Cooperation Agreement between

the Danish Medical Association and the Danish Association of the Pharmaceutical Industry

on clinical drug trials

Statement of object

This Agreement concerns all cooperation between physicians and the pharmaceutical industry (in the Cooperation Agreement referred to as the parties) on the conduct of clinical drug trials. The object of the Agreement is – based on existing rules and regulations – to provide joint approved guidelines for the cooperation between physicians and the pharmaceutical industry on the conduct of clinical drug trials.

The overall objective of clinical drug trials is to ensure the continued development of drugs at a high professional and scientific level for better patient care.

Cooperation on clinical drug trials should be conducted in such a way that there is no doubt about the independence of the parties and that all possibility of scientific and financial pressure or dependency is excluded.

It is the responsibility of both parties that clinical drug trials are conducted in accordance with international ethical conventions, national legislation, including the Danish Medicines Act, the Danish Act on a system of scientific ethics committees and treatment of biomedical research projects with related executive orders, the Declaration of Helsinki and rules on Good Clinical Practice, and that the collegiate and ethical rules of the Danish Medical Association (DADL) are observed.

Definitions

Clinical drug trial:
Any trial on humans that aims to establish or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational drugs and/or to identify adverse reactions to one or more investigational drugs and/or to examine the absorption, distribution, metabolism and excretion of one or more investigational drugs with a view to assessing their safety and/or efficacy.

The definition does not distinguish between the development phases of the clinical trials. Clinical drug trials are a natural part of the daily clinical work in the primary care and hospital sectors in connection with the ongoing evaluation of diagnostics, treatment and care.

Sponsor:
A natural or legal entity (firm, institution or organisation) undertaking to initiate, manage and/or finance a clinical drug trial.

Investigator:
A person who has a profession that is recognised for research purposes, e.g. via employment as a researcher or PhD student, or who is otherwise occupied with concrete research work, and who is responsible for the practical conduct of the trial at a specific trial site.

Trial protocol:
A document describing the objective, design, methodology, organisation, statistical considerations, scientific ethics, financial conditions, publication conditions and information to participants.

Scientific dishonesty
Scientific dishonesty means intentional or grossly negligent conduct in the form of falsification, plagiarism, non-disclosure, etc. implying undue misrepresentation of the researcher's own scientific activities and/or scientific interest.

The definitions used are in accordance with the definitions stated in the Danish Act on a system of scientific ethics committees and treatment of biomedical research projects and the Executive Order on the Danish Committees on Scientific Dishonesty (UVVU), respectively.

Guidelines for contracts on clinical drug trials
Contracts on clinical drug trials between the parties must be in writing regardless of who is the initiator. The parties to the contract must agree on the protocol.

Only persons sufficiently qualified by education, training and experience can assume responsibility for a clinical drug trial at the institution where the trial is conducted. It lies with the sponsor to ensure this.

The liability and insurance-related aspects must appear clearly from the contract concerning the clinical drug trial in question. Subjects participating in drug trials are covered by the public insurance schemes enshrined in the Danish Patient Insurance Act and the Danish Act on Damages for Pharmaceutical Injuries.

Clinical drug trials typically include testing and development of patented or patentable products. The right to exclusive use of this knowledge is regulated by the legislation on medicinal products and legislation on intellectual property rights (IPR) in general. In addition, each contract must determine who has a right to use the knowledge obtained. As a general rule, the party who finances the trial has this right.

If a physician who participates in a clinical drug trial and co-signs the contract concerning the trial changes his place of work, e.g. hospital or work area, the contract must be renegotiated with a newly appointed investigator who is responsible for the trial at the institution where the trial is conducted.

Contracts that have been entered into and any breaches of contract are subject to Danish contract law.

Authorisation
Prior to the commencement of a clinical drug trial, an authorisation must be obtained from the Danish National Committee for Research Ethics and the Danish Medicines Agency. Furthermore,

the trial must be notified to or be comprised by a general authorisation from the Danish Data Protection Agency and possibly other authorities depending on the nature of the trial.

If it includes general practice, the protocol for clinical drug trials must be submitted to the multi-practice investigation committee for assessment prior to the implementation of the drug trial. The opinion of the committee must then be submitted to each participating physician and the sponsor as it is the individual physician's responsibility to assess his participation in the trial.

Information to participants
The trial protocol must contain a section on "patient information". In addition to relevant clinical information, it must provide all relevant information concerning the budget of the drug trial, including information about the financial relations to the pharmaceutical company of the physicians involved.

Publication of results
The knowledge obtained through a clinical drug trial is public property.

In order to respect the public ownership of the knowledge generated through the clinical drug trial, its results must also be published in the public domain.

