



Nordic Cooperation in Clinical Research – Opportunities and Challenges

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APPENDIX 1: Nordic Forum for Innovation in Health Care and Medicine

Summary

A discussion forum, Nordic Forum for Innovation in Health Care and Medicine (cf. Appendix), has proposed a project to improve cooperation between clinical research centres in the Nordic countries, with the goal of obtaining a common Nordic process and possibly a single point of entry. Cooperation between clinical centres of excellence allows larger and more efficient clinical studies and has a potential to further improve the research quality. To mention just one example, early phase clinical research in children is an important and very demanding area, but there are also other specialized networks that would be favourable. In addition, a common process would facilitate for young research-based biotech companies, as well as for multi-national pharmaceutical companies. Today the Nordic countries risk being regarded as too small for many phases of clinical trials.

This report was commissioned by the Forum as a starting point for discussions with clinical networks, authorities and national as well as Nordic research and innovation funding agencies.

Three of the five Nordic countries already have a national organisation which is linked to ECRIN, the European Clinical Research Infrastructures Network with the aim to harmonise clinical procedures and operate a 'one-stop-shop' service to investigators and sponsors in multinational studies. DCRIN, SweCRIN and Finn Trials, which are networks of trial units including many of the university hospitals, have all expressed keen interest in Nordic cooperation. They have contacts in Norway, both at Oslo University Hospital and Haukeland University Hospital, and several actors are working towards establishing a Norwegian ECRIN. Norway and other Nordic countries also have representatives in a new OECD Working Group to facilitate International cooperation in non-commercial clinical trials. It should be noted that ECRIN, which is funded by EU Frame Programme 7, is also primarily intended for non-commercial trials.

The national networks, with relevant non-members added, would make a good basis for a Nordic cooperation. In order to utilize the current interest in clinical research, e.g. by the Nordic Innovation Centre (NICE), we propose involvement by these networks and representatives from Norway and Iceland, for a project including a report on Nordic clinical trial infrastructure. Issues that need further elucidation could include some or all of the following

- unique Nordic infrastructures *per therapeutic area* (Centres of Excellence, patient cohorts, biobanks, equipment);
- existing Nordic networks *per therapeutic area*;
- cooperative possibilities for the national Competent authorities (medicines agencies);
- cooperative possibilities for the national/regional Ethics committees;
- vision for a pan-Nordic network organisation (board/management, mission, financing etc.).

Discussions and possible co-funding for a NICE project (with 50% co-funding requirement) could be sought from the very interested clinical Contract Research Organisations as well as international sponsors.

1. Introduction

The Nordic Forum for Innovation in Health Care and Medicine started in 2008 as an independent forum for exchange of ideas and debate between different stakeholders, such as healthcare providers, patient groups, pharmaceutical industry, academia and governmental authorities, including the Nordic Council of Ministers. Additional information about the Forum is enclosed as Appendix 1. The discussions have focused on pharmaceutical healthcare challenges that are experienced by all the Nordic countries, not the least the struggle to achieve the twin goals of ensuring affordability and availability of medicines. In February 2009 a working group with members from the Forum was established to put forward proposals for Nordic cooperation in the area of clinical research. This group decided to commission a report, which could form the basis for a proposal of action to governments and national clinical research centres, as well as to national and Nordic funding agencies and sponsors.

The background for the interest in clinical research is well described and a matter of concern for all the Nordic countries at present. Until recently, Norden was a region of excellence for clinical research, when measured *per capita* as number of clinical trials, number of clinical publications in top medical journals, and number of evaluations from the Medicines Agencies (also as rapporteurs for the European Medicines Agency). This was achieved by i.e. the high scientific quality, well-organised healthcare systems and compliant patients.

Today the number of publications is only increasing in Norway (#9), while it is unchanged or falling in Denmark (#4), Sweden (#6) and Finland (#7), although the positions by international ranking are still amazing (2004-2006, field normalised citation rates). The negative trend has been observed by the national research councils, and there is a hope in the academic community that it will be counteracted with additional funding of clinical research and infrastructure.

The number of clinical trials also appear unchanged or decreasing, not only trials by multi-national sponsors but also by Nordic-based research companies and clinical Contract Research Organisations (CRO). One reason is the limited population spread over five countries, which require separate approvals of clinical trials. A second reason is that the Nordic population is already well-treated medically, which makes it very hard to find sufficient numbers of *new* patients with certain diseases in a single country. Another fact is that most multinational pharmaceutical companies only see *one* Nordic or maybe one North-European market, which is a challenge for obtaining sponsored studies unless we cooperate. There is also an impression of the Nordic area as expensive, which makes clinical trials in Eastern Europe, including the Baltic states, more interesting. And - most importantly - since the emerging Asian markets with huge populations in India and China are becoming much more important, they also claim a higher proportion of the clinical studies.

This report describes the present situation in the Nordic countries and the (sometimes embryonic) national networks of clinical research centres that potentially could become the basis for a Nordic cooperation. "Together we should be able to offer clinical research second to none, if we focus on a common goal", as stated by a CRO.

The aim is to initiate a project to establish Nordic cooperation in clinical research and work for an agreement on a pan-Nordic process for performing studies and obtaining study approvals by Medicines agencies and Ethics committees.

2. Clinical trials for evidence-based clinical practice

Clinical testing is required to provide a basis for selecting the best and safest treatment of patients.

A clinical trial is a comparison between a new intervention and a placebo (non active intervention) or the best available treatment to date. Interventions can be a new medicine, a surgical procedure, a medical device or a psychological treatment etc. The element of randomisation is a key element in a trial, as it makes the groups of trial participants even, in terms of known and unknown prognostic factors, and therefore comparable. The risks and benefits of all types of intervention should be assessed in clinical trials before a new treatment is introduced into the healthcare system.

