

**The infrastructure and framework of clinical research in
Denmark: prepared to
The European Clinical Research Infrastructures Network
(ECRIN)**

By

**Christian Gluud and Knud Lambaa for the Danish Clinical Research Infrastructures
Network (DCRIN) – the Danish part of ECRIN**



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Address for correspondence:

Christian Gluud
Copenhagen Trial Unit
Centre for Clinical Intervention Research
Department 71 02
Rigshospitalet
Copenhagen University Hospital
DK 2100 Copenhagen
Denmark
Tel: + 45 35 45 71 75
Fax: + 45 35 45 71 01
Email: cgluud@ctu.rh.dk

Introduction

Clinical research is most important for how preventive measures should be used and how patients should be diagnosed, treated, and cared for. Clinical research is also mandatory for testing which interventions work and which do not, in order to examine a market potential. Yet, vast areas are without clinical research. And most researched areas have been insufficiently researched both quantitatively and qualitatively.^{1 2 3 4}

Clinical research is international. No country alone can produce enough clinical research to sufficiently support clinical practice decision making in the health care system. Therefore clinical research should be conducted with the same high-quality standards all over the world. Further clinical research ought to be transparent.

There are always three partners in clinical research: participants, investigators, and sponsors. The three partners should of course be treated equally well with unrestricted access to the research plans as well as the data originating from the research.

Danish clinical research has previously been described in detail, eg, in connection with a white paper description from 1995 on how to plan and fund Danish health research,⁵ in connection with the 25th anniversary of Danish Society of Clinical Pharmacology,⁶ and in a number of articles in the Danish weekly medical journal in 2003⁷ related to the introduction of the EU Directive on clinical research.^{8 9}

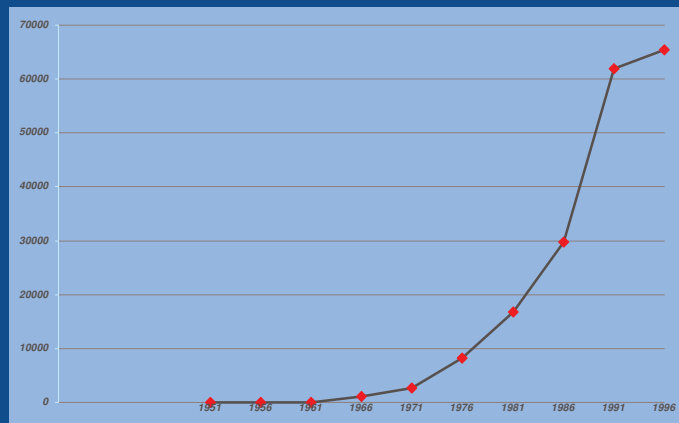
Denmark's contribution to clinical research

Denmark is a nation with about 5.4 million inhabitants. In spite of our small size, Denmark is producing a number of important clinical research studies.

Randomised clinical trials represent the most important research design within clinical research. Therefore, the conduct of randomised clinical trials may be seen as an important measure of the productivity of clinical research. The largest collection of references of randomised and controlled clinical trials in the world are the 427,807 references published during 1948 to 2004 found in The Cochrane Central Register of Controlled Trials (CENTRAL) of The Cochrane Library.² Based on the CENTRAL register, one can see the exponential increase in the publication of abstracts and articles on controlled clinical trials¹⁰ since the research design was adopted internationally after the Second World War.¹¹

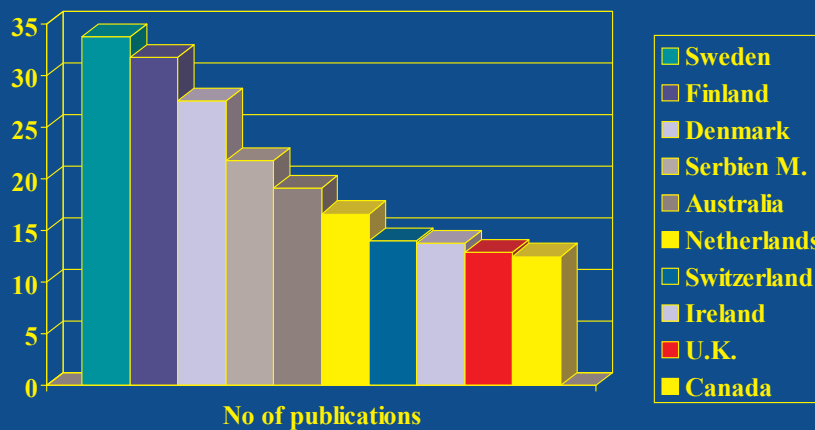
We have examined the national production of clinical trials based on the origin of these references.⁹ We could only link about half of the references to a particular country of origin and are aware of the fact that a number of the trials are multinational clinical trials.⁹ We are also aware that a number of the publications may represent the same controlled clinical trial.⁹ In spite of these limitations, USA, UK, Germany, Italy, Canada, the Netherlands, France, Sweden, Japan, and Australia are the top ten nations publishing most controlled clinical trials during the 1948 to 2004 period.⁹

Number of controlled clinical trials per five-year interval

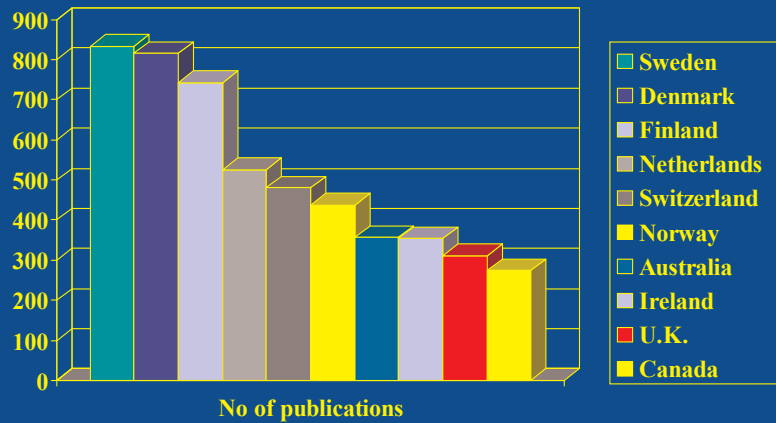


If we calculate the number of controlled trials published from 1948 to 2004 per million inhabitants per country in 2003 or per billion \$ in gross domestic product (GDP) in 2001, Denmark's position improves markedly.

Number of controlled clinical trial publications per billion \$ GDP (2001)



Number of controlled clinical trial publications 1948-2004 per million inhabitants (2003)



Calculated according to the number of inhabitants in 2003, Denmark is only after Sweden regarding number of published controlled clinical trials. Calculated according to billion \$ GDP in 2001, Denmark is only after Sweden and Finland in publishing controlled clinical trials. Irrespective how you calculate the top ten countries, Sweden seems to be a world leader or among the world leaders in publishing controlled clinical trials.

The figures demonstrate the huge potential, which exists for conducting more clinical trials in the World.⁹ First, a number of countries are lagging behind in their publication of clinical trials. Second, the research potential is far from being exploited in countries carrying out most controlled clinical trials. Therefore, the huge need for more clinical research should be met by carrying out more clinical trials to the benefit of the patients.

Danish Clinical Research Infrastructures Network (DCRIN)

In response to the formation of ECRIN, DCRIN has been established through bilateral discussions between Christian Gluud and interested parties. The 23rd of September 2004, a national workshop was held at the Copenhagen Trial Unit to examine the possibilities of forming DCRIN in order to link to and collaborate with ECRIN.

The DCRIN Workshop was attended by about half of the clinical research centres/clinical trial units (CRCs/CTUs) connected to DCRIN (see Annex 1). We estimate that the DCRIN CRCs/CTUs represent about 25% of all CRCs/CTUs in

Denmark. This report reflects the discussions during this workshop and will serve as Denmark's contribution to the establishment of the ECRIN.

The participants were informed about the objective of the ECRIN. Namely to formulate guidelines for an infrastructure, which will serve as basis for harmonisation of the support, training, and conduct of clinical trials on an European level, and to provide international support for both public funded and industrial sponsored multicentre clinical trials (see Annex 2).

The ECRIN Consortium already comprises the existing national study-centre networks and the European Forum for Good Clinical Practice (GCP). At present, there are 8 networks with more than 100 study centres representing six European countries (see Annex 2).

It was not possible to address all significant aspects during the workshop. Because of this, some of the information, eg, about developments with regard to trial registration, has been updated. The present report therefore reflects the personal view of the authors.

Structure and objectives of the centres of DCRIN

Denmark has around 30-50 academic groups that are involved in conducting clinical trials, some of them being more formalised than others. In addition, Denmark has only a few units dedicated to the conduct and management of especially large clinical trials. The participants of DCRIN meeting represented about half of these. Furthermore, Denmark has 6-10 contract research organisations (CROs), depending on one's definition of a CRO.

