SWECRIN

Swedish clinical research infrastructures network

– an overview of clinical research networks with an emphasis on implementing the EU Directive 20/2001 into national legislation

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The initiative

In Sweden 2003 an initiative originating from the University of Örebro and the University of Lund gathered clinical researchers from the whole country to the first national meeting (bottom-up initiative). The main focus was on training the clinical research organisation due to the introduction of new legislation, with a special focus on its relevance for investigator-initiated trials. A special report on the proceedings from these meetings is enclosed below. In brief, meetings have been undertaken with Inspectors from the Medical Products Agency and representatives from the Ethical Review Boards, as well as with other parties. Working parties within the network are a) preparing a syllabus' for training of the clinical research team, b) producing core SOPs for the non-commercial sponsor, and c) preparing approaches to monitoring, data management and drug handling within the non-commercially sponsored clinical study. The overall aim is to rescue investigator-initiated academic non-commercially sponsored clinical study from suffocating in a time when study costs are increasing 5 times and thresholds for clinical trials are set for commercial business (rather than for the non-commercial university research). A secondary aim is to foster an exchange of experience to avoid duplicate work and establishment of new networks for clinical research. The ECRIN project was presented at a national meeting in September 2004. It was decided that some centres should participate in this network to explore its possibilities from a Swedish perspective. Participating centres in SWECRIN are shown in Enclosure 1.

SWECRIN

The Swedish network is based on 15 research centres in Sweden. There have been five National meetings. There are some centres presenting themselves on webpages:
www.bcrc.nu
www.ucr.uu.se
www.scri.se
www.karolinskauniversitetssjukhuset.se/ (search for KPE, CRC or CTC)
www.orebro.se/uso
www.skane.se/rskc

National meetings

The first meeting (2003-11-28) established common experiences and defined goals for the network and the project.

The second meeting (2004-01-30) discussed the need for clinical research centres in view of the EU Directive. Need for education, exchange of experiences in monitoring, case record forms (CRF), standard operating procedures (SOP's), and financing of investigator-initiated studies were identified as corner stones.
Four working groups were initially established: 1) statistics – how many trials a year are approved annually in Sweden 2) Inventory of CRC/CTU's in Sweden 3) What education is available and 4) What registries are available for clinical research in Sweden.

In the third meeting (2004-03-19) some of the working groups reported. In 2003 there were close to 500 drug studies involving close to 2000 centres in Sweden. For medicinal products nearly 80% were sponsored by pharmaceutical industry. When studies are rejected by the Competent Authority (Medical Product Agency, MPA) the following reasons were found: a) questions on manufacturing, b) questions on toxicology, c) missing good laboratory practice

(GLP) or good clincial practice (GCP) standards, d) incomplete protocol, e) unsatisfactory monitoring or f) safety reporting.
A syllabus for a two-day introduction to clinical trials was presented.
A diagnosis registry at the National Board of Health and Welfare (.sos.se/mars/kvaflik) was reported. ECRIN was mentioned.

The forth meeting (2004-05-27) invited two inspectors from the MPA. Adverse events, SUSAR, use of CIOMS forms, code break, SOPs, monitoring, interventional and non-interventional studies, application, education, data management och drug accountability, definition of sponsor were discussed in an open dialogue. New working groups were formed on: 1) education 2) monitoring 3) SOPs

The fifth meeting (2004-09-30) reported from some of the working groups:
1) A syllabus for a two day training of clinical investigators and study team was approved. It was agreed that such training should involve Head of Clinics and upper management levels, in view of the increased responsibilities. 2) A draft for a general monitoring plan was discussed 3) SOPs needed for investigator-initiated trials was discussed. What content, how to balance SOP vs. guidelines in daily work, and how to implement SOPs were discussed. It was concluded that more financial resources are needed if general SOPs for clinical trials at university hospitals can be created. The ECRIN project was presented and discussed. Ten research centres reported interest to join ECRIN.