Clinical trials take a lot of planning and interaction with different regulatory authorities, experts and clinical trial sites (clinics), and the complexity increases rapidly for multinational trials. Figure 1 depicts the most fundamental steps of a clinical trial.

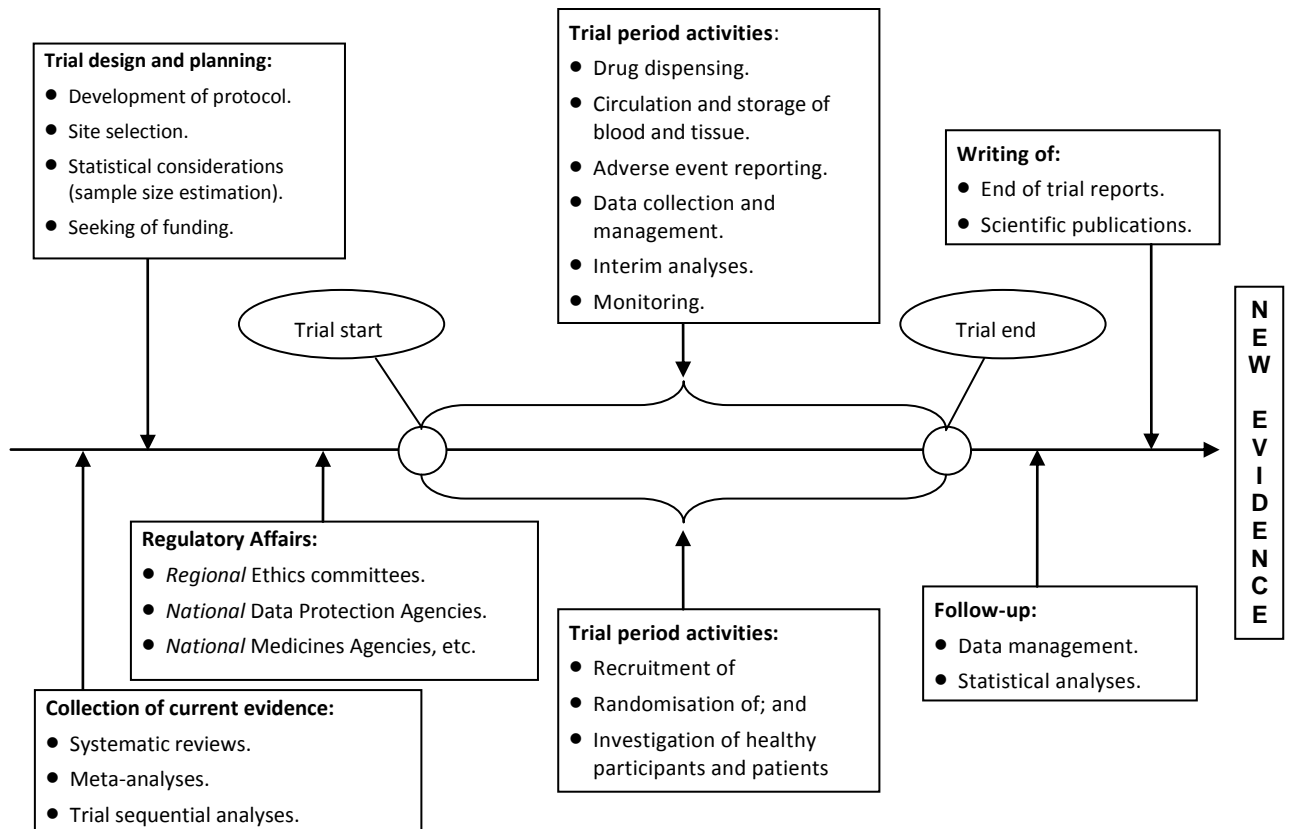


Fig 1: Simplified outline of a clinical trial. With permission from DCRC (2009)

3. European and international initiatives

EM(E)A, the European Medicines Agency (now www.ema.europa.eu) is EU:s authority for pharmaceuticals. The European regulation on clinical research for medicinal products was harmonised in 2001 by implementation of the CTD, the Clinical Trial Directive (2001/20/EC). EMA produces many documents on clinical trials, including the current relevant papers:

- *Clinical trials submitted in marketing authorisations applications to the EMEA: Overview of patient recruitment and the geographical location of investigator site (2005-2008)* with 27% of patients from EU-15, 11% from EU-12, 35% from the US; 27% ROW;
- *Public consultation on the functioning of the Clinical Trials Directive (Oct 2009-Jan 2010)*;
- *Guidance document for a Voluntary Harmonisation Procedure for the assessment of multinational clinical trial applications*, published by CTFG = Clinical Trials Facilitation Group

CTFG is a working group set up by the national regulatory medicines agencies to support harmonisation related to clinical trials. The group is represented on EMEAs webpage by Dr Hartmut Krafft (kraha@pei.de).

ECRIN, European Clinical Research Infrastructures Network, is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of clinical research centres and clinical trial units. ECRIN is funded by the Frame Programmes (at present FP7) to contribute to the European Research Area by

- constructing and operating an infrastructure for EU-wide clinical trials and biotherapy;
- striving for harmonisation of European clinical research;
- providing a 'one-stop-shop' service to investigators and sponsors in multinational studies.

The FP6 phase of ECRIN produced quality assurance documents describing details of conducting clinical trials in Europe. The open part of the webpage offers reports on promotion of harmonisation, integration of clinical research infrastructure and GCP-compliant data management in multinational clinical trials (see references).

ECRIN will cooperate with other ESFRI (European Strategy Forum on Research Infrastructure) projects, especially BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) and EATRIS (European Advanced Translational Research Infrastructure in Medicine), to develop synergies and avoid duplication. ECRIN intends to apply for the status European Research infrastructures Consortium during 2010.