The CTUs offer expertise and infrastructure for the planning, conduct, and evaluation of clinical trials in Denmark. These services are provided for academic trials and for the private sector. Some of the clinical trial units also offer education and training in all aspects of the clinical trial. Activities of clinical trial units for investigator-initiated trials consist of study design, protocol development, translation, case record form design, recruitment of investigators, regulatory and ethics approval, investigator meetings, trial coordination, data management, reporting to sponsor, databanking, biostatistics, and trial reporting. The clinical trial units are also offering study monitoring. In addition, individual sites offer a specific expertise in other areas or have a special focus, eg, information technology used in clinical trials, clinical pharmacology, pharmacogenomics, pharmacovigilance, drug development, health economics, methodology research, meta-analysis, and systematic reviews.

The CTUs focus on specific disease or non-specialty oriented entities. The CTUs promote interdisciplinary co-operation between basic scientific research and clinical research and one of their principal activities is to conduct clinical trials.

Some of the CTUs focus on particular medical specialities or special types of studies, such as cancer or haematology. In Denmark within the area of oncology, through networking with the EORTC, there is more clinical research activity compared to other specialities. At present, however, there are very few units with research beds.

One of the CTUs, The Copenhagen Trial Unit, is not oriented towards one speciality. The Copenhagen Trial Unit was established in 1995. The main tasks are to conduct

trials and meta-analyses, develop these areas, and teach the topics of these areas. Since then it has conducted about 22 investigator-initiated randomised clinical trials randomising more than 12,000 participants. The Copenhagen Trial Unit is hosting The Cochrane Hepato-Biliary Group, one of the 50 systematic review groups within The Cochrane Collaboration.² The budget is approximately of 0.8 million Euro per year.

In accordance to the positive experience of the GCP Unit at Aarhus University Hospital established in 1995 and in response to the EU Directive, the other two university hospitals in Denmark - Copenhagen and Odense - established their own GCP-units in 2003 or 2004. The main tasks of these three GCP units are to assist in the planning and to offer monitoring of clinical trials. All three GCP units are connected in a national network, which participates in DCRIN.

In addition, DCRIN consists of research units focusing on prognostic studies, phase I and phase II trials, and the Danish Clinical Intervention Research Academy (DIRAC). DIRAC is a virtual research academy established in January 2004. DIRAC strives to raise the quality of the research education in clinical intervention research and has the goal to raise the quality of research education in Denmark by offering courses, summer schools, workshops, and seminars.

There is agreement upon the need for extra funding and all participants in DCRIN stress that the participation should not create an extra workload. On the other hand, the DCRIN participants also realise that there is a need for a well-functioning network with good collaboration.

Financing and sponsoring of Danish medical research

In Denmark about 3.2 billion Euro were used for research and development in 2000.¹² About 24% or 0.87 billion Euro were spent on health-related research. A total of 0.31 billion Euro came from public funding and 0.56 billion Euro came from industry funding. The industry funding has increased steadily.

About 80-90% of the public financing goes into basic medical and biological research. Only 10-20% of the health-care research funding goes into clinical research. Most clinical projects are paid and run by the industry. There is a large deficit in the sponsorship of clinical trials. Overall, sponsorship of clinical trials in Denmark is grossly inadequate. Considerably more financial support for the conduct and quality assurance of clinical trials is necessary. This increased support is needed to improve the quality of clinical research, to secure scientific progress, and to enable Denmark to guarantee compliance with national and international legislation.

Ethics

Denmark has eight ethics committees, plus one for the Faroe Islands and one for Greenland. In addition to international guidelines and ethical standards,^{13 14} the responsibilities of the ethics committee for clinical trials at national level are regulated by Danish laws.^{15 16 17 18} (Lov no. 402 of 28/05/2003; Lov no. 440 of 09/06/2004; BEK no. 806 of 12/07/2004; and VEJ NOV/2004)

Before conducting biomedical research in humans – with the exception of exclusively retrospective epidemiological investigations – physicians must consult with their

competent ethics committee in accordance with a state law on ethical and legal aspects.^{19 20} (LBK no. 656 of 28/07/1995 with changes LOV no. 382 of 28/05/2003; and BEK no. 295 of 26/04/2004) In accordance with the law of ethics, mentioned above, a drug can only undergo clinical testing in humans if the regional ethics committee has given its approval. The application for approval has to be made by the sponsor to the competent independent ethics committee responsible.

The Danish Medicines Agency²¹ and the International Conference on Harmonization – Good Clinical (Research) Practice (ICH-GCP) guidelines²² regulate the procedures for clinical drug/device trials. One complete notification is sent to the Danish Medicines Agency, including the names of the participating centres. Further to this the regional scientific ethical committees shall, pursuant to the law on the scientific ethical committee system and the handling of biomedical research projects, submit a recommendation on the scientific ethical evaluation to the Danish Medical Agency. The ethics committee reaches its final decisions within a maximum of 60 days. Special periods are valid for trials with gene transfer preparations, somatic cell therapeutics, genetically modified organisms (additional 90 days plus 90 days more if advice from public advisory boards is necessary) and xenogenic cell therapeutics (no time limit for a permission). In addition to this, the ethics committee(s) approve amendments to study protocols and the addition of new study centres (also here one has to wait for the approval before starting the trial, the clock is stopped). Within defined periods, the ethics committees also have to be informed of any incidents that alter the risk-benefit assessment, premature discontinuation of the study at any study centre, premature discontinuation of the entire study, and serious adverse events. For trials with genetically modified organisms, the law about gene technology and working environment applies.^{19 20 23}

Legislation, regulatory affairs, GCP, and insurance regarding clinical research involving participants

The clinical trials are being performed according to national and international legislation, guidelines, and standards. The new rules for clinical trials with pharmaceutical preparations were implemented by the 1st May 2004 by the Danish Medicines Agency.¹⁹ The EU Directive 2001/20/ EF became embodied in the Danish law.¹⁷ (LOV nr 382 af 28/05/2003)

A clinical trial must not start before the competent authorities have approved the trial protocol. The application procedure for approval is described in the Danish guideline on notification of clinical trials of medicinal products in humans, Danish Medicines Agency JAN 2004. The new regulations are not restricted only to trials intended for regulatory submissions, but are valid for all trials with pharmaceutical preparations.

The clinical trials also have to fulfil the Data protection law.^{24 25 26 27} (LOV no. 429 of 31/05/2000; VEJ no. 125 of 10/07/2000; VEJ no. 126 of 10/07/2000; CIS no. 11836 of 19/03/2001) The principal provisions are that medical findings collected during clinical research may only be processed with the explicitly agreement of the patient and only for the purpose of the research being conducted.

Patients enrolled in clinical trials must be insured for the potential consequences resulting from the research. Insurance can be problematic for clinical trials not governed by the industry, such as trials on surgical techniques or psychosomatic trials.

According to the Danish Medical Agency there shall be a specification for the insurance conditions of the patients.¹⁹

Damages incurred from a drug trial is covered by the Law of compensation of medicinal product damages.^{26 27 28 29 30} (LOV no.1220 of 20/12/1995; LOV no.1228 of 27/12/1996 §5; LBK no. 509 of 01/07/1998; LOV no.493 of 07/06/2001 §3; LOV no.430 of 10/06/2003 §2)

Damages of patients participating in non-drug research are covered by the Law of patient insurance.^{31 32 33 34} (LBK no.228 of 24/03/1997; LOV no.395 of 02/06/1999 §2; LOV no.430 of 10/06/2003; BEK no. 1097 of 12/12/2003)

In Denmark, investigators do take the role as sponsors. They are covered through the Act of compensation of medicinal products damages and the Act of patient insurance.

Harms (pharmacovigilance)

Pharmacovigilance procedures are governed by a national Danish guideline¹⁹ on notification of clinical trials of medicinal products in humans and European legislation about clinical safety data management for expedited reporting.²⁰ (ICH E6: Good Clinical Practice: Consolidated guideline CPMP/ICH/135/95 (2002))

The terms 'adverse reaction/event', 'serious adverse reaction/event', and 'unexpected adverse reaction' are defined in CPMP/ICH/135/95 (2002).²⁰ A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. The reporting requirements for sponsors and investigators are set out in the GCP regulations. In accordance with these, serious adverse reactions/events must be reported to the sponsor without delay, except for those that the protocol or investigators' brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed written reports.

The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the ethics committee and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the ethics committee concerned as soon as possible, but within a maximum of 15 days of first knowledge by the sponsor. The sponsor shall also inform all investigators.

Further details of reporting requirements are laid down in the Danish Medical Agency¹⁹ and GCP regulations.²⁰ Detailed guidance on the collection, verification,

and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (CT 3)^{35 36} and detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (SUSARs)³⁷ (Eudravigilance - Clinical Trial Module)(CT 4) have been published.