Clinical research networks in Sweden

In Sweden there are networks in clinical research at many levels, literally hundreds of them. They are typically geographical or within a therapeutic area. They may involve clinics at university hospitals, or emerge from such hospitals to include local hospitals. Some networks stretches between a university hospital and the regional primary care. Usually there are different networks for non-interventional (epidemiological) or interventional research, but in a few cases they mix (e.g. cardiovacular). There are also networks completely within primary care and family medicine, usually with a certain focus, e.g. gastrointestinal (GI). The most redundant networks are found in oncology, heamatology, paediatrics, cardiovascular, stroke/neurology, GI, multiple sclerosis, dementia disorders, psychiatry, overweight, neonates, burns, emergency care, but also in radiology, laboratory chemistry, surgery and pathology. Most of these networks are further subdivided, sometimes formed into national networks. Most networks include researchers/physicians. They more rarely include patient organisations. Many networks have originated in a single successful clinical trial. Most of these networks are formed around a clinical researcher and his team. Last year many hospitals have initiated Core Facility functions in a response to the effects of the Clinical Trial Directive. This means that specific teams (co-ordinating centres) are formed, with the task to support other research teams in topics related to good practice in clinical research.
In epidemiological research the situation is not as scattered, but there are different networks. Mostly they are connected in one way or another to clinical researchers, assuring access to patient data. This way several epidemiological networks are focused on a specific therapeutic area, and sometimes they are part of clinical trialist's network. In some areas (e.g. cardiovascular) clinical epidemiologists manage a complete national registry. This registry is then used for clinical research and sometimes also evaluating clinical quality between hospitals. Thus, some networks in epidemiology are on a national scale, including university and/or medical faculty and including governmental statistical providers. There are also national networks in therapeutic areas. Regional epidemiological networks are usually found

for drug consumption and cost issues. Finally there are hospital epidemiological centres following cost and treatment outcome in a specific hospital or a region.
New networks are now formed on storing of human tissues, as a result of a new law. From routine clinical diagnosing many millions of samples are stored in freezers at different institutions and hospitals. They must now be collected, identified, and stored safely. To achieve this most hospitals are joining local universities creating tissue bank networks. Researchers with a research interest can here apply to have access to samples for research. The researcher can also join a network to store samples from his research. This way he does not need to establish a complete new and approved storage system on his own (which is costly and may be an administrative burden).

Organisation of hospital care, universities and medical research

Hospitals are mainly managed by regional, political organisations interlocated between the state and communities/cities (they are called *landsting*). They are financed through taxes. A few private hospitals exist, mainly in elective surgery. The primary care is a discipline in its own. Many landsting are running family medicine by own management, while others are buying this service from private physicians. There are six University Hospitals with a medical faculty (Lund, Linköping, Örebro, Göteborg, Uppsala, Umeå). In Stockholm there is a also a medical University (Karolinska Institute), with four university hospitals connected to it (Karolinska, Huddinge, Södersjukhuset, and Danderyd). The Huddinge and Karolinska Hospital are presently merging into a new organisation, Karolinska University Hospital. Beyond university hospitals there are central county hospitals (when there is no university hospital in a landsting), and local county hospitals.
The universities are operated by the state. They buy medical education from the county's for training of new physicians and other medical professions. These money (called *ALF*) are transferred to the county's university hospitals basically as allocations intended for research. They are handled by the county's and hospitals R&D organisation in collaboration with the medical faculty. Basically these money are available for all types of clinical research, in a broad scope (e.g. including nursing care) . The Swedish Research Council (*Vetenskapsrådet*) is a governmental office allocating research grants for all disciplines (member of ESF, European Research Organsation). During the years the grants for medical research from this source have been substansially lowered. The *Vetenskapsrådet* is heading the country's central research ethical committee (CEPN). At CEPN decisions from the six regional research ethical committees can be appealed. The new law (2004) on research ethics state that only interventional research must apply. Other types of research may apply, if the sponsor wishes. However, as the law is based on the EU Directive 20/2001, and is applicable to all types of interventional research, Sweden have in reality implemented the ethical part of Good Clinical Practice for all types of interventional human research. There is a possibility for the CEPN to inspect specific projects, but due to lack of resources this have never happened. Applications for clinical drug research must also be made to the national medical products agency (MPA). MPA regularly inspects pharmaceutical research, including this with academic sponsorship.
In summary grants for clinical research are provided by ALF, Vetenskapsrådet or from private funds (commercial actors or private foundations).