Presently ECRIN is represented by networks in AU, FR, DE, HU, IR, IT, ES, CH, UK, plus

- Denmark (DCRIN contact: Christian Gluud, Copenhagen),
- Sweden (SWECRIN contact: Peter Westerling, Stockholm),
- Finland (FINNCRIN/Finn Trials contact: Matti Eskola, Tampere).

The Nordic CRIN organisations will be presented further in chapter 4. The Scientific board of ECRIN will assess multinational clinical trials, and Christian Gluud is a member of the board.

The ECRIN Programme coordinator, Professor Jaques Demotes-Mainard, will be speaking at a special preconference at the forthcoming Nordic University Hospital Research Conference in Bergen in May 2010 (cf. www.nrcnetwork.com).

ESF (European Science Foundation) Investigator-Driven Clinical Trials: An ESF Forward Look

The European Medical Research Councils of ESF mandated the undertaking of a foresight study on *Investigator-Driven Clinical Trials*. This project marks the most comprehensive examination and analysis of the issue in Europe and proposes particular steps towards better clinical research in Europe. Investigator-driven clinical trials – i.e. trials initiated by academic researchers aimed at acquiring scientific knowledge and evidence to improve patient care – deal with potential diagnostic and therapeutic innovations that do not attract commercial interest. Through a series of five workshops covering different themes a total of 26 recommendations emerged, addressing needs and solutions, the top five of which are the following:

- To improve the education, training and career opportunities for clinical scientists.
- To increase levels of funding for investigator-driven clinical trials.
- To adopt a *risk-based approach* to the regulation of investigator-driven clinical trials.
- To streamline procedures for obtaining authorization for investigator-driven clinical trials.
- To ensure that investigator-driven clinical trials are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are *correctly powered*.

OECD Global Science Forum recently established a Working Group to facilitate *International cooperation in non-commercial clinical trials*. The ESF Forward Look (above) with its many recommendations are used as background material for the Working Group. International cooperation is hindered by different interpretations/implementations even of the European regulation in the member states regarding:

- Sponsorship rules (EU requires a single PAN-European sponsor)
- Translations (full protocol or patient information only)
- Ethics approvals (lengthy procedures)
- Drug import applications

The Working Group therefore plan to

- Make a survey of current regulatory differences in various regions (worldwide) and a detailed analysis of existing administrative hurdles in conducting multi-national clinical trials
- Initiate a debate over the feasibility of a *risk-based approach* for clinical trials.

At present, all clinical trials of investigational medicinal products involve identical regulations. An example of a risk-based approach could require different approvals depending on the studies:

- Level A- low risk (e.g. non-interventional pathophysiology, imaging)
- Level B- similar to usual care (equivalent to most phase IV clinical trials)
- Level C- moderate risk
- Level D- high risk (most phase I-II drug trials and phase III in general with advanced therapy).

Scandinavian representatives at the first meeting came from the Danish Agency for Science, Technology and Innovation, the Academy of Finland, the Research Council of Norway and the Ministry of Education and Research in Sweden.

4. Current status and trends in the Nordic countries

4.1 Nordic

The Nordic Council of Ministers is chaired by Denmark in 2010, and has made a programme for developing the Nordic cooperation during the year. In the health and welfare area, the following topics are highlighted (Norden I fremdrift, 2009):

- Prevention and treatment of life style diseases
 - *Clinical (intervention) research via Nordic cooperation*
- Further development of the healthcare systems with centralised hospitals
 - Analysis and Nordic comparison of decentralised healthcare services.

The sector programme for Nordic cooperation within education and research also lists

- Research infrastructure including e-Science

NOS-M, The Joint Committee of the Nordic Medical Research Councils, aims at coordinating and promoting medical research in the Nordic countries, to monitor its progress, and to facilitate information exchange among the countries. The Norwegian Research Council is responsible for the NOS-M office from 2010. Presently NOS-M is developing a *White Paper on Nordic medical research* for public launch at a seminar during the autumn. The work is delayed, however, due to changes of personnel e.g. at the Swedish Research Council (NOS-M/SIørdahl, Norway).

NordForsk is a Nordic research board with responsibility for cooperation on research and researcher training. It focuses on research areas in which the Nordic countries are international leaders, and prioritises additional value from cooperation. NordForsk has three main functions – coordination, funding and policy advice. Presently, researcher networks include *NorPen*, a pharmaco-epidemiology network of 11 research groups, and networks for *Comparative alcohol and drug research*, *Mental health and evidence* and *Dementia diagnostics*. There is a single medical project financed as Nordic research infrastructure (*Prenatal stress cohort*) and three Centres of Excellence in *Molecular medicine* (Disease genetics, Water imbalance disorders and Neuro-degeneration). Earlier research programmes included epidemiology (e.g. *Nordic Biological Specimen Banks working group on Cancer Causes and Control*). NordForsk will be preparing for new, large projects within health and welfare, especially if the Nordic ministers agree on a second Top-level Research Initiative (the first is a 500 MSEK project on climate, energy and environment which started in 2009). NordForsk projects are normally co-financed by Nordic national research councils.

NICe, Nordic Innovation Centre, is focusing on removing barriers between Nordic countries and on strengthening innovation and the economic impact by cooperation within Norden. NICe is involved in the Top-level Research Initiative together with NordForsk. Support for userdriven innovation projects included two in the healthcare sector. *Medical sensors* was the subject of a foresight report in 2006 and a project on patient monitoring (Personalised health and safety). In 2009 NICe organised a feasibility study and a conference on *Nordic cooperation in health services*. The barriers towards integration of health services included culture/language, demographic density, geographic distance, mentality and prestige, national health care systems, national legislations and quality development.

NICe may have interest in commissioning a study on clinical research cooperation in the Nordic countries, as a preparation for a new focus area. NICe projects (not feasibility studies) are normally co-financed by industry or public organisations.