Methodology and data management

The European Guideline 2001/20/ EF³⁸ and the internationally valid Guidelines ICH E6 Good Clinical Practice and ICH E9 Statistical Principles for Clinical Trials³⁹ specify requirements for the methodology of trials and management of data from clinical trials to different extents. Further requirements are given in documents issued by the Food and Drug Administration in the USA (Guidance for industry: computerised systems used in clinical trials, April 1999, and 21 CFR 11: electronic records, electronic signatures, March 1997). The basic principles are that standard operating procedures (SOPs), specifically for data management processes and validated study software, need to be used.

Regarding the methodology of randomised clinical trials neither the laws nor the guidelines give sufficient information on how to conduct adequate generation of the allocation sequence, adequate allocation concealment, adequate double blinding and adequate intention to treat analyses. If these components are not adequately performed there is a substantial risk of overestimating intervention effect.³ We therefore hope that the insufficient nature of the laws and guidelines become urgently revised.

Data management procedures at the Danish CRCs/CTUs are varied and have seldom been externally audited.

The validated study software is based upon the standard commercial statistical analysis software (eg, SAS, SPSS). The Copenhagen Trial Unit has evaluated study software with a focus on remote data entry. A number of different questions are presently being investigated regarding validation of study software, use of Clinical Data Interchange Standards Consortium (CDISC), incorporation of mobile computing in the study software, and the production of standardised macros for analysis. In addition to this, the Copenhagen Trial Unit offer a range of IT services (eg, online phone randomisation) and remote and local functionalities for the support and working processes (eg, Lotus Notes Databases).

Despite significant advances in the area of data management for clinical trials in Denmark, there are still many problems in academia. Many centres do not have professional, validated study software. Financial means to purchase study software must be provided, although in some cases the very high prices for licences represent a considerable barrier for academic centres. Because of uncertainties in the software marketplace, the use of 2 or 3 different software products is certainly recommended, provided that suitable interfaces can be implemented. An important topic for the future is the integration of study software and hospital information systems, especially electronic patient records.

Quality management, SOPs, and audits

The aim of quality management is to ensure that the laws, regulations, and standards governing the conduct of clinical trials are fulfilled. Clinical trials on pharmaceutical preparations must be conducted in accordance with valid legislation and GCP. To improve quality, these requirements – and in particular GCP – now have to be applied to trials conducted for research purposes on all interventions (investigator-initiated trials).

The implementation of a quality management (QM) system is principally intended to improve the quality and efficiency of multicentre clinical trials. The basis for a QM system is standard operating procedures (SOPs). The objective of the Quality Assurance Working Group of the Copenhagen Trial Unit is to develop QM SOPs for the CTU and support their implementation, in order to achieve harmonisation of procedures across all sites. Each clinical trial unit needs its own quality manager. This person is responsible for the implementation of the Working Group results, supervises the local SOPs, working procedures/instructions and technical procedures, conducts internal training, and generally manages all quality assurance measures taken within the units. The oncology CRCs and the three GCP units in Denmark have now developed harmonised SOPs. Also the Copenhagen Trial Unit have developed SOPs for all aspects of randomised clinical trials.

An external system audit has been conducted in some of the GCP units. The basis for the evaluation was the fulfilment of the requirements for the conduct of clinical trials in accordance with GCP and valid legislation. The audits certified that the GCP units conform with GCP in their work. In addition to system audits, successful at site study audits have also been conducted.

There is a risk that the bureaucracy kills or significantly hampers the conduct of a sufficient number of clinical trials. This risk should be weighted against the fact that the majority of trials conducted until now have been conducted with grossly inadequate methods. There are therefore all good arguments to try to turn the influence of the directive on clinical trials into something, which may increase the methodological quality of trials in Europe. Further, increased collaboration is necessary so that a clinical trial may obtain a sufficient size to reduce the risks of type I and type II errors.

Communication and partnership

When conducting individual trials, the CRCs/CTUs often collaborate with principal investigators and study groups, often with close links to the professional societies. In setting up these collaborative groups, not at least from the point of view of obtaining funding, is of great importance.

One of the primary objectives of DCRIN will be to improve communication with sponsors, the public, and patient organisations. The aim is to inform 'customers' about the range of services that may be offered. Further activities are representation and lobbying, public relations and publications, collaboration with national and international scientific groups, and support for the establishing of a register for clinical trials.

The CTUs are in regular contact with the pharmaceutical industry and CROs. Several smaller projects and some large study projects have been established. At different

sites, different models for collaboration between pharmaceutical industry, CROs, and CTUs are being developed or tested. This collaboration has to be intensified in the future.

Communication with patient organisations (eg, self-help groups) is in its early stages at present. Activities so far have been involvement in events for patients and the general public, and the production of information materials (eg, patient brochures). Further, the Cochrane Hepato-Biliary Group has very positive experiences with consumer involvement. Collaboration with patient organisation should be very much intensified in order to increase patient awareness of clinical trials. This could improve the image of clinical trials and have a positive influence on recruitment.

Study register

The EU Guideline 2001/20/EF (ICH E6: Good Clinical Practice: Consolidated guideline CPMP/ICH/135/95 (2002) about clinical safety data management for expedited reporting and the Danish guideline on notification of clinical trials of medicinal products in humans; Danish Medicines Agency JAN 2004) require that trials on pharmaceutical preparations are registered in the EudraCT Database. However, this database is not publicly accessible.

The necessity for a global, independent, publicly accessible clinical trial registry is therefore obvious. Numerous organizations have demanded the implementation of such a register for ethical and scientific reasons (Annex 3).

The Ottawa Group has been formed, to formulate the requirements for such a register, and to develop a concept for implementation. The Ottawa Statement on principles for trial registrations has been formulated (Annex 4). To avoid entering data twice one public database internationally is to be preferred. The Ottawa Group will meet in Portland, USA, in 2005 in order to discuss details and practical aspects of trial registration.

The editors of leading medical journals are demanding a central study register with free, public access.⁴⁰ This move is really a masterpiece because it forces investigators and industry to register, while they are hoping for a positive result. Once in the open, the chances for getting all results, including negative ones, increases. In its Mexico Statement, the WHO said that registration was necessary and declared that it would be prepared to assist in setting up a network for an international study register with one entry portal and unique identification of trials.⁴¹

In September 2004, PhRMA – and similar regional industry organizations - launched a Clinical Study Results Database (ClinicalStudyResults.org) to provide a centralized repository for this information in a standard format and presentation. In keeping with their commitment to transparency in the area of clinical trials, PhRMA member companies now support the registration of new and ongoing clinical trials. However, PhRMA member companies commit to the registration of only company-sponsored hypothesis-testing (non-exploratory) clinical trials conducted on drugs and biologics marketed in the US or intended for marketing in the US, regardless of disease studied or the location of the trial. PhARMA explains that the reason for not registering and reporting data from exploratory studies is that they have significant scientific limitations. Further, PhRMA registration is voluntary. PhRMA member

companies will utilize the U.S.government's (National Library of Medicine's) website, www.clinicaltrials.gov, to voluntarily register new and ongoing hypothesis-testing studies, regardless of the disease or condition studied, and will follow that site's informational and timing provisions as outlined in Section 113 of the Food and Drug Administration Modernization Act (FDAMA). The unique identifier, which is already provided on the Clinicaltrials.gov website, can be used to cross reference specific clinical studies in various databases and publications.

Although these actions point in the right direction, they do not take long enough steps. For the sake of trial participants' health, the industry must stop keeping their negative studies secret. This of course also applies to academic investigators.

Therefore, DCRIN and ECRIN support more definitive steps towards global, independent and public trial registration (Annex 5).

Education and training

Pursuant to the European legislation (ICH E6: Good Clinical Practice: Consolidated guideline CPMP/ICH/135/95 (2002) about clinical safety data management for expedited reporting), ethics committees, approving a planned study, have to consider the suitability of the investigator, the study team and the study facility. This is described in greater detail in the Central Ethics Committee Guidance NOV 2004. Therefore, the ethics committee must be supplied with suitable proof of the qualifications of the investigator and information on the suitability of the study facility, in particular the suitability of the premises and equipment, and of the qualifications of the team that will be conducting the study, and also information on previous experience with conducting clinical trials. There are no further requirements. No further details of what constitutes suitable proof of qualifications are given. In practice, this is to be fulfilled by submitting curricula vitae and training certificates.

Apart from DIRAC (which is still under construction), there are no institutionalized postgraduate education programs in the area of clinical trials. At present, there are some – albeit few harmonized and institutionalized – courses for the training and further training of study staff (e.g. investigators and study nurses).

The Copenhagen Trial Unit has previously in collaboration with the Danish drug industry conducted short courses for clinical investigators and study nurses and runs courses in meta-analyses. As far as the Copenhagen Trial Unit is concerned, the tasks for the future in this area are to make the course organization more professional, to reach further agreement on courses to be offered, and to conduct exams and issue certificates.

Future

The future of DCRIN and ECRIN is going to be discussed at an international meeting in Brussels in February 2005 (see Annex 6).

