long-term goal of harmonisation of ethical procedures for health research in the Nordic countries is needed, and the NTA alternatives (i)-(iii) form a natural starting point.



VISION AND NEXT STEPS

The Nordic ambition for research on health and welfare requires the following conditions (5), all of which are available in principle, but which require harmonisation and simplified processes for joint set-up and use across national borders:

- 1) High-quality registers comprised of population data, clinical data, health data, heredity and socio-demographic factors;
- 2) Access to high-quality study materials with patient samples stored in biobanks and associated longitudinal environmental and clinical information;
- 3) Access to high-tech analysis platforms for the analysis of DNA, RNA, proteins and metabolites across borders;
- 4) A new way of working in which the necessary critical mass of expertise is achieved through large-scale cooperation between different specialties and different universities in the various Nordic countries.

This report details many important initiatives that have been taken at the national level in the Nordic countries and by NordForsk, the Nordic Council of Ministers (NCM) and other actors for exploring the potential of Nordic collaboration on research in welfare and health, including the use of registers and biobanks.

A coordinated commitment from the governmental level is now needed in order to align the infrastructure for registers and biobanks. The most urgent task is to harmonise legislation and legal procedures as well as the ethical review process for cross-Nordic research. Equally important, but as a longer term vision, is to set up a joint Nordic technical platform, a *Nordic Commons*, for secure handling of data and tools for cross-border research.

The focus for actions is given below with a suggestion for responsible actors and timelines.

Harmonised legislation and ethics in the Nordic region following new EU regulations

Since the Nordic countries share very similar moral values, cultures and healthcare and legal systems, they could pursue harmonisation relevant for research based on the EU General Data Processing Regulation (GDPR) and the EU Regulation on Clinical Trials more quickly and perhaps to a wider degree than the EU as a whole. In particular, attention needs to be paid to the various existing practical requirements for the scope of consent and for ethical review pertaining to both secondary and primary use of personal data. The possibility of introducing a mutual recognition principle for ethical review in the Nordic region merits careful assessment. Moreover, it is worth noting that Nordic scientists lack knowledge about how ethical matters are considered in the different Nordic countries and about how Nordic ethics committees operate and what is needed to obtain an approval. This slows down internationalisation and sharing of data across borders.

Suggested action:

A group is appointed from relevant ministries/research councils in the Nordic countries by the respective Nordic governments. The timeline is determined by the timeline for EU member state adoption of two new EU regulations.

Development of a secure federated Nordic Commons for data sharing and tool development

Parallel to harmonising legal and ethical procedures, safe technical solutions for distributed documentation, storage and analyses of sensitive personal data are needed, preferably in the form of a coherent Nordic platform. An ambitious long-term goal could be a *Nordic Commons*, i.e. "A shared virtual space where scientists can work with the digital objects of biomedical research. This is a system that will allow investigators to find, manage, share, use and reuse data, software, metadata and workflows." A *Nordic Commons* is in line with the Nordic eScience Action Plan 2.0 (2), and with the visions of the Nordic eInfrastructure Collaboration (NeIC) (30) and the Nordic Information for Action eScience Centre (NIASC) (34), funded through the Nordic eScience Globalisation Initiative (NeGI). It further aligns with the US National Institutes of Health concept of *The Commons* (40), with work carried out by the Danish Ministry of Health and with the recent initiative on a Medical Research Map for Finland, including the Finnish Sitra-based project Isaacus (12). A *Nordic Commons* would build on an open access policy and transparency.

A recent PM was sent to the Nordic Council of Ministers (NCM) and NordForsk from Nordic participants at the conference on "Studying genomic variation that underlies health and disease: the unique contribution of the Nordic Health Systems," Banbury Center at Cold Spring Harbor, February 2016 (9). The message urged the Nordic prime ministers to initiate a process to identify and fund a programme for developing and using Nordic infrastructures for research to address global health challenges. Such a new Nordic health research and innovation programme should develop partnerships between academic institutions/researchers, patient groups, civil society, and the private sector, and seek synergies and collaboration with the EU and NIH, e.g. the NIH precision medicine and data science initiatives (40) for which Nordic cohort data could play a crucial role as precursor.