Other Nordic medical research networks include the following *examples*, where most appear to carry out clinical studies across the Nordic countries:

Nordic asthma consensus group
Nordic cooperative bladder cancer study group
Nordic gastrointestinal tumour adjuvant therapy group
Nordic lymphoma group
Nordic obstetric surveillance study
Nordic medical society of paraplegia
Nordic myeloma study group
Nordic MDS (myelo-dysplastic syndrome) study group
Nordic MPD (myelo-proliferative disorders) study group
Nordic RLS (restless legs syndrome) study group
Nordic society of gynaecological oncology
Nordic society for paediatric haematology and oncology
Scandinavian breast group
Scandinavian neuro-oncology society
Scandinavian prostate cancer group (from Scandinavian Association of Urology)
Scandinavian sarcoma group
Scandinavian society for head and neck oncology
Scandinavian society for the study of diabetes
Øresund diabetes association

The Nordic University Hospital Research Conference has already been mentioned (chapter 3).

4.2 Denmark

According to ClinicalTrials.gov Denmark had 742 ongoing (recruiting) clinical trials in January 2009.

The Danish Medicines Agency approve about 300 new applications for clinical trials every year. The five largest areas were cancer (42 ongoing studies), airways (39), infection (28), inflammation (22) and reproduction (22). The GCP unit at Copenhagen University hospital was monitoring 134 studies in December 2007 (Implement/COWI 2008).
/From EMEA, DMA received 8 new rapporteur/co-rapporteur assignments in 2008./

According to a *Lif+Danish Biotech* report for the year 2008 (published September 2009), there were

- many more pharma/biotech employees working with clinical trials outside than in Denmark 230 persons with domestic trials (14%) versus 1400 persons with international trials (86%);
- 308 trials run by Lif+Danish Biotech members in Denmark, 100 new from 2008;
- a fairly constant number of individuals in the trials (22,700 vs 19,200-24,100 during the previous years), but fewer in Phase 1 and Phase 2 trials compared to previous years;
- 5 companies with more than 30 clinical studies running (unchanged from previous years).

Like in the other Nordic countries there is a fear that clinical trials will move outside the country, since young clinicians appear to lack both time for, and interest in, conducting clinical studies. A strategic programme was launched in 2008 with an additional 50 million DKK/year.

Lif and Danish Biotech propose improvements of the framework for clinical research in the public hospitals. It is also expected that a revision of the Danish Ethics Committee system will make study approvals more rapid, and that the present focus on clinical research on the national level will also increase the number of sponsored studies in Denmark.

DCRIN (2009) made a detailed proposal for establishing a *national* clinical research infrastructure, called *Danish Clinical Research Consortium, DCRC*. This consortium should comprise the Copenhagen University Hospital and Copenhagen University as well as the university hospitals of Odense and Aarhus, while also maintaining and developing the interaction with the private sector. In total 15 clinics or departments are listed, including five GCP/clinical research units, two pharmacology and the SSI Epidemiology Centre, in addition to haematology, oncology, psychiatry, endocrinology/ diabetes and human nutrition. A greater synergy of research and patient treatment would be ensured through incentives, including

- Performance-related contracts
- Earmarked funds
- Improved procedures, by establish 9 working parties to develop standard operating procedures (SOPs) for the new virtual institution:
 - Trial design
 - Interaction with ethics committees
 - Interaction with competent authorities (4 trialists /pref. physicians are included in the budget)
 - Drug dispensing
 - Circulation and storage of blood and tissue samples
 - Data management (6 data managers are included in the budget)
 - Adverse event reporting
 - Sample size estimation, interim analyses and statistical analyses (3,5 statisticians are included)
 - Site selection and recruitment of patients or healthy volunteers
 - Clinical trial monitoring.

The proposed funding is 10 million DKK annually during a 4 year implementation period, to be compared to the existing GCP units with a total budget of 50 million DKK/year.

Copenhagen also houses a *Cochrane Collaboration centre* with responsibility for hepato-biliary studies (<http://ctu.rh.dk/chbg>).

4.3 Finland

According to ClinicalTrials.gov Finland had 281 ongoing (recruiting) clinical trials in January 2009.

An international panel evaluated clinical research in Finland and Sweden in 2008. In spite of high publication numbers and citation rates, the panel had concern about the research careers for health professionals, the research funding, the long-term research strategies for university hospitals, and the lack of core facilities including technical and administrative support. An interesting statement about infrastructure is that all visited centres cited access to large cohorts of patients and infrastructure for clinical care and basic research as major assets, while *infrastructure for clinical research* and access to specialised healthcare and research assistants or research support modalities were lacking or difficult to approach (Academy of Finland 5/09).

TeKes presently runs a programme called *Pharma - Building Competitive Edge* (2008-2011, budget €58 million), which is established to boost pharmaceutical development processes by improving links between research data, clinical results and pharmaceutical R&D, and help eliminate bottlenecks in the pharmaceutical industry (cf. IMI, Innovative Medicines Initiative). One of the areas for support is “the development of a national model for clinical drug research” with e.g. development of therapy-specific clusters. Research organisations can apply in addition to companies/subsidiaries in Finland.

The Finnish ECRIN network, nowadays called *FinnTrials*, is coordinated by Finn-Medi Oy in Tampere. There is an expectation that it will be supported by the Pharma programme (to be published in February 2010, personal communication with Tekes).

4.4 Norway

According to ClinicalTrials.gov Norway had 426 ongoing (recruiting) clinical trials in January 2009.

/The Annual Report of the Norwegian Medicines Agency, NoMA, does not disclose statistics about clinical trial applications or EFPIA rapporteur assignments/.

The new Assignment document 2009 (No: Oppdragsdokument) for the Norwegian healthcare organisations put a requirement on them to

- Produce a comprehensive overview of the clinical infrastructure in all Norwegian hospitals
- Produce a national database over all clinical studies. The work is to be combined with a database organised by the regional ethics committees.