Annex 1

Danish National Network Meeting on ECRIN
Thursday, September 23, 2004
Copenhagen Trial Unit, H:S Rigshospitalet,
Copenhagen University Hospital
Copenhagen, Denmark

Participants present

Geske Daugaard (GD), consultant, director of Clinical Oncological Research (phase II-IV), Clinical Research Unit, Department of Oncology, H:S Rigshospitalet, Copenhagen and EORTC member.

Ulrik Lassen, MD, Director of Clinical Oncological Research (phase I), Department of Oncology, H:S Rigshospitalet, Copenhagen, a unit connected to EORTC.

Karin Friis Bach (KF), Head of Good Clinical Practice Unit, KAS Gentofte Hospital, Copenhagen University Hospital, Copenhagen.

Christian Gluud (CG), Head of Department, director of Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Jørn Wetterslev (JW), Chief Physician, The Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Per Winkel, consultant, The Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Knud Lambaa, Chief-pharmacist, The Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Pia Hughes, Trial Coordinator, The Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Participants absent

Annette Jørgensen, Good Clinical Practice Unit, Aarhus University Hospital.

Kim Brøsen and Per Damkier, professors and directors of the Institute of Public Health, Clinical Pharmacology, University of Southern Denmark, Danish Clinical Intervention Research Academy (DIRAC), and Good Clinical Practice Unit, Odense University Hospital.

Peter Gimsing, Chief physician, H:S Rigshospitalet, Department of Haematology, H:S Rigshospitalet, Copenhagen University Hospital, Copenhagen

Sjurdur Frodi Olsen, Maternal Nutrition Group, Danish Epidemiology Science Centre, State Serum Institute, Copenhagen Denmark.

Ove Andersen, Clinical Research Unit, Hvidovre Hospital, Copenhagen University Hospital, Denmark.

Presentation of the national network and its participants

Welcome and introduction by CG including information of formation and progress of the ECRIN.

The role of networks in Denmark

GD explains the good experiences gained through collaboration with EORTC.

Pro: common platform for research.

Con: Translation of protocols expensive, economical support per patient too small, patient insurance different in different countries (co-operation with former Eastern Europe has been dropped because of

difficulties regarding patient insurance), 'all or nothing attitude' restricts research with new substances, data-centre very expensive.

KF notifies of the possibility of having shared Standard Operating Procedures in the GCP units. These may later be shared with the other members of the national ECRIN network.

Description of the CRCs/CTUs by a standardised form

CG will organise the collection of the description forms from the different parties. The participants – as well as those not present - are asked to fill out and send the form within 14 days from the meeting.

Topics for possible future working areas for the international network

The participants agree on the following:

DCRIN should be a loose collaboration between the CRCs/CTUs not requiring extra work or only minimal extra work for the involved parties.

There was a need for more openness and transparency both regarding academic and industry funded research.

Shared database for research protocols (e.g, opening of the Eudract database) was something being fully supported.

Future meetings and attendance

CG and KF will attend the next international ECRIN meeting in Brussels December 16th -17th, 2004 and present the DCRIN.

CG, KF, PH, KL, PW plus others will attend the ECRIN meeting in Brussels February 14th – 15th, 2004. At least one representative per centre is invited (for preliminary program please see Annex 6).

Annex 2



European Clinical Research Infrastructures Network: promoting harmonisation and quality in European clinical research

Health and legislative systems in Europe fragment clinical research and dampen its competitiveness, reducing the capacity to enrol patients in clinical studies, increasing the costs of clinical research, and hampering scientific productivity.^{1,2} For academic infrastructures of clinical research and investigators doing multinational studies in Europe, fragmentation raises obstacles: national regulation, informed consent, ethical review, data monitoring, adverse events, insurance, costs, funding, training, and language are bottlenecks in the conduct of multinational studies. Because of their major drain on national budgets, health systems are expected to remain dependent on the policies of European Union member states. Although European directives promote top-down harmonisation of the legal and regulatory framework, implementation at the national level still results in partly divergent regulation and practice. Thus improvement in the efficiency of European clinical research requires a simultaneous bottom-up harmonisation.

Funded by the 6th Framework Programme, the European Clinical Research Infrastructures Network (ECRIN)³ was designed to bridge such fragmented organisation and to improve the quality and efficiency of clinical research in Europe. ECRIN also plans to develop services to provide public or private sponsors with support for multicentre clinical studies in Europe.

ECRIN is based on the interconnection of national networks of academic infrastructures for clinical research—clinical research centres and trial units⁴—with the European Forum for Good Clinical Practice providing a focus on good clinical practice and ethics across the network (panel). Although some centres specialise in one disorder, networks cover the whole spectrum of disease and act as a non-specialised infrastructure. As they reach critical mass in their own country, national networks allow ECRIN to spread harmonised professionalism, and to affect national regulation and practice. A major objective of ECRIN is to stimulate the creation of national networks in member states not yet covered, for their subsequent connection to ECRIN. ECRIN's objectives meet the expectations of clinical research partners.^{1,5}

For public sponsors, whose role as a single sponsor in multinational studies is made increasingly complex because of the implementation of the Directive on Clinical Trials,⁶⁻⁹ ECRIN could provide substantial support through services facilitating transnational trials. Such support is relevant when international co-operation is required to address scientific challenges (eg, in studies on the mechanism of disease), public-health challenges (eg, trials beyond the scope of industry investment, including orphan drugs, rare diseases, strategy, surgery trials), or research and development challenges (eg, biotechnology, in which public-private partnership is common).

For industry sponsors, increased harmonisation of practice within Europe will facilitate the conduct of industry-driven drug development. Moreover, ECRIN could provide support to small and medium enterprises (eg, biotechnology and medical-device companies), acting as sponsor in the development of innovative diagnostic or therapeutic tools.

For the European Union, ECRIN will promote bottom-up harmonisation, spread quality standards, and increase the competitiveness of Europe as a knowledge-based economy.

ECRIN is developing an initial programme in a series of workshops addressing: the description of centres, national networks, and their institutional partners; and the comparison of national specificity in the organisation of clinical research (funding, sponsorship, ethical review, legislation, regulatory authorities, good clinical practice, insurance, pharmacovigilance, drug dispensing, data management and analysis, quality control, audits and evaluation, communication with patients, study registers, education and careers). This step will be followed by a meeting in Brussels (Feb 14-15, 2005) to define priorities: networking activities required to promote harmonisation of training, tools, and practice; and services for sponsors in multinational studies. This meeting will allow working groups to begin their activities, and invite more national networks to join ECRIN.

In addition, ECRIN can affect the organisation of clinical research, at national and European levels, through participation in discussion on new regulations (eg, trial registers) and programmes (eg, education), promoting shared and harmonised policies. And as a non-specialised infrastructure, ECRIN can act as a partner in specialised research programmes (eg, networks of excellence or integrated projects) in which clinical studies are planned, which would allow to increase their European value.

European Clinical Research Infrastructures Network (ECRIN)

ECRIN consortium currently covers six European countries representing 260 million citizens, and constitutes 112 centres doing 1500 clinical studies:

Institutions

Réseau des Centres d'Investigation Clinique INSERM-Hôpitaux, France
Netzwerk der Koordinierungszentren für Klinische Studien, Germany
Consorzio Italiano per la Ricerca in Medicina, Italy
French Clinical Trial Unit Network, ISPED, France
Danish Clinical Research Infrastructures Network, Denmark
Istituto di Ricerche Farmacologiche Mario Negri, Italy
Swedish Clinical Research Infrastructures Network, Karolinska, Sweden
Spanish Clinical Research Network, Spain
European Forum for Good Clinical Practice

Contacts

Jacques Demotes-Mainard
Christian Ohmann
Nicola Fabris
Jean-Pierre Pignon
Christian Gluud
Silvio Garattini
Pierre Lafolie
Xavier Carné
Francis P. Crawley

Coordination:

Jacques Demotes-Mainard
CIC INSERM-CHU de Bordeaux, 33604 Pessac, France
Tel +33 5 57 65 61 70, demotes@bordeaux.inserm.fr

References

- 1 Bassand JP, Martin J, Ryden L, Simoons M: The need for resources for clinical research: the European Society of Cardiology calls for European, international collaboration. *Lancet* 2002;360:1866-69.
- 2 Remuzzi G, Schieppati A, Boissel JP, Garattini S, Horton R: Independent clinical research in Europe. *Lancet* 2004;364:17232-6.
- 3 www.eclin.org
- 4 Bell J: Resuscitating clinical research in the United Kingdom. *BMJ* 2003;327:1041-43.
- 5 Clumeck N, Katlama C. Call for network of Centres of Excellence in clinical research in Europe. *Lancet* 2004;363:901-02.
- 6 Editorial. Who's afraid of the European Clinical Trials Directive? *Lancet* 2003;361:2167.
- 7 Meunier F, Lacombe D. European Organisation for Research and Treatment of Cancer's point of view. *Lancet* 2003;362:663.
- 8 Mayor S. Squeezing academic research into a commercial straitjacket. *BMJ* 2004;328:1036.
- 9 Crawley FP: New European Clinical Trials Directive: is European research possible? *BMJ* 2004;328:522.