Laws, insurances, courses and adherence to Good Clinical Practice

The last years, often in response to European Directives, several new laws in the area of clinical research have been implemented. After a few years introduction the law on handling personal information (*Personuppgiftslagen*) came to full force in 2002. It divided personal information into two categories, non-sensitive and sensitive. Sensitive information is among other things medical records. For any data storage of personal information the subject can ask

for a copy yearly, and corrections asked for by the subject must be included in the darabase. For sensitive information the general rule is that informed consent must be obtained from the subject. The research ethical committee may overrule this request. The law on storage of human tissues dated 2003 ask for safety procedures in tissue storing, very similar to what is asked for from storing and handling computers when storing sensitive personal information. The general rule is that informed consent must be obtained from the subject before storage, and then again for each specific research project. Use, export or constructing second tissue storage is restricted. The ethical board may make approval for exception. Samples for research immediately falls under this law, while samples from routine hospital care falls under this law after two months (to avoid interference with clinical routines). A new law on research ethic was released in January 2004. It basically follows the EU Directive 20/2001. There is a system for appeal within the system (only by applicant). The new law has created some turmoil, and is already under revision. In May 2004 a new Pharmaceutical Act was released, following the EU Directive 20/2001 closely.
In Sweden there is a state insurance governing actions instituted by a hospital on a patient (malpractice). This insurance also covers clinical trials, if the researcher have done everything according to law and regulations. For governmental bodies there is a general state insurance covering experiments in phase one. The pharmaceutical industry has a common insurance covering malfunction of marketed drugs (within approved dose and indication). Most commercial companies provide specific insurance when entering clinical trials. This means that investigator-initiated trials on new drugs or in new doses/indications are hard to complete with full insurance coverage. No hospital or university have yet started a QA department or commenced auditing investigator-initiated trials. There is no complete and approved system for data management and data storage for investigator-initiated trials. There is no national syllabus for GCP training. There are a lot of GCP courses all over the country, ranging from a few hours to 20 weeks, from private initiatives to university educations, intended for researchers and/or others in the clinical research team. But no formal diploma are requested by granting bodies, other than those asked for by MPA in pharmaceutical studies (senior physician with a scientific degree).

Drug handling and pharmacovigilance

There is a pharmacy state monopoly. Any drug trial must make an agreement with the local pharmacy on drug handling. It is possible to negotiate drug handling at the site of the investigator, but exception is only approved by the MPA, and the pharmacy still have to have some fees paid. Most investigators uses pharmacy since drug handling is complex and heavily regulated. Drug count and accountability during trials are regulated in the law, and may be inspected by the pharmacy while ongoing. Normally hospital pharmacist controls this, if agreed between the hospital and the hospital pharmacy. Usually in the investigator-initiated trial, drug handling is not monitored or audited, if not inspected by the MPA. Reporting of AE, SAE and SUSAR are regulated in the law. Most drug protocol specify how they should be handled, basically as they always are approved by the MPA. Some protocols are unclear whether the university or the hospital is acting “sponsor”, and there is to date no clear definition of their role (other than it exists in the laws).

Data handling and archiving

In Swedish law medical records must be archived for ten years. Most universities have explicit rules on how to store scientific data, not always congruent with GCP. In epidemiological and interventional studies independant data monitoring committees are

usually formed. It is rare that investigator initiated studies other than epidemiological uses “clean file” and “data lock” before analysing the projects clinical data.

Patientorganisations

Some patientorganisations are very active, lobbying and influencing science and politics. For other areas there are virtually no organisation. Large organisations sometimes engage in clinical research, e.g. in cancer or cardiovascular, often by funding and/or lobbying. It is rarely heard that they are involved in early trial planning, other than for HIV/AIDS.

Career

The merit of participating in clinical research has dimished during the years. Longer time for publication, more costly study settings and more authors in the list reduces the interest for this career path, when compared to pre-clinical research. For nurses the situation is different. The research nurse is becoming a recognised profession in its own, with particular skills, specified training, and a defined area of competence.

Summary

The EU Directive 20/2001 have been implemented in several national laws. As Sweden since 1989 adhered to the Nordic GCP guidelines, the threshold to implement ICH-GCP and the Directive for industrial pharmaceutical research was low and easy. For investigator-initiated research without commercial sponsor, the new regulations have introduced a major change. This have lead to a reduced number of projects, and difficulties in finding commercial sponsors to academic initiatives. As the Directive is the ground for the new Research Ethics Law, also non-drug clinical trials are affected by the Directive in Sweden.

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Networks and people connected to Swecrin

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