NSG, The national cooperation group for medical and health-related research, is a strategic advisory group with members from universities, healthcare organisations, the Health directorate, the Public Health Institute, the Norwegian Research Council and the Departments of Health & Welfare and Research & Education. While the universities and the specialist healthcare service (No: spesialisthelsetjenesten) are responsible for medical research, this group's mandate is to (i.a.)

- Assist in *national division of assignments in the research area*
- Assist in coordination of establishment and use of biobanks and health registers
- Assist in coordination of research-based innovation and commercialisation
- Assist in coordination of ethical practice and standards used in research

The regional cooperative organisations between the universities and the regional healthcare organisations has the main responsibility for prioritising and *coordinating research and especially relevant clinical research in each region.*

A network has been established between the clinical research support units at the university hospitals in each regional health authority, as well as with four research units in the primary health care sector. This could become the national network to cooperate with the other Nordic CRIN-organisations, There is also a potential to establish a Norwegian CRIN network. Norway will be active in the OECD Working Group to facilitate *International cooperation in non-commercial clinical trials*, cf. chapter 3, with Øyvind Melien from Oslo University Hospital as member. Melien has also expressed great interest in a Nordic cooperation, and proposed a subgroup working with pediatric pharmacotherapy.

Oslo Cancer Cluster (OCC) is hoping to build a European network with cancer centres cooperating around Phase I and Phase IIA trials. At present the Karolinska University Hospital (Phase I unit), Skåne University Hospital and Copenhagen University Hospital (Rigshospitalet Phase I unit) have been approached in addition to Heidelberg, Toulouse, Barcelona and Madrid. The network would allow trials for pharma and biotech companies as well as for investigator driven trials. OCC's Bjarte Reve favours the idea of specialised networks also in other areas, e.g. neurologic or cardiovascular research.

4.5 Sweden

According to ClinicalTrials.gov Sweden had 514 ongoing (recruiting) clinical trials in January 2009.

Swedish Medical Products Agency approved about 400 applications for clinical trials in 2008 (compared to 440 in 2007). Of these 78% were industry-sponsored and 22% from academy (Annual Report 2008). 80 studies were stopped for “commercial reasons” or due to slow inclusion of patients. The Nordic MPAs are competitors for rapporteurship to EMEA. In 2008, Swedish MPA had 39 out of 207 ongoing EMEA cases (19%), out of which 16 were new.

The Swedish Delegation for cooperation about clinical research presented its final report in December 2009 after two years of investigations and meetings throughout Sweden. It has produced a number of reports (cf. references) but most importantly some very concrete proposals:

- Improved funding of infrastructure, including quality registries, biobanks, patient data banks
 - proposed 500 MSEK/yr
 - A pilot project, *KUR*, was tested for Rheumatoid arthritis research and care
- Improved funding of research on clinical treatment, i.e. via large, randomised clinical trials (KBFF, Swe: klinisk behandlingsforskningsfond)
 - by the government and the regions/county councils
 - proposed 500 MSEK/yr
 - Private funding can be added.
- *A national coordination of clinical research centres*, as proposed via *SAMS* (L. Wallentin)
 - A network of many academic groups and clinics, incl. clinical research centres
 - offering professional support for developing protocols, applications etc.
 - offering support for accomplishment and follow-up of studies, including sponsored
 - offering services to industry
 - working with registries and networks
 - in close cooperation with pharma and medtech industry
 - help initiate large clinical trials, enlarging biobanks and increasing medical knowledge in addition to the primary outcome questions of the trials.
- *A Swedish Working Committee* (Swe: Beredning) for clinical research, which can
 - promote dialogues between governmental, regional and private actors,
 - identify and propose solutions for mutual needs regarding clinical R&D, cooperation and innovation within the healthcare sector.

Swecrin, the Swedish network for clinical studies has many clinics and some Clinical Research Organisations as members, including the university hospital units in Stockholm (KTA, also coordinator), Uppsala (UCR), Lund (RSKC) and Örebro (CRS). The network has no funding, which reveals the discrepancy between the present reality and the political rhetoric/ intentions. In spite of that it has kept the contacts with ECRIN and arranged 1-2 seminars per year in addition to the annual meeting. There is a clear interest in cooperation within the Nordic countries, contacts with DCRIN and FinnCRIN have been ongoing via ECRIN meetings and there has also been contact to interested parties in Norway.

For a Nordic collaboration also a forthcoming *SAMS* network should be invited (i.e. including non-members of *Swecrin*).

4.6 Iceland

According to ClinicalTrials.gov Iceland had 14 ongoing (recruiting) 14 clinical trials in January 2009.

All except one are multicentre studies and, interestingly, 7 (50%) are Nordic academic studies, with *three having pan-Nordic sponsors*: Nordic Society for pediatric hematology and oncology, Scandinavian Prostate Cancer Group, and the NordForsk network SYSDIET (Nordic recommended diet effect on metabolic syndrome). The other academic studies are coordinated from Aarhus University Hospital, Rigshospitalet/Copenhagen University Hospital (2), University of Eastern Finland, and the Norwegian Department of Health. The 7 sponsored studies were performed for large multinational companies (GSK, Janssen-Cilag, Novartis, Wyeth).

A European expert panel evaluated education, research and innovation policy in Iceland in 2009. It points to the health sector and to the dominating firm *deCode genetics*. deCode, was delisted from Nasdaq (New York) in early January 2010, and a new privately owned deCode was announced on Jan 21 to continue its work on gene discovery (with 140,000 Icelandic participants) in relation to disease data.

5. Private experiences in Nordic countries

5.1 Pharma and Biotech Associations

It is striking that pharma and biotech associations as well as cluster organisations are presently organising networks, conferences and information/education about clinical studies in several Nordic countries. There is little information across borders – such as telling how many of the current studies that are performed in many Nordic countries. In Medicon Valley, however, it is well-known that companies perform testing on the ‘other’ side or both sides of Øresund. One example is BioInvent AB’s phase I studies in Copenhagen. The opposite example is ALK-Abelló A/S, with studies in Sweden and the first product approval from the Swedish Medical Products Agency.