Annex 3:

Principles of International Registration of Protocol Information and Results from Human Trials of Health-related Interventions

Karmela Krleža-Jerić, An-Wen Chan¹, Kay Dickersin, Ida Sim, Jeremy Grimshaw, and Christian Glud for the Ottawa Group²

Corresponding author:

Karmela Krleža-Jerić, M.D., D.Sc.
Randomised Controlled Trials / Essais randomisés et contrôlés
CIHR/ IRSC - Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
Ph: (613) 957-6130
email: kkrleza-jeric@cihr-irsc.gc.ca

¹ This does not imply CIHR's official endorsement of the Ottawa Statement

² Members listed at the end of paper

Background

Since at least the 1960s, individuals and institutions have endorsed the benefits of trials registration, a system for recording the existence of all trials with a common characteristic, such as a particular healthcare area^{1,2,3} or sponsor.¹ There are numerous ethical and scientific reasons for registering trials (see Box).^{4,5,6, 7} Most importantly, when humans participate in a research study, the investigators and sponsors are ethically bound to make information about the study protocol and the results publicly accessible,⁸ so that the knowledge gained in the research is neither lost nor kept invisible.

Concomitant with the increased publication and use of systematic reviews, a burgeoning research literature has focused on the scientific issues associated with the failure to publish,⁹ publication bias,¹⁰ selective outcome reporting,^{11, 12} duplicate publication,¹³ time lag to publication,^{14, 15} and the difficulty of linking individual studies with publications.¹⁶

These ethical and scientific concerns, as well as the need to facilitate participant recruitment in trials,¹⁷ have led to renewed calls for trials registers, not only by scientists, but also by consumer groups.¹⁸

By the early 1990s, a handful of mostly paper-based trials registers existed worldwide.¹⁹ Widespread access to the Internet subsequently led to hundreds of prospective trials registers.²⁰ However, there has been no standardisation (for example of a unique identifying number such as the International Standard Randomised Controlled Trial Number or ISRCTN²¹) or oversight, and none of the existing registers has aimed to be comprehensive in encompassing all types of trials.

In the spring and summer of 2004, international furor erupted following the publication of two systematic reviews on the effects of selective serotonin reuptake inhibitors for childhood depression.^{22, 23, 24} Each showed that published studies produced more favourable outcomes compared to unpublished studies; when unpublished data were included in the meta-analyses, all but one of the antidepressants lacked efficacy compared to placebo. Even the published data demonstrated an association between antidepressants and adverse events, including an increase in suicidal behaviour.

These revelations led to several important actions. First, the New York Attorney General's Office successfully sued Glaxo Smith Kline, manufacturer of paroxetine, for suppression of trial data.²⁵ Second, the American Medical Association advocated for United States legislation to create a clinical trials register.²⁵ Finally the International Committee of Medical Journal Editors published a new policy requiring that trials published in their pages be registered,²⁶ followed by a similar statement from the British Medical Journal editor.²⁷ These actions attracted sustained media attention and public interest in the summer and fall of 2004, leading to intensification of registration efforts that had been waxing and waning for decades. These efforts, including federal legislation in the United States, vary considerably in their approaches, leading to concern that by moving quickly to take advantage of heightened public interest, legislators and others could take a wrong turn and support less than optimal registers (for example a register focusing only on drug trials).²⁸

In this context, as an interested and neutral party that has been registering the trials that it funds,²⁹ the Canadian Institutes of Health Research hosted an open meeting on October 4, 2004 in Ottawa, Canada, and invited interested parties to contribute to a plan for trials registration. Because of the confluence of interested investigators, consumers, journal editors, policymakers, industry representatives, and others, the meeting was held concurrently with the annual Cochrane Colloquium.³

The assembled group discussed a set of guiding principles for the development of trials registers. These principles, refined and agreed to over the subsequent two months by those attending the meeting and others,

³ (<http://www.colloquium.info/>)

are presented below as the Ottawa Statement, Part 1. Some individuals, although supportive of the statement, were unable to sign because it might imply a position taken by their organisation. Others were generally supportive, but were concerned that registration of all trials, as opposed to randomised trials only, was too ambitious as a first step. These individuals nevertheless provided valuable feedback at the meeting and during refinement of the Statement.

In the coming year, Ottawa Group- consisting of authors and signatories to the Statement- will continue to consult broadly and solicit proposals as to the most effective and practical ways to operationalise these principles. Operationalisation will undoubtedly require difficult decisions related to timely and feasible implementation. Those who wish to contribute further to the Ottawa Statement are invited to become involved. The group will meet in May 2005 during the Annual Meeting of the Society for Clinical Trials to finalise Part 2 of the Statement, which will focus on implementation recommendations.

Already, a group assembled by the World Health Organisation to guide development of a global trials registration³⁰ has used an earlier draft of the Ottawa Statement to guide its own plans. The Ottawa Group encourages others to do the same and to contribute to the public discussion of this important issue.

Box

Ethical and Scientific Reasons to Support Trials Registration

Ethical

Respect for investigator-participant covenant to make trial methodology and results public
Global open access to information
Reduction in unnecessary duplication of invested research resources through awareness of existing trials
Accountability with regards to global ethical/ research standards
Ability to monitor adherence to ethical principles and process

Scientific

Improvement in trial participation
Transparency of trial design and methodology
Open review of protocols to improve the trial quality and refine the methodology
Identification and prevention of biased under- or over-reporting of research
Increase in opportunities for collaboration
All these is expected to accelerate the pace of the knowledge creation

Literature

1. Levine J, Guy W, Cleary P. Therapeutic trials of psychopharmacologic agents: 1968-72. In: McMahon G, ed. *Psychopharmacological Agents*. Futura Publishing Co., 1974.
2. Chalmers TC. Randomize the first patient! *NEJM*. 1977;296:107.
3. Verstraete M. International Committee on Thrombosis and Haemostasis Basil, 8-11. September 1974 Subcommittee on Clinical Trial Investigations: Registry of prospective clinical trials. *Thromb Diath Haemorrh*. 1975;33:655-63.
4. Ad Hoc Working Party of the International Collaborative Group on Clinical Trials Registries. International Collaborative Group on Clinical Trial Registries. Position paper and consensus recommendations on clinical trial registries. *Clin Trials Metaanal*. 1993;28:199-201.
5. Antes G, Chalmers I. Under-reporting of clinical trials is unethical. *Lancet*. 2003;361:978-9.
6. Dickersin K, Rennie D. Registering clinical trials. *JAMA* 2003; 290:516-523.
7. Rennie D. Trial registration; a great idea switches from ignored to irresistible. *JAMA*. 2004;292:1359-62.
8. Declaration of Helsinki. <http://www.wma.net/e/policy/b3.htm>. Accessed January 4, 2005.
9. Godlee F, Dickersin K. Bias, subjectivity, chance, and conflict of interest in editorial decisions. Ch. 6 In: Godlee F, Jefferson T (eds). *Peer Review in Health Sciences*. 2003; London: BMJ Books, 2nd Edition. pp. 91-117.
10. Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ. Publication and related biases. *Health Technol Assess* 2000;4(10) 2
11. Chan A-W, Krlježa-Jerić K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *CMAJ* 2004; 171:735-40.
12. Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials. *JAMA* 2004; 2457-2465.
13. Gøtzsche PC. Multiple publication of reports of drug trials. *Eur J Clin Pharmacol*. 1989;36:429-32.
14. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 315(7109):640-5, 1997.
15. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA*. 1998;279:281-286.

16. Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet*. 1996;347:1024-26.
17. Hubbard S, DeVita VT. PDQ: An innovation in information dissemination linking cancer research and clinical practice. Ch. 13. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology*. 1987. Philadelphia: JB Lippincott Co. pp. 263-277.
18. Consumers' Union. Prescription for change. <https://secure2.convio.net/cu/site/Advocacy?JServSessionIdr010=5okc9aify1.app14b&page=UserAction&cmd=display&id=307>. Accessed December 22, 2004.
19. Dickersin K. Why register clinical trials? - Revisited. *Control Clin Trials* 1992; 13:170-7.
20. TrialsCentral.org. www.trialscentral.org. Accessed December 22, 2004.
21. The ISRCTN. <http://www.controlled-trials.com/isretn/>. Accessed December 22, 2004.
22. Jereidini, JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AI. Efficacy and safety of antidepressants for children and adolescents. *BMJ* 2004; 328: 879-83.
23. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004; 363:1341-45.
24. Editorial. All above board. *New Scientist*. 2004; March 6: 3
25. Marshall E. Antidepressants and children. Buried data can be hazardous to a company's health. *Science* 2004; 304: 1576-7.
26. DeAngelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusić A, Overbeke AJPM, Schroeder TV, Sox HC, Van der Weyden MB. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. *Lancet*. September 9, 2004. <http://image.thelancet.com/extras/04cmt26web.pdf>.
27. Abassi K. Compulsory registration of clinical trials will be a requirement before submission to the BMJ from July 2005, *BMJ* online first *BMJ* Sept 2004
28. Herxheimer A. Open access to industry's clinically relevant data. *BMJ*. 2004;329:64-65.
29. Moher D, Bernstein A. Registering CIHR-funded randomized controlled trials: a global public good. *CMAJ* 2004;171:750-751
30. Evans T, Gülmezoglu M, Pang T. Registering clinical trials: an essential role for WHO. *Lancet*. 2004; 363(9419):1413- 4.

