Translation by LIF from the Swedish original agreement, for the use by our member companies. The translation is provided in good faith as a language help for non-Swedish speakers, but is not a part of the agreement signed with SKL. Only the Swedish version can form basis for solving disputes.

National strategy for conducting clinical trials and non-interventional studies in Sweden

Sveriges Kommuner och Landsting (SKL - Swedish Association of Local Authorities and Regions) and *Läkemedelsindustriföreningen* (LIF- The Swedish Association of the Pharmaceutical Industry)

Common objective

In Sweden there has for a long time been an extensive and constructive cooperation between the health care sector, universities, colleges and the pharmaceutical industry in the development of new medicines, and as follow-up after market introduction. This cooperation is crucial for development of new medicines and thereby of significance for the patients through improved health and increased quality of life – and as a further consequence also for Sweden's growth and economy.

The County Councils has, apart from the responsibility to give good healthcare to the entire population, also responsibilities for research and development within the healthcare system. The universities and the colleges contribute through their education and research with necessary knowledge in order to develop new medicines, as well as follow-up of existed therapies to ensure that they are used in a correct way. The pharmaceutical industry is responsible for research and development of new medicines, and follow-up of medicines on the market.

Many investigators that conduct trials has double employment with responsibilities both within county councils and within a medical faculty, which makes it crucial that common fundamental principles are applied in the conduct of clinical trials/studies.

In order for a pharmaceutical to be approved it must be tested in clinical trials. Even after an approval the authorities demand that the pharmaceutical is monitored in clinical practice, which can be done through clinical trials but also through so-called non-interventional studies, i. e. studies that are not clinical trials according to the Medical Products Agency's definition. These studies show how the medicine is used in clinical practice. Clinical trials as well as non-interventional studies (NIS) (can be made only within the framework of the healthcare system, why a positive attitude to these activities from the county council’s side is a precondition for the innovation of pharmaceuticals. Participation in clinical trials/non-interventional studies also contributes to increased knowledge and competence for the staff that is involved in the trial/study.

The contracting parties agree to jointly work for that Sweden will stay as an attractive country to conduct clinical trials/ non-interventional studies in by way of ensuring that;

• The clinical trials/studies will be conducted with high quality.

• The clinical trials/studies will be conducted within established time-frames.

• The clinical trials/studies will be conducted with a high ethical standard.

• The clinical trials/studies will be conducted cost-effectively.

• The contracting parties will, before each individual clinical trial/study, agree about which conditions will apply, which clarifies the parties' responsibilities.

• The parties will jointly carry out a continuous development work in aim to increase the quality and the effectiveness in the trials/studies.

• The clinical trials shall be conducted in a way as to ensure the integrity, autonomy and safety of the research subject/patient.

Main agreement

Between *Sveriges Kommuner och Landsting* (SKL) and *Läkemedelsindustriföreningen* (LIF) concerning clinical trials and non-interventional studies.

Definitions:

Klinisk prövning (Clinical trial) = clinical trial that requires approval from the Medical Products Agency and *etikprövningsnämnd* (Committees with the remit to conduct vetting of the ethics of research involving humans = Ethics committee).

Icke-interventionsstudie IIS (non-interventional study = NIS) = "A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients, and epidemiological methods shall be used for the analysis of collected data."(LVFS 2003:6)

The words *stöd, ersättning* (remuneration, grant) and similar covers compensation for costs and others economic contributions as well as remunerations and grants of other kinds.

This main agreement is within the rules in the LIF-SKL agreement *"Överenskommelser om samverkansformer med hälso- och sjukvården m fl"* (Agreements on forms of collaboration with healthcare etc.).

This agreement concerns two different shapes of trials, defined by initiator:

A: Clinical trials/non-interventional studies that has been initiated by a pharmaceutical company and where the company is sponsor.

B: Clinical trials/non-interventional studies that are initiated and in its totality are conducted by the county council with remuneration from pharmaceutical companies (investigator-initiated trial/study)

The aim of this agreement is:

- to state the conditions for the parties' cooperation around clinical trials/non-interventional studies,
- to constitute the starting point for agreements between companies and concerned county councils.

A. Conditions for clinical trials/non-interventional studies that has been initiated by a pharmaceutical company

The contracting parties are in agreement about the following conditions for clinical trials/ non-interventional studies:

1. For every clinical trial/non-interventional study a separate agreement (below "the agreement") shall be formed between the company and the county council. The investigator shall support and sign the agreement. No economic agreements can be concluded solely between the company and employees within the public healthcare. In those cases where universities participate in the trial/study, sub-agreements shall be established between the university, the county council and the company.