Trade Associations for Research-based Pharma Industry The Danish Lif is planning a Nordic conference in Copenhagen about clinical research with a general, political focus on June 3-4, 2010 (www.lif-uddannelse.dk). The Association of clinical trials in Sweden and the Nordic trade associations have scheduled a more process-focused conference with participation of the Nordic Medical Product Agencies for October 6-7, 2010 (venue Stockholm/Arlanda).

Danish Biotech Association presented a report together with Lif regarding clinical research during 2008 (cf. chapter 4).

Norwegian Bioindustry Association has selected clinical studies as one of the prioritised topics (see 4.3). A recent analysis of the clinical development pipeline based on Norwegian R&D indicated that 41 projects were in clinical phases, whereof 11 new studies in Phase I. Cancer is the clearly dominating indication (64%). Innovation Norway uses several means to assist SMEs, one is Skattefunn which is a tax incentive of 20% of external costs for internal and external development costs per year up to 1.1 + 1.1 M NOK. Public private cooperations, such as clinical trials in hospitals, can also be supported with up to 50% for SMEs via OFU-contracts. Finally, there is a possibility of innovation loans of up to 50% of the development costs.

SwedenBIO monitors the Swedish-originating clinical pipeline annually (not including AstraZeneca). The total number of studies decreased from 76 to 74 while five products were approved during 2009. Unfortunately, only 8 of 13 ongoing phase III projects had trials in Sweden. The dominating therapeutic categories were neurological disorders (19%) and cancer-related conditions (16%), but the pipeline is very diversified compared to Norway. SwedenBIO has initiated a new cooperation with the Medical Products Agency is seen in a number of road shows to educate about clinical trials in Sweden (starting in Uppsala and Stockholm during February 2010).

Medicon Valley Alliance has a viable network of Contract Research Organisations preclinical and clinical research, which also promotes cooperation between the Clinical Trial units in the Øresund region and has produced a new report on Outsourcing patterns in Medicon Valley (January 2010).

5.2 Pharmaceutical companies

AstraZeneca, with about 40% of the R&D personnel in Sweden during 2009*, runs 76 clinical development *projects* world-wide, plus 23 products in clinical trials for line extensions. Astra Zeneca’s VP Global Clinical Development Region Sweden commented a proposal of clinical cooperation in the Nordic countries: “ Cooperation and standardisation would facilitate a lot for

pharmaceutical companies but it must not slow down the processes or increase the overhead costs. It is rational with cooperation between hospitals and/or regions in small countries, and often necessary to also cooperate internationally.”

*In March 2010 AstraZeneca made public that the forthcoming reduction of in house R&D personnel will be performed by closing a number of research sites, including the one in Lund, with 900 employees (160 PhDs). Some projects from Lund will be transferred to the site at Mölndal (which first reduces its current number of projects).

J&J has a Nordic marketing organisation but national presence in all Nordic countries, with monitors for clinical trials. The largest organisation is in Sweden, where 60% of the clinical studies are performed although most include at least one more Nordic country. Today the Nordic countries must work hard with promotion of the high scientific level and quality of clinical research. Janssen Cilag’s Clinical R&D Manager also points out that the Nordic cooperation in clinical research was more evident before the EU legislation (when NLN was active, standardising in all Nordic countries), and that a new network would be very valuable, especially if it could also include ethics approvals.

There is a growing number of examples of big pharmaceutical companies cutting their clinical research in the Nordics significantly- or even exiting from some or all Nordic countries altogether.

GSK, for instance, has made a decision to concentrate its clinical trials to some Nordic markets and significantly reduce from others. “This kind of decisions risk delaying Nordic patients’ access to the newest medications. It complicates physician’ opportunities to keep up with the latest science and drug development, and destroys one natural way of collaboration between academia, authorities and industry. It will create hurdles for market access as local data are increasingly requested by local payers/decision makers. If the trend of declining clinical activity in the Nordics gets stronger and lasts long, it will inevitably have negative impact of the know-how. Trained and experienced staff must start looking for other career options, which will affect not only pharmaceutical industry but also authorities and clinical institutions”. (Glaxo Smith Kline OY/ CEO and Medical Director).

To fight the trend that Big Pharma disregards small countries for clinical trials, Norden must collaborate and play on its strengths, such as high quality investigators, compliant patients, readiness to run trials requiring high-tech infrastructure, world’s best registries, fast and predictable processing of trial applications (at least in some countries), cf. chapter 6.

5.3 Contract Research Organisations

Norwegian CRO *Smerud Medical Research International A/S* was the main organiser of the conference “Is the grass always greener over there? Pros and cons related to conducting clinical trials in selected world regions” (Oslo, November 2009). Knut Smerud, the founder and owner, talked about the Nordic area for clinical studies, based on a similar background for 25 million inhabitants, an excellent regulatory reputation and with separate unique selling points per country, such as:

- Norwegian leadership in cancer, including registry and excellent health surveys
- Swedish MPA acknowledged by the FDA; KI for world class medical training, plus important registries and international opinion leadership in cardiology and health economics/outcome

- Danish clinical trial approval by day 30, strong pharmaceutical tradition and international leadership in cardiology and diabetes
- Finnish international leadership in vaccination studies and public health, plus good infrastructure and work attitude

Together the Nordic area has pros and cons according to Smerud:

PRO	CON
Long history of Good Clinical Practice	Small populations
Rapid implementation of EU directives	Cost level in general is high
Efficient, transparent clinical application	Work attitude in young physicians is less research-driven
Reliable data and comprehensive registries	Low funding for clinical trials
Very low drop-out rates	

Trial Form Support AB (TFS), with HQ in Lund, is today one of the large CROs in the world with 480 employees and offices in 16 countries including Japan, India and the U.S. The founder and owner, Daniel Spasic, believes in a unified Nordic market for clinical trials. "The present globalisation and consolidation, where the new markets (the BRIC countries) are growing quickly, requires that the Nordic countries act together. We have everything, good healthcare, good patient populations, good registries, good compliance BUT too few rapid actions. Norden needs more professional clinics working with trials, and also more private initiatives. Clinical research must get higher priority, instead of being performed as a hobby. Furthermore, we should learn from each other: Finland can recruit thousands of patients for vaccine studies, Sweden and Denmark can recruit patients for diabetes and obesitas, and Norway can perform excellent oncology research. Together we should be able to offer clinical research second to none, if we focus on a common goal."