Annex 4:

The Ottawa Statement on trials registration: Proposal for international registration of protocol information and results from human trials of health-related interventions

Part 1. Principles

Karmela Krleža-Jerić, An-Wen Chan, Kay Dickersin, Ida Sim, Jeremy Grimshaw, and Christian Gluud for the Ottawa Group⁴

A. Objective

The Ottawa Statement aims to establish internationally recognised principles for trials registration (Part 1) as well as their proposed operationalisation (Part 2).⁵

B. Definitions

'Trial' refers to a prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants. For example, a trial may investigate interventions related to one or more of the following: prevention, health promotion, screening, diagnosis, treatment, rehabilitation, or organisation and financing of care.

'Intervention' refers to a deliberate act applied to an individual or group of individuals. Health-related interventions include but are not limited to the use of pharmaceuticals, biological products, surgery, procedures, radiation, devices, education, counselling, behaviour change, complementary health modalities, and management or economic policies.

'Registration' of a trial involves the assignment of a unique identification number; the recording and public release of protocol information; as well as the recording and public release of trial results.

'Protocol' refers to a document written before participant enrolment to describe the objectives, methodology, statistical analyses, organisation, and administrative details of a trial.

'International' refers to the applicability of the principles presented in this document to trials conducted in any country or countries worldwide.

'Sponsor' is defined as an individual, company, institution, or organisation that takes responsibility for the initiation, management, and/or financing of a trial. The sponsor does not actually conduct the investigation unless the sponsor is an investigator-sponsor.

'Principal investigator' is defined as the person responsible for the overall conduct of the trial

⁴ A full list of contributors appears at the end of the document.

⁵ The operationalisation of these principles is under development and will be presented in a separate document as Part 2 of the Ottawa Statement.

C. Rationale for international trials registration

C.1. Ethical rationale

C.1.1. Above all, international trials registration is necessary to fulfill ethical obligations to research participants.

When members of the public agree to participate in trials, it is on the understanding that they are contributing to the global body of health-related knowledge. It is thus unethical to conduct human research without ensuring that descriptions of the study and its findings are publicly available.

C.1.2. Potential trial participants, care providers, researchers, institutional review boards/independent ethics committees (IRB/IECs), and sponsors should have access to information about trials that have been previously performed.

C.1.3. Potential trial participants, care providers, researchers, IRB/IECs, and sponsors should have access to information about trials that are currently open for enrolment.

C.1.4. The availability of information about all initiated trials contributes to global open access to knowledge, which constitutes a public good.

C.2. Scientific rationale

Public access to trial protocol information (as approved by the IRB/IEC) and results will help to:

C.2.1. Minimise known risks and potential harm arising from unnecessary exposure to previously tested interventions;

C.2.2. Accelerate research by making knowledge available about prior experiences with interventions;

C.2.3. Identify and deter unnecessary duplication of research and publications;

C.2.4. Identify and deter selective reporting of research (reporting biases);

C.2.5. Provide a means of comparing the original protocol upon which ethics approval was based with the study as it was carried out;

C.2.6. Enhance collaboration among researchers by informing them of ongoing trials.

D. Principles regarding the scope and nature of international trials registration

D.1. Types of trials to be registered

Protocol information (D.4) and results (D.5) from all trials related to health or healthcare – regardless of topic, design, or outcomes examined – should be registered and publicly available.

D.2. Elements of registration

Registration of each trial comprises three distinct parts: obtaining an internationally unique identification number (D.3), registering the original protocol approved by the IRB/IEC along with subsequent amendments (D.4), and registering the trial results (D.5).

D.3. Principles relating to unique identification number (Unique ID)

D.3.1. Assignment of Unique ID

Every trial should have a Unique ID assigned by a single international source prior to participant enrolment. The Unique ID should be verifiable and have built-in error-detecting logic.

D.3.2. Application of Unique ID

The Unique ID should appear on all trial documentation, including the consent form given to participants as well as subsequent presentations and publications.

D.4. Principles relating to protocol registration

D.4.1. Definition of protocol information to be registered

Protocol information in the register should consist of (1) a minimum set of standardised, structured, key items from the protocol approved by the IRB/IEC (“minimum protocol items”); (2) the consent forms approved by the IRB/IEC; and (3) any subsequent protocol amendments. Protocol information from each of these components should be irreversibly recorded and dated at the time of submission to the register (D.4.2). Furthermore, the full protocol as approved by the IRB/IEC, and the data collection forms, should be available in the public domain to enable the interpretation of trial findings.

D.4.2. Timing of protocol registration

Registration of the minimum protocol items and the consent forms should occur prior to enrolment of trial participants. Amendments to the registered protocol information should be dated and registered as they occur.

D.4.3. Timing of public access to registered protocol information

The public should have cost-free access to the Unique ID, minimum protocol items, and consent forms prior to participant enrolment. Registered amendments should be made publicly available as they occur. The full protocol as approved by the IRB/IEC, and the data collection forms, should be made publicly available as soon as possible and no later than the date of completion of data analysis.

D.5. Principles relating to registration of trial results

D.5.1. Definition of trial results to be registered

At a minimum, results for outcomes and analyses specified in the protocol (as approved by the IRB/IEC), as well as data on harms, should be registered regardless of whether or not they are published. If a trial is terminated prematurely, any available results should be registered along with the reason for termination.

The summary results recorded for each outcome should be sufficient for performing meta-analyses, and should not enable identification of any individual trial participant to the public.

Full citations to trial publications should be registered as they become available. However, listing of study publications alone does not constitute adequate registration of results.

D.5.2. Timing of registration of trial results

Trial results should be registered once the analyses are completed and verified.

D.5.3. Timing of public access to registered results

Investigators should have sufficient time to publish their findings in a peer-reviewed electronic or print forum before the registered results are released for public, free-of-charge access. Timely public access to results should ultimately be assured regardless of their publication status.

D.6. Organisation and language of registries

The source assigning the Unique ID can exist separately from the register or registers that contain protocol information and trial results. However, all three components (Unique ID, protocol information, trial results) must be cross-referenced.

To facilitate efficient searching, multiple national or regional registers should be linked. Furthermore, registered information must be presented at least in English and also preferably in the major language(s) of the region where the main study site is located.

E. Responsibilities of involved parties

E.1. Sponsors

The sponsor(s) of the trial has ultimate responsibility for obtaining the Unique ID (D.3) as well as for registering the protocol information (D.4) and results (D.5). The sponsor should also ensure that the full protocol as approved by the IRB/IEC, and the data collection forms, are made publicly available. When there are multiple sponsors, each sponsor is individually responsible for ensuring that these tasks are fulfilled.

E.2. Investigators

The principal investigator has a responsibility to ensure that the sponsor(s) obtains a Unique ID and registers his or her contact information, the protocol information (D.4), and the trial results (D.5). Investigators also have the responsibility to perform analyses in a timely fashion and to submit the findings for publication in a peer-reviewed electronic or print forum.

E.3. Institutional review boards/independent ethics committees

IRB/IECs have a responsibility to ensure that approved trials have a Unique ID; that minimum protocol items and consent forms, as approved by the board, are registered prior to participant enrolment; and that subsequent protocol amendments are reported and registered. They are also responsible for ensuring that the Unique ID appears on the consent form. Furthermore, they are responsible for encouraging the publication of trial results in a peer-reviewed electronic or print forum. When a trial receives approval from multiple IRB/IECs, each board is responsible for ensuring that these tasks are fulfilled.