As stated in e.g. Erlangsen and Fedyszyn 2015 (41), privacy concerns are of the utmost importance when dealing with personal data for scientific purposes. Today the Nordic countries are restrictive in allowing research on national data to be carried out outside the country of origin. The notion of a *Nordic Commons* would require modern security solutions and safeguards that are anchored and accepted at the national political level and by national data owners and citizens in the countries concerned.

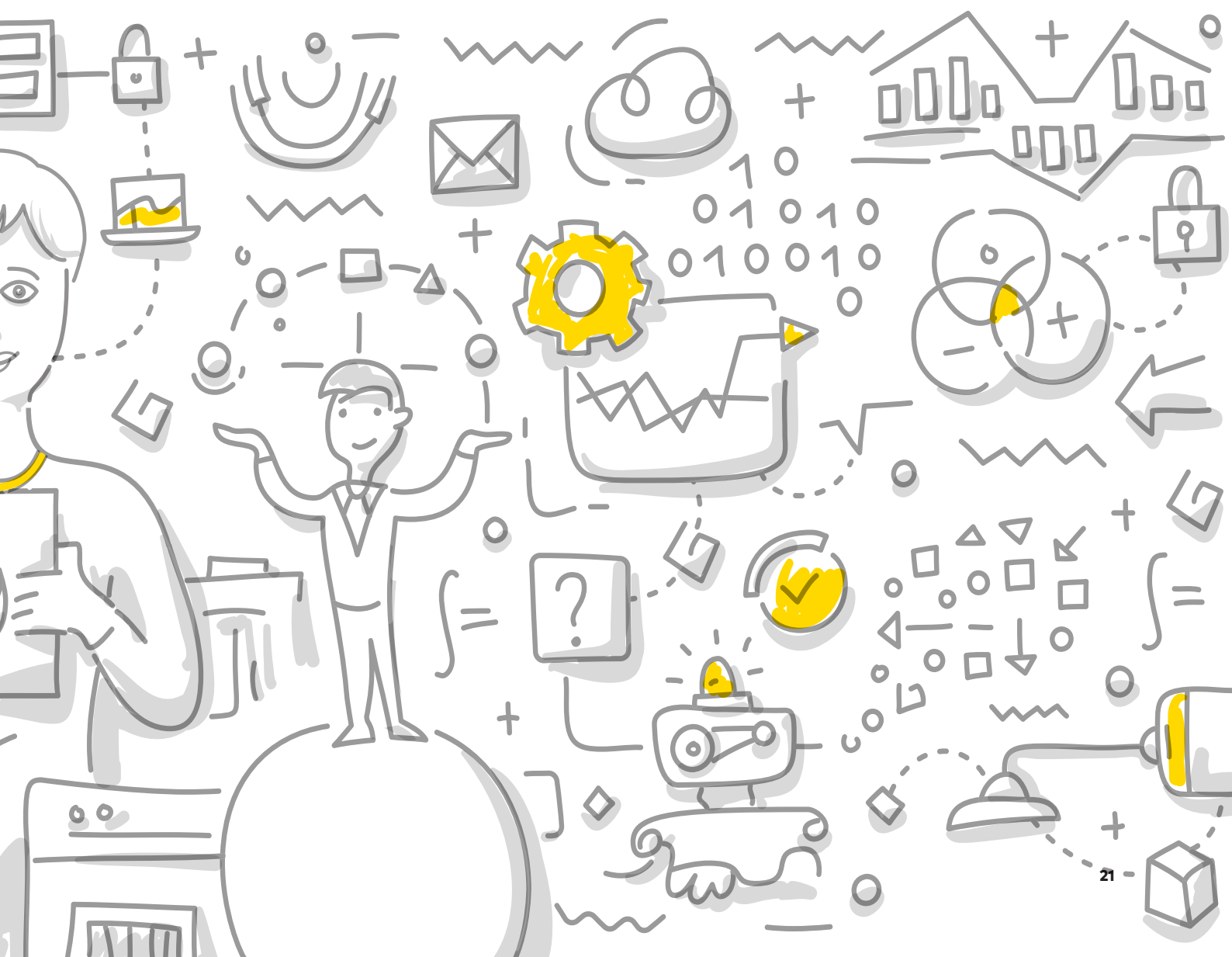
Suggested action:

To guide this work a Nordic expert group could be appointed under the NordForsk Programme on Health and Welfare. The expert group should cover political, technical and legal expertise for infrastructure involving sensitive personal data. Ideally the group should be appointed during 2016 or early 2017. It is suggested that the action plan involves a multi-step procedure:

- Step 1:** First, a review of existing and planned solutions in Europe and the US are outlined, followed by an implementation plan in which the timeline, budget and needed expertise are specified. Clear guidelines for securing budget and expertise should be set up as well as a five year implementation plan with timelines and deliverables. The planning and implementation should also tap into the ongoing discussions on Open Science and data sharing in the context of the European Open Science Cloud. First report during 2017 or early 2018.
- Step 2:** Builds on the first step and involves technical data and tool sharing solutions, preferably through the notion of a *Nordic Commons*. Preferred start-up in 2018 based on a detailed plan from Step 1 for 2018–2022.

REFERENCES





REFERENCES

- (1) Nordic Trial Alliance: <http://nta.nordforsk.org/>
- (2) The Nordic eScience Action Plan 2.0. NordForsk Policy Paper 2:2015
https://www.nordforsk.org/en/publications/publications_container/nordic-esience-action-plan-2.0
- (3) Open Access to Research Data – Status, Issues and Outlook. NordForsk Policy Paper 1:2016
https://www.nordforsk.org/en/publications/publications_container/open-access-to-research-data-2013-status-is-sues-and-outlook/view
- (4) The Future Nordic Co-operation on Health. Bo Könberg. Nordic Council of Ministers 2014.
<norden.diva-portal.org/smash/get/diva2:723237/FULLTEXT01.pdf>
- (5) Nordic Potential in Medical Research – Cooperation for Success. Nordic White Paper on Medical Research. NOS-M 2014: nos-m.org
- (6) Joint Nordic Registers and Biobanks – A goldmine for health and welfare. Policy paper from NORIA-net on Registers and Biobanks. NordForsk Policy Paper 5:2014
https://www.nordforsk.org/en/publications/publications_container/joint-nordic-registers-and-biobanks-a-goldmine-for-health-and-welfare-research/view
- (7) Conference on Research Infrastructure Joint Nordic Focus on Research Infrastructures - Looking to the Future. Swedish Presidency for the Nordic Council of Ministers (NCM), 2013: <http://www.vr.se/NordicInfra2013>
Conference report: http://www.vr.se/download/18.7e727b6e141e9ed702b150d3/1396510667091/Conference+report_Joint+Nordic+Focus+on+Research+Infrastructures.pdf
- (8) Reinforced Collaboration on Data Resources – Challenges from six perspectives. Sandberg TemaNord 2012:514.
<http://norden.diva-portal.org/smash/get/diva2:702828/FULLTEXT01.pdf>
- (9) Letter to Nordic Council of Ministers and NordForsk from Nordic participants at the conference on "Studying genomic variation that underlies health and disease: The unique contribution of the Nordic health systems". Cold Spring Harbor, US. February 2016.
- (10) ESF Forward Look report "Personalised Medicine for the European Citizen, 2011.
<http://www.esf.org/coordinating-research/forward-looks/biomedical-sciences-med/current-forward-looks-in-biomedical-sciences/personalised-medicine-for-the-european-citizen.html>
- (11) Danish National Biobank: <http://www.nationalbiobank.dk>
- (12) ISACUUS project: <http://www.sitra.fi/en/archive/isaacus>
- (13) Open Science and Research in Finland: <http://openscience.fi/#sthash.gptSAPFh.dpuf>
- (14) Norwegian strategy for health data and clinical research: https://www.regjeringen.no/contentassets/8a-b2fd5c4c7746dfb51e3f64cd4d71aa/helseomsorg21_strategi_web.pdf?id=2266705
- (15) Norwegian action plan for health data and clinical research
https://www.regjeringen.no/contentassets/3dca75ce1b2c4e5da7f98775f3fd63ed/handlingsplan_ho21.pdf
- (16) Norwegian strategy for personalised medicine 2016
<https://helsedirektoratet.no/publikasjoner/strategi-for-personilpasset-medisin-i-helsetjenesten>
- (17) Biobank Norway: <http://www.ntnu.edu/biobanknorway>
- (18) Health Registries for Research in Norway: <http://hrr.b.uib.no/>