Both national and international CROs are reacting to the increasing competition. Phase-one-trials in Copenhagen had to close in September 2009, in spite of an expected market of 300 million DKK from early clinical studies outsourced by Danish biotech and pharma companies. Lundbeck commented that "they should have focused more on niche competencies instead of trying to compete with international CROs" (Business.dk 2009-09-03). Another Danish CRO, Cyncron, closed their phase I unit in 2008.

In January 2010, Parexel decided to keep only one office in Scandinavia (in Copenhagen) and closed the office in Stockholm "since the number of clinical studies in Scandinavia is too low and Sweden cannot always offer the required number of patients" (Press release, January 2010). Covance runs Scandinavia from the European HQ in the UK, with home-based employees in Stockholm. Quintiles, which bought PMC in Uppsala in 1995 is still big in Scandinavia, with 250-300 employees in Uppsala (Nordic HQ, phase I/IIA unit), Luleå (Hermelinen clinical unit), Copenhagen (24 monitors/site managers) and Espoo.

6. Opportunities and Challenges for Nordic cooperation

Based on the governmental/regional visions, reports from industry associations and statements from sponsors or Contract Research Organisations, the following SWOT is proposed for discussion:

<p>STRENGTH</p> <p>Excellent standard of authorities Excellent biobanks and registries High scientific standard of medical research High standard of clinical research Studies performed rapidly and with high quality High compliance of patients English-speaking professionals Nordic cooperation has been or is presently being established within certain therapeutic areas (e.g. cancer)</p>	<p>WEAKNESS</p> <p>Small populations (and small markets) National approvals Ethics committees require translated protocols Studies regarded expensive Low funding for investigator-initiated studies Limited time and interest in clinical research</p>
<p>OPPORTUNITY</p> <p>Larger pool of patients (25 million inhabitants vs. 5-9 mill/country)- faster recruitment or larger studies possible Differentiation (biopharmaceuticals, patient groups, therapeutic area, clinical phases etc.) Improved, standardised procedures, incl. legal approvals (Competent Authorities, ethics) Nordic co-funding of non-commercial studies Utilize Nordic key opinion leaders Advantage for public health in Nordic countries Advantage for Nordic medical research Advantage for CROs and sponsors wanting to perform studies in Nordic countries</p>	<p>THREAT</p> <p>Legal obstacles (not allowing Nordic approval) National, regional and opinion leader competition Too few new candidate drugs to keep phase I clinics in several/all Nordic countries Lack of interest in Nordic cooperation if national funding is not established Pharma and biotech companies choose big “preferred suppliers” Even fewer Nordic offices for CROs and big pharmaceutical companies (reduction is already obvious)</p>

Summarising, the threat of losing clinical trials from the Nordic countries is imminent and must be counteracted. A common Nordic approach has some advantages over separate national approaches- provided that it never adds to the bureaucracy but reduces parallel work with many authorities and languages. The Nordic countries already have collaborations between authorities and universities as well as industries, with the Nordic Forum behind this report as one good example (Appendix). The well established Nordic organisations NICE (Nordic Innovation Centre) and NordForsk (Nordic Research Council) are proposed to be used for coordinating a mutual (public-private) effort to meet the clinical trial challenge (cf. chapter 7).

7. Proposal

There seems to be a window of opportunity in 2010, since

- the Nordic states now have clinical research on the agenda (albeit not always funded);
- the difficult situation for Nordic pharmaceutical research has become even more obvious after AstraZeneca's recent decision to close a large research site in Sweden;
- the Nordic organisations want to be proactive in view of a potential Top-level research initiative within health and welfare;
- there are international and European initiatives to improve cooperation for multi-national clinical studies;
- the existing (sometimes embryonic) national networks are eager to cooperate.

The Nordic Forum for Innovation in Healthcare and Medicine propose:

- i) To initiate a process where extended Nordic CRIN units plus representatives for Norway and Iceland form a strong Nordic network, which for example can be pasted on the proposals for the Danish DCRC (section 4.2) and the Swedish SAMS (section 4.5). One possibility to fund this network would be to apply for (pre-)project money from Nordic Innovation Centre (NICE) and run one or a few pilot projects together with the national Competent Authorities and Ethics committees.
- ii) To initiate an extended analysis of the barriers and possibilities around the Nordic cooperation, including selection of the most relevant therapeutic areas, with the expectation that
 - a. the Nordic networks can participate with input (possibly also writing) from their experiences, and
 - b. NICE or, better, NICE and NordForsk proceed to select Nordic clinical research as prioritised areas for continued funding.
- iii) To contact relevant national and Nordic stakeholders in order to support the two activities above and also to promote and, if possible, speed up the decision on a second Nordic Top-level research programme within health and welfare.

The overall aims are to initiate a project for establishing Nordic cooperation in clinical research, to secure funding of such research, and to reach an agreement on a *pan-Nordic* process for performing studies and obtaining study approvals by Medicines agencies and Ethics committees.