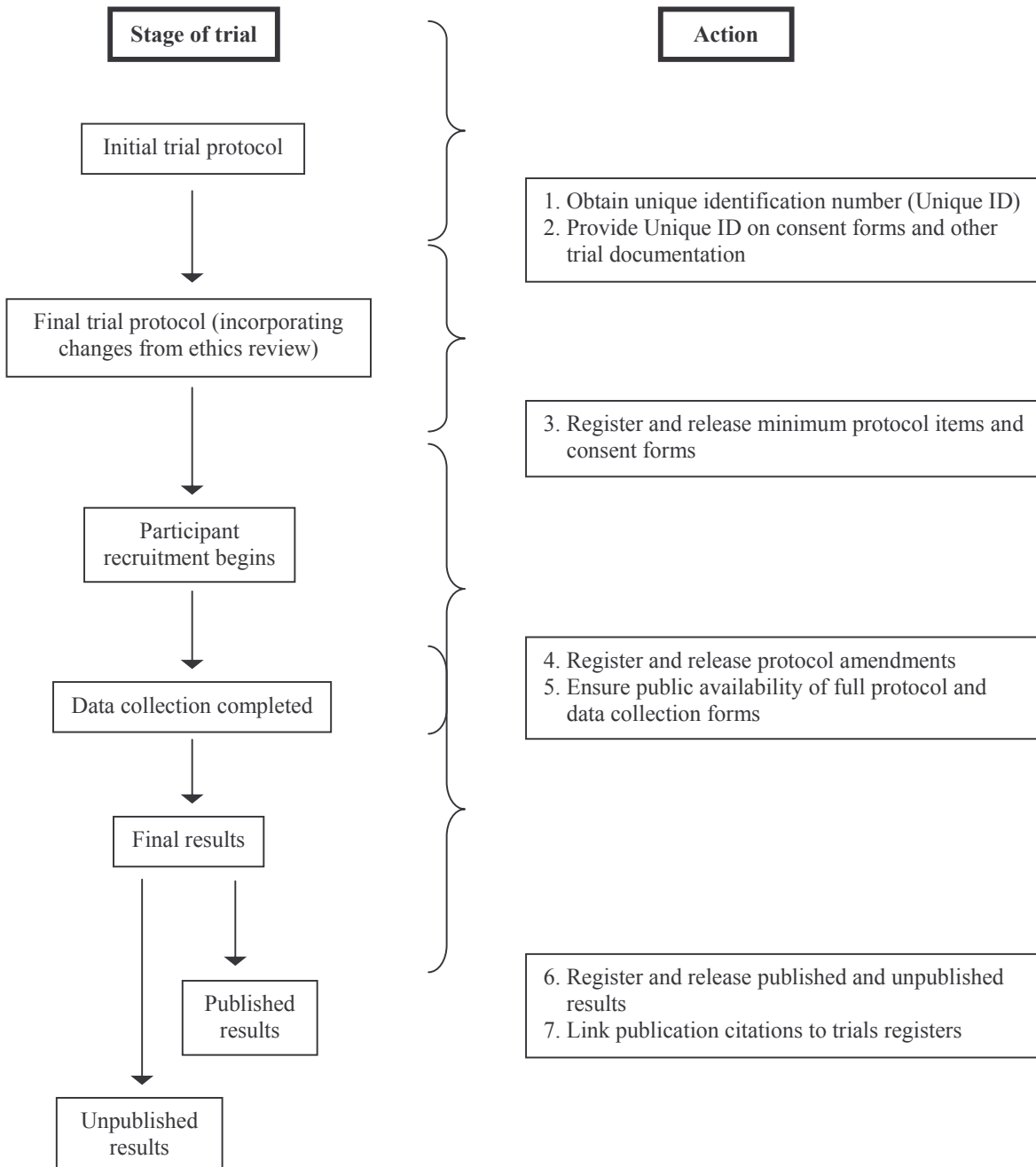
E.4. Journal editors

Journal editors have a responsibility to promote trials registration by requiring that any trial being considered for publication has a Unique ID, and to include the Unique ID in any resulting publication.

E.5. Policing and sanctions

Trials registration should be a legal requirement, with enforcement of meaningful sanctions against those found to be in violation.

Figure 1. General time-line for process of trials registration



Annex 5:

ECRIN commentary:

Toward a global, independent, and public clinical trial registry crossing the frontiers to health

A global, independent, and public clinical trial registry (GIP-CTR) is needed to improve the conditions for ethics and science in clinical research. A GIP-CTR can provide the public with accurate and objective information regarding the advance of science against diseases. It can also reduce bias in the reporting of research while helping to restore justified public confidence in clinical trials. The necessity for a GIP-CTR is rapidly becoming apparent.²⁸

Some of the recent discussion on CTRs came from the European Science Foundation,²⁹ the CONSORT Group,³⁰ and the World Health Organization (WHO).³¹ However, what initiated activity was the threat of medical editors to only publish results of registered trials.^{32,33} Supporting the editors' demand, the Canadian Institutes of Health Research,³⁴ The Cochrane Collaboration,³⁵ and other parties expressed the need to expand transparency in clinical research. In October 2004, about 40 researchers drafted the Ottawa Statement requesting mandatory registration of all clinical trials.³⁶ Later in October 2004 the WHO held a meeting at the Rockefeller Foundation on the topic with representatives from industry and academia. This meeting helped prepare the Ministerial Summit on Health Research in Mexico City.³⁷ The resulting Mexico Statement requests all major stakeholders, facilitated by the WHO, to establish a platform linking CTRs to ensure a single point of access and the unambiguous identification of trials.³⁸

Since its inception in 2003, The European Clinical Research Infrastructures Network (ECRIN)³⁹ has discussed trial registration. The ECRIN experience of working across borders points to a need for a GIP-CTR. ECRIN supports the Ottawa Statement published in this issue of *The Lancet*.⁹ Each and every clinical study should be registered in the GIP-CTR prior to the enrolment of the first participant. Each study should receive a unique identifier. Each study should register key protocol information in English, as well as the entire protocol, once regulatory authorities (where necessary) and ethics committees have approved the study. In addition, protocol amendments, data, results, and publications should be registered. Free access to this information should be assured to the scientific community and the public.

Current Controlled Trials has proposed creating a GIP-CTR by forming a trust together with the WHO and others to build on the experiences of the International Standard Randomised Clinical Trials Number Registry.⁴⁰ Such a registry should be easily accessible for uploading information and have shared formats with other CTRs. Compatibility with local, regional, or global databases should allow current CTRs to adapt existing tools and overcome linguistic hurdles. The GIP-CTR needs to develop unique identifiers for all clinical studies, irrespective of scope or phase. Stakeholders will need to work together to achieve a smooth and efficient process that meets the objectives of ethics and science in clinical research as well as the needs of researchers and their institutions. The administrative burden related to clinical research should be kept at a minimum.

The GIP-CTR will shift values and practices for medical science. Some sponsors, funders, academic institutions, and even scientists are likely to resist this openness. This is nonetheless a debate that we must engage in if we are to ensure, not only the necessary conditions for sound science and ethics in the development of medical interventions, but also the best means for genuine innovation and competitiveness in health research.

Clinical trial registration has been perceived as a threat to innovation and competitiveness in developing new medical interventions. The argument has been that such transparency is a danger to guaranteeing intellectual property rights and patents. This perception is, however, in need of correction. Innovation can only increase with greater access to scientific information, reducing the overall investment of society in needless repetition and proven dead ends. True competitiveness (including profitability) depends upon a level playing field where all parties have access to the needed information and where they are appropriately rewarded for their successes. The GIP-CTR will be an enhancing instrument for clinical innovation and competitiveness.

Resistance to the registration of clinical trials is ebbing. Recently, the pharmaceutical industry released a joint statement indicating cross-company and cross-national agreement to voluntarily make use of clinical trial registries for reporting trial information and results.⁴¹ The industry's statement represents a leap forward. However, it does not live up to the intentions of the Ottawa Statement.⁹ More consultations and actions are required to achieve the fully transparent and well functioning GIP-CTR. One immediate step would be to expand and open to the public the European Clinical Trials Database (EudraCT), where all European medicinal trials are required by law to be registered since 1 May 2004.

New pressures are slowing agreement on the implementation of registering clinical trials and their results. Alongside the hesitancy expressed by the pharmaceutical industry, academic and public sponsors as well the American publishing industry are also raising issues of their own regarding disclosures and transparency. Funding and profit interests here too seem to conflict with the interests of science, health, and the public. These are related to already existing concerns about the relationship between the NIH, the US military establishment, and the pharmaceutical industry.^{42,43}

At the national, European, and global levels we are confronted with the need for a decision: Should medicine and healthcare be developed as an instrument for creating wealth by fostering science and industry, or should science and industry be seen as instruments for developing improved medicines and healthcare? It is not a choice between, on the one hand, health and, on the other hand, science and industry, but rather a decision as to their relationship. Society seems to have little choice in making this decision. The advancement of the GIP-CTR should foster true innovation and competition in clinical research for the benefit of public health.

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**Christian Gluud, Francis P. Crawley*

*The Danish Clinical Research Infrastructures Network (DCRIN – the Danish ECRIN correspondent), The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (e-mail: gluud@ctu.rh.dk)

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1. Rennie D. Trial registration: a great idea switches from ignored to irresistible. *JAMA* 2004; **292**: 1359-62.
2. European Science Foundation Policy Briefing. Controlled clinical trials. May 2001. <http://www.esf.org/medias/ESP13.pdf>. (accessed Oct 15, 2004).
3. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**: 1191-4.
4. Evans T, Gülmezoglu M, Pang T. Registering clinical trials: an essential role for WHO. *The Lancet* 2004; **363**: 1413-14.

5. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet* 2004; **364**: 911-2.
6. Abbasi, K. Compulsory registration of clinical trials. *BMJ* 2004; **329**: 637-8.
7. Moher D, Bernstein A. Registering CIHR-funded randomized controlled trials: a global public good. *JAMC* 2004; **171**: 750-1.
8. The Cochrane Collaboration statement on registering clinical trials prospectively. The Cochrane Collaboration supports prospective registration of trials. <http://www.cochrane.org/news/articles/2004.07.26.htm> (accessed Oct 15, 2004).
9. Krelža-Jerić K, Chan A-W, Dickersin K, Sim I, Grimshaw J, Gluud C for the Ottawa Group. The Ottawa Statement on trials registration: Proposal for international registration of protocol information and results from human trials of health-related interventions. Part 1. Principles. Submitted to *The Lancet* 2005.
10. The Mexico Statement: strengthening health systems. *The Lancet* 2004; **364**:1911-12.
11. The Mexico Statement on Health Research. Knowledge for better health: strengthening health systems From the Ministerial Summit on Health Research, Mexico City, November 16-20, 2004. http://www.who.int/rpc/summit/agenda/en/mexico_statement_on_health_research.pdf (accessed Dec 19, 2004).
12. Demotes-Mainard J, Ohmann C, ECRIN. European Clinical Research Infrastructures Network: promoting harmonisation and quality in European clinical research. *Lancet* 2005;365:107-8.
13. Current Controlled Trials. Response from Current Controlled Trials concerning the International Committee of Medical Journal Editors' statement on clinical trial registration. <http://www.controlled-trials.com/news/CCT%20response%20to%20ICMJE.doc> (accessed Oct 15, 2004).
14. International Federation of Pharmaceutical Manufacturing Industries, Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases. 6 January 2005. <http://www.ifpma.org/News/NewsReleaseDetail.aspx?nID=2205> (accessed Jan 6, 2005).
15. Singer EA, Druml C. Collateral damage or apocalypse now for European academic research. *Intensive Care Medicine*. 2005; Jan 20 [Epub ahead of print].
16. Weiss R. NIH scales back plan for access to medical study results. *The Washington Post*. 18 January 2005 <http://www.aic.com/health/content/health/0105/19nih.html> (accessed Jan 22, 2005).

References

- ¹ Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated March 2004]. In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.
- ² The Cochrane Library 2004, Issue 4. Content ©2004 The Cochrane Collaboration. Published by John Wiley & Sons Ltd.
- ³ Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001;135:982-989.
- ⁴ Als-Nielsen B, Chen W, Gluud LL, Gluud C. The methodological quality of randomised clinical trials. Submitted.
- ⁵ Det nationale strategiudvalg for sundhedsvidenskab (NASTRA) (The National Strategy Committee for Health Research). (Juhl E, et al. Sekretariat: Gluud C, Rasmussen B, Holstein M von). Forslag til en national strategi for sundhedsvidenskab (Proposal for a national strategy for health science). Forskningsministeriet, Betænkning nr. 1284, Statens Information. Copenhagen 1995, 1-196.
- ⁶ Kampmann JP, Andreasen PB, Gram LF. Clinical Pharmacology in Denmark – Past, Present, and Future. Danish Society for Clinical Pharmacology (Klinisk Farmakologi i Danmark – Fortid, Nutid og Fremtid. Dansk selskab for Klinisk Farmakologi). 2002. 1-78.
- ⁷ *Ugeskr Lager* 2003;165(16).
- ⁸ The EU Directive.
- ⁹ Gluud C. The GCP directive - consequences for clinical drug research. *Ugeskr Laeger*. 2003;165(16):1662-4.
- ¹⁰ Gluud C, Nikolova D. Which countries conduct the 427,000 publications on controlled clinical trials found in the CENTRAL register? Manuscript in preparation.
- ¹¹ <http://www.jameslindlibrary.org/>
- ¹² *Forskningsstatistik 2000. Forskning og udviklingsarbejde i sundhedssektoren*. København: Analyseinstitut for Forskning, 2002:1:101.
- ¹³ Helsinki II Declaration. <http://www.mcg.edu/research/octc/hac/decofhelsinki.pdf>
- ¹⁴ ICH GCP. http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254.
- ¹⁵ Lov nr. 402 af 28/05/2003 Lov om et videnskabsetisk komitéssystem og behandling af biomedicinske forskningsprojekter med senere ændringer til forskriften.
- ¹⁶ Lov nr. 440 af 09/06/2004 Lov om det etiske råd.
- ¹⁷ Bekendtgørelse nr. 806 af 12/07/2004 Bekendtgørelse om information og samtykke ved inddragelse af forsøgspersoner i biomedicinske forsøg'.
- ¹⁸ Vejledning 15. november 2004 Vejledning om anmeldelse m.v. af et biomedicinsk forskningsprojekt til det videnskabsetiske komitéssystem'. Den Centrale Videnskabsetiske Komité.
- ¹⁹ LovBekendtgørelse nr. 656 af 28/07/1995 med ændringer ved LOV nr. 382 af 28/05/2003 Bekendtgørelse af lov om lægemidler (Kliniske forsøg med lægemidler, bivirkningsindberetning, inspektioner i forbindelse med lægemiddelovervågning m.v.).
- ²⁰ Bekendtgørelse nr. 295 af 26/04/2004 Bekendtgørelse om kliniske forsøg med lægemidler på mennesker.
- ²¹ Danish guideline on notification of clinical trials of medicinal products in humans, Danish Medicines Agency JAN 2004.
- ²² ICH E6: Good Clinical Practice: Consolidated guideline CPMP/ICH/135/95 (2002).
- ²³ Bekendtgørelse nr. 642 af 28/06/2001 Lov om miljø og genteknologi.
- ²⁴ LOV nr. 429 af 31/05/2000 Lov om behandling af personoplysninger.

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- ²⁵ VEJ nr. 125 af 10/07/2000 Vejledning om anmeldelse i henhold til kapitel 12 i lov om behandling af personoplysninger.
- ²⁶ VEJ nr. 126 af 10/07/2000 Vejledning om registreredes rettigheder efter reglerne i henhold til kapitel 8-10 i lov om behandling af personoplysninger.
- ²⁷ CIS nr. 11836 af 19/03/2001 Cirkulæreskrivelse om anmeldelse til Datatilsynet.
- ²⁶ LOV nr.1220 af 20/12/1995 Lov om erstatning for lægemiddelskader.
- ²⁷ LOV nr.1228 af 27/12/1996 §5 Lovbekendtgørelse af lov om offentlig sygesikring.
- ²⁸ Lovbekendtgørelse nr. 509 af 01/07/1998.
- ²⁹ LOV nr.493 af 07/06/2001 §3 Lov om ændring af lov om lægemidler, lov om apoteksvirksomhed og lov om erstatning for lægemiddelskader.
- ³⁰ LOV nr.430 af 10/06/2003 §2 Lov om ændring af lov om patientforsikring og lov om erstatning for lægemiddelskader og om ophævelse af lov om erstatning for vaccinationsskader.
- ³¹ LBK nr.228 af 24/03/1997 Bekendtgørelse af lov om patientforsikring (Patientforsikringsloven))
- ³² LOV nr.395 af 02/06/1999 §2 Lov om ændring af lov om sygehusvæsenet og lov om patientforsikring.
- ³³ LOV nr.430 af 10/06/2003 Lov om ændring af lov om patientforsikring og lov om erstatning for lægemiddelskader og om ophævelse af lov om erstatning for vaccinationsskader.
- ³⁴ BEK nr. 1097 af 12/12/2003 Bekendtgørelse om dækningsområdet for lov om patientforsikring
- ³⁵ CT 3: Retningslinier for indberetning af bivirkninger opstået ved kliniske forsøg (Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use' as required by Article 18 of Directive 2001/20/EC revision 1.
- ³⁶ BEK nr. 589 af 26/06/2003 Bekendtgørelse om indberetning af bivirkninger ved lægemidler m.m.
- ³⁷ CT 4: Retningslinier for SUSAR-databasen. (Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)' as required by Article 11, Article 17, and Article 18 of Directive 2001/20/EC revision 1.)
- ³⁸ Europa-Parlamentets og Rådets Direktiv 2001/20/EF af 4. April 2001 om indbyrdes tilnærmelse af medlemstaternes love og administrative bestemmelser om anvendelse af god klinisk praksis ved gennemførelse af kliniske forsøg med lægemidler til human brug.
- ³⁹ Note for guidance on statistical principles for clinical trials CPMP/ICH/363/96 (ICH Topic E 9 Statistical Principles for Clinical Trials).
- ⁴⁰ Drazen JM, Frizelle FA, Haug C, Hoey J, Horton H, Kotzin S, Laine C, Marusic A, Overbeke AJPM, Schroeder TV, Sox HC, Van der Weyden MB: Clinical trial registration: a statement from the international committee of medical journal editors. NEJM 2004; 351: 1250-1251
- ⁴¹ World Health Organization: The Mexico statement on health research. Knowledge for better health: strengthening health systems. From the ministerial summit on health research. Mexico City, November 16-20, 2004 (<http://www.who.int/rpc/summit/en/index8.html>).