- (19) Infrastructures for register-based research in Sweden: www.registerforskning.se
- (20) Robert Eriksson och Linus Andersson-Rydell. Nationell samordning av frågeundersökningar och längdsnittsstudier. Vetenskapsrådet 2014: <https://publikationer.vr.se/wp-content/uploads/2014/03/Rapport-VR1401.pdf>
- (21) Westerberg, Bengt. Unik kunskap genom registerforskning (SOU 2014:45) 2014
<http://www.regeringen.se/49b715/contentassets/2e42baeaa76e4e918dd852f2a3e43fca/unik-kunskap-genom-registerforskning-sou-201445>
- (22) NORIA-net on Health and Welfare
<https://www.nordforsk.org/en/programmes-and-projects/projects/noria-net-on-health-and-welfare>
- (23) NORIA-net in Sports Science
https://www.nordforsk.org/en/publications/publications_container/policy-paper-1-2012-sport-sciences-in-the-nordic-countries/view
- (24) NORIA-net on Registers and Biobanks
<https://www.nordforsk.org/en/programmes-and-projects/projects/noria-net-on-registries>
- (25) Nordic Biobank Network: <http://www.ntnu.no/biobanknorge/nordic-biobank-network>
- (26) Nordic Biobank-Based Study on Causes and Biomarkers of Colorectal Cancer: Pilot Implementation Study. Scientific and Financial Report. Pilot study of Causes and Biomarkers of Cancer. NordForsk 2016.
<https://www.nordforsk.org/en/news/unik-nordisk-studie-av-tarmkreft-ved-hjelp-av-felles-biobankregister>
- (27) Nordic Trial Alliance: nta.nordforsk.org
- (28) Nordic High-Level Expert Group on Research Infrastructure
<https://www.nordforsk.org/en/news/ny-hojniveau-radgivningsgruppe-for-forskningsinfrastruktur-udpeget>
- (29) Nordic platform on sensitive data, Tryggve 2014: <https://wiki.neic.no/wiki/Tryggve>
- (30) Nordic e-Infrastructure Collaboration, NeIC: neic.nordforsk.org
- (31) Nordic Microdata Access Network, NordMAN
<https://www.nordforsk.org/en/news/nordforsk-invests-millions-in-nordic-cooperation-on-statistics>
- (32) Nordic Clinical Quality Registers: <https://www.nordforsk.org/en/news/high-ambitions>
- (33) Nordic Programme on Health and Welfare
<https://www.nordforsk.org/en/programmes-and-projects/programmes/nordisk-program-om-helse-og-velferd>
- (34) Nordic Centre of Excellence in Health-related eSciences (NIASC)
<https://www.nordforsk.org/en/programmes-and-projects/projects/nordic-information-for-action-escience-center-niasc>
- (35) Ethical review, data protection and biomedical research in the Nordic countries: a legal perspective. NordForsk Policy Paper 1:2017
https://www.nordforsk.org/en/publications/publications_container/ethical-review-data-protection-and-biomedical-research-in-the-nordic-countries-2013-a-legal-perspective/view?set_language=e
- (36) Ludvigsson JF, Håberg SE, Knudsen GP, Lafole P, Zoega H, Sarkkola C, von Kraemer S, Weiderpass E, Nørgaard M. Ethical aspects of registry-based research in the Nordic countries. Clinical Epidemiology 2015; 7: 491–508. DOI.
<https://dx.doi.org/10.2147/CLEP.S90589>
- (37) LERU on the new EU General Data Protection Regulation
<http://www.leru.org/index.php/public/news/the-new-eu-general-data-protection-regulation-why-it-worries-universities-researchers/>
- (38) Report on the Ethical Review Process for Clinical Trials in the Nordic Countries. Nordic Trial Alliance Working Group on Ethics. 2016: http://nta.nordforsk.org/files/NordForsk_NTAREPORT_Ethics.pdf
- (39) Letter dated 2016-04-18 from the Norwegian Ministry of Health and Care Services and the Ministry of Social Affairs and Health in Finland calls for a joint Nordic effort to revise the ethical review process in the Nordic region.
- (40) National Institutes of Health Data Science Initiative <https://datascience.nih.gov/commons>
- (41) Erlangsen A and Fedyszyn I. Danish nationwide registers for public health and health-related research. Scandinavian Journal of Public Health 2015;43:333-339



NordForsk is an institution under the Nordic Council of Ministers that facilitates and provides funding for Nordic research and research infrastructure cooperation.



NordForsk

Stensberggata 25, N-0170 Oslo
www.nordforsk.org