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Iceland

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Norden

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NorPEN, Nordic Pharmacoepidemiological network www.nhv.se/norpen

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Norway

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OECD / International

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respiratory diseases (1/2008), oncology (8/2009), CNS (1/ 2009) and endocrinology (12/2009), and in *geographic* areas: West to East Europe (1/2008,)US (3/2008), Asia (5/2008), China (8/2008), South Korea (9/2008), BRIC countries (6/2009) <http://www.cticon.org/default.aspx>

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Sweden

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Attachment 3: Review of societal effects of clinical research (Roback & Carlsson)

SNS Report Medicine for Sweden (Medicin för Sverige)

SwedenBIO/ISA/VINNOVA: The Swedish drug development pipeline (May 2009)

9. Interviewed organisations / persons

BIOTECH ASSOCIATIONS

MVA, Medicon Valley Alliance / Senior Project Managers Torsten Jepsen & Peter Nordström
Norsk BiotekForum / CEO Thor Amlie
SwedenBIO / Project Manager Karin Aase

CRIN, Clinical Research Infrastructure Networks

DCRIN, Danish Clinical Research Consortium, Copenhagen Trial Unit/Christian Gluud, Ass Prof.
FinnCRIN (Finn Trials), Finn-Medi Research Ltd / CEO Matti Eskola, Tampere
Proposed contact: FinnCRIN European Correspondent Merja Kurkinen, Dir, Finn-Medi, Tampere
SweCRIN, Karolinska Trial Alliance (Stockholm)/Peter Westerling, Unit Manager, Dr Med Sc

CRO, Contract Research Organisations

Berzelius Clinical Research Centre (Linköping) / CEO Stig Blom
Smerud AS (Norwegian CRO) / CEO Knut Smerud (also DK, SE, FI +PL, UK, RU)
TrialFormSupport (Swedish CRO) / CEO Daniel Spasic (also DK, NO, FI +11 Eur+ India, Japan, US)
Proposed contacts: aCRONordic A/S (DK, also SE, FI), Encorium Oy (FI, also SE, DK)

NATIONAL

Swedish Delegation on Clinical Research Cooperation / professor Nina Rehnqvist
Uppsala Clinical Research Center (UCR) / professor Lars Wallentin
Oslo University Hospital, Clinical Research Unit / chief physician Øyvind Melien
Oslo Cancer Cluster / CEO Bjarte Reve
Proposed contacts:
Danish Medicines Agency/IRF / Steffen Thirstrup
Medical Products Agency (SE) / Ingrid Wallenbeck (Head of Clinical Trials department)
Norwegian Medicines Agency
Finnish Medicines Agency (FIMEA)/Esko Nuotto (Head of Clinical Trials department)
Central Ethical Review Board, EPN (SE)/Eva Grönlund

NORDIC

NOS-M /Stig Slørdahl, Prof. NTNU, Trondheim

PHARMA

LIF (SE)/ Karin Eriksson, Research Director
Lif (DK)/ Jakob Bjerg Larsen, Special consultant
Pif (FI)/Mia Bengtström, Senior consultant
Proposed contact: LMI (NO)/Ellen Høeg or Monica Kjekken, Senior consultants
AstraZeneca / Anders Åkerlund, VP Global Clinical Development Sweden
GSK Finland / Harry Råstedt, CEO, and Petteri Knudsen, Medical Director
GSK Sweden /Johanna Sanner, Head of Clinical Operations Sweden
Jansen Cilag Norden / Ingela Larsson, Clin R&D Manager
Genmab A/S / Agneta Svedberg, previous Clinical R&D

APPENDIX 1: Nordic Forum for Innovation in Health Care and Medicine

Background

National Health Care systems are challenged by financial constraints and raising expectations, including on the quality of their performance. Governments are struggling to achieve the twin goals of ensuring affordability and availability of medicines. In the search for solutions to these challenges there is a need for cooperation and exchange of ideas. There is a history of Nordic cooperation in many fields. The Nordic Health Care Systems share similarities, and yet the respective countries have chosen different paths when facing common challenges. Discussing these issues could stimulate new solutions.

The Nordic Forum for Innovation in Health Care and Medicine has been established in order to bring together different stakeholders in Health Care. Its purpose is to encourage exchange of ideas and experiences and to stimulate debate in an open and constructive way, promoting mutual understanding and, eventually, sustainable, holistic solutions.

Participants Stakeholders with background from the following areas will be invited to participate:

- Health care providers
- Patient groups
- Pharmaceutical industry
- Government and Nordic intergovernmental organisations
- University institutions and Academia

Participation should be based on fulfilling a specific role in the health care chain and related policy fields. Due to their different roles, the participants will together represent a unique mix of knowledge, experience and perspective.

Themes The Forum will address issues of concern and interest for all stakeholders, with a focus on challenges within pharmaceutical health care. Sample themes could be:

1. Interaction models between the health care sector and the pharmaceutical industry
2. Value of medicine and reward based on value
3. Stimulating innovative research in the Nordic region aligned with society, payer, patient needs
4. Balanced offering of and access to medicines.

Concrete outcomes Potential deliverables are to be decided and agreed by the members of the Forum, but could include summary papers of discussions (based on “The Chatham House Rules”, i.e. no quotes connected to individuals), case studies/white papers, surveys and pilots on concrete ideas.

Key points and statute

- Focus on content, knowledge enhancement and open dialogue
- Open dialogue exceeds the protection of own interests
- Participants are personally invited, no delegating allowed and is not a representative forum of formal organizations
- A code of ethical behaviour will be defined; participants have to adhere
- The Forum does not serve political interests

Approach, organization and sponsorship The first meeting of the Forum took place in September 2008, and two meetings were held in 2009 and are planned for 2010. Location will vary within the Nordic countries. The meetings will be facilitated by Accenture and led by a chairman chosen among the Forum members. Initiators and sponsors are the pharmaceutical companies GlaxoSmithKline and Janssen-Cilag. Each participant will cover own costs.