Therefore, the contract must describe how the results obtained are to be published by the parties within an agreed time frame and in the agreed publication media, i.e. public databases, scientific journals, conference abstracts, lecture posters, the Internet, press releases, etc. The data analyses on which the publication is based must be in accordance with the trial protocol, which must describe the statistical method used. The publication must respect good scientific practice, the protocol provisions on publication and the Danish Act on the processing of personal data.

The right of both parties to publish the results is acknowledged. Both negative and positive trial results must be published as soon as possible and when professionally justifiable.

On publication of trial results, the ICMJE guidelines on the publication of articles in scientific journals dated 15 September 2004 and the guidelines of 6 January 2005 of the international organisations of the pharmaceutical industry, EFPIA, IFPMA, JPMA and PhRMA, must be observed.

The scientific ethics committee system has the authority to supervise that both positive and negative research results are published.

Both parties are entitled to supervise their own data with each other. If publication may affect a patent application, the parties must agree on a publication strategy.

On publication in a journal, the pharmaceutical company must be given the opportunity to comment on manuscripts within an agreed time frame, always provided that this does not significantly influence the final wording of the manuscript.

If a drug trial is conducted as a multicenter study, special publication rules may apply. The rules must be specified in the protocol.

A physician who has participated in a clinical drug trial must ensure that his participation in the

publication does not take on an aspect of advertising, cf. section 20 of the Danish Medical Association's ethical rules.

Finance

Contracts concerning clinical drug trials with a pharmaceutical company acting as sponsor must stipulate the services, fees and other expenditure to be paid by the sponsor. The fees may be calculated on the basis of the estimated number of hours. A budget for the drug trial must be annexed to the contract. The contract and the budget must be available prior to the commencement of the trial.

If the drug trial has direct or indirect financial consequences for the public hospital services or the national health service, e.g. through the use of premises, infrastructure or manpower, it is the investigating physician's duty to check that an agreement has been entered into with the relevant administrative authorities.

In connection with clinical drug trials initiated by physicians, a budget must be available in addition to the contract, stating the parties to defray the various costs. In addition, a position must be taken on the costs in connection with the examination or treatment of patients covered by the sponsor or public funds.

It lies with the investigating physician to see that the contract budget is available to the physicians participating in the trial and that the physician's employer has been duly informed.

Payments received for the clinical drug trial must be deposited on a research account administered by the investigating physician or the institution (hospital or department) where the trial is conducted. Payments made must be registered and reported according to current legislation. Payments to general practitioners may be made using their tax registration numbers.

The Danish National Committee for Research Ethics determines the scope of the financial information to be submitted, including:

- financial support received by the investigator from private enterprises, foundations, etc. for the conduct of the pharmaceutical research project concerned;
- financial support for the remuneration of researchers, ancillary staff, payment for laboratory tests or other analyses;
- whether individual researchers have such personal interests in the drug trial as to cause doubts regarding the effect this may have on the result of the drug trial;
- the amount of any payments to subjects.

Financing of other expenditure

The pharmaceutical company may sponsor participation in conferences where the result of the clinical drug trials is to be presented. The pharmaceutical company may also defray expenditure for conferences, courses, etc. when this is important for the updating and maintenance of the physician's professional knowledge that is to ensure a high professional level of preparation and conduct of a specific clinical drug trial.

Scientific dishonesty

If one of the parties suspects scientific dishonesty, this must be reported to the Danish Committees concerning Scientific Dishonesty (UVVU). Suspicions of fraud may lead to informations and/or claims for damages.

In relation to the individual contract entered into by the physician and the company concerning the clinical drug trial, entry of the following sentence is therefore recommended:
"By signing this contract, the parties accept that any suspicion of scientific dishonesty in connection with the clinical trial may be brought before UVVU."
If UVVU finds that the suspicion is reasoned it should be assessed whether for a specified period of time the person(s) in question should be banned from participating in clinical drug trials. The parties to the Agreement will raise this issue with the appropriate public authorities to undertake this task.

Breach of agreement
Breaches of or disputes in connection with the present Agreement shall be brought before and settled by a court of appeal consisting of two representatives appointed by DADL, two representatives appointed by LIF and the chairman of the Danish Board of Drug Advertising (NMI).

DADL is responsible for ensuring that the present Agreement is observed by physicians and medical organisations. In the event of a breach of the Agreement, the physician in question shall be brought before the Medical Ethics Board of the Danish Medical Association for consideration in accordance with the ethical rules of the Danish Medical Association.

Coming into force and termination
The Agreement shall come into force at the time of signing and shall be terminable by the parties at six months' notice. The Agreement shall be evaluated on an ongoing basis and revised not later than two years from the time of signing.

Copenhagen, 8 February 2006

The Danish Medical Association (DADL)

The Danish Association of the Pharmaceutical Industry (LIF)