2. The economic compensation will be used to cover the county council's additional costs for the conduction of the trial/study and may only be used in accordance with the agreement "*Överenskommelser om samverkansformer med hälso- och sjukvården m fl*" about collaboration between pharmaceutical companies and employees in the health care sector, concluded between SKL and LIF, as well as in accordance with the at any given time relevant LIF ethical rules.

3. Participation in the trial/study is conditional on the investigator/study nurse participating in national/international investigator meetings, education in clinical research i.e. GCP, reporting of side effects and e-CRF and in other for the trial/study adequate further education whereupon the cost for travels, allowances and possible lost working time is covered in the agreement. When meetings are co-located in connection with medical scientific congresses, the company can pay for the congress charge.

4. The company and county council will agree about who will be the responsible investigator, and his/hers approval is needed.

5. Both parties will regularly ensure that the trial/study is conducted according to the agreement.

6. It is the responsibility of the county council that adequate resources needed for the trial/study is available during that time the trial/the study is taking place. This will also be confirmed in the application to the Ethics Committee.

7. When the trial/study is aborted or in other respect undergoes big changes this shall be reported without delay to the other contracting parties. When the trial/the study is completed the company shall report this to the county council. In the agreements for the individual trial/study it should be stated what will apply if the trial/study is aborted in any other way than according to the protocol, or if it undergoes a major modification. When the trial/study has ended, a final reconciliation against the agreements shall be made.

8. The company is responsible for that a by the *Läkemedelsförsäkringsföreningen* provided insurance coverage, or a corresponding such insurance coverage, applies for the trial/the study. It is the responsibility of the county council that *patientskadelagen* is followed. The insurance coverage will also cover placebo studies and trials/studies on healthy volunteers.

9. Possible questions about intellectual properties (IP) rights will be regulated in the agreement.

10. For reasons of secrecy and personal integrity the county council deals with possible payment of economic compensation to participating research persons relating to costs in connection with the trial/study, i.e. lost working time and/or travel costs.

11. According to the Helsinki declaration, which are ethical principles decided by the World Medical Association, considerations will be taken to patients' treatment after the trial's/study's end. What will apply after the trial's/study's end shall be covered in the agreement.

12. The company is obliged to report both ongoing clinical trials and results of completed clinical trials to a database that are publicly available, for example via http://clinicaltrials.ifpma.org/ . The company is urged to similarly report non-interventional studies.

13. The result of the trial/the study will be notified to participating clinics no later than 12 months after the completion of the trial/study.

Clinical trials

Clinical trials may be started on the conditions that:

1. Approval has been given by an Ethics Committee as well as by the Medical Products Agency.

2. Agreements concerning tissue samples have in relevant cases been signed with the county council/authorized representative of the bio bank.

3. Permission is in relevant cases been given by the local *Strålskyddskommitté* as well as the *Datainspektionen*.

4. Agreements that stipulate the trial's conduct and compensation are concluded between the company and the county council for the hospital/clinic where the trial is intended to be conducted. Possible annexes to the agreements should be signed.

5. The trial is conducted in accordance with current legislation as well as with by an Ethics Committee and the Medical Products Agency approved study protocols.

6. The county council is responsible for that the *Läkemedelskommitté* within the county be notified about the trial.

Clinical trials and secrecy

Information in connection with clinical trials is covered by secrecy according to i.a. the Secrecy Act (*sekretesslagen*). A contracting party has the possibility to waive the secrecy in its entirety or partially. The parties agree that the concerned clinic/laboratory will be considered to have gotten the concession to the effect that the pharmaceutical company cannot refer to secrecy as an obstacle for the clinic/laboratory to submit necessary information to the county council for decisions regarding resource allocation for the trial or for follow-up and control of the trial's conduction.

Non-interventional study

A non-interventional study (NIS) may be started on the conditions that:

1. Agreements that regulate conduction and possible compensation are signed between the company and the county council. Agreement with the county council is also required when a private caregiver conducts a study where the county council covers the costs for the prescription.

2. Application is submitted with the Ethics Committee for assessment. The study shall not be conducted if the *Ethics Committee* in its reply opposes this.

3. The NIS is to be conducted so that the parties maintain full confidence and an independent standing in relation to one another. The study should not result in undertakings or expectations concerning prescribing or use of the pharmaceutical company's products conducted

LIF has binding rules for their members for conducting of non-interventional studies (see www.lif.se).

B: Conditions for clinical trials/non-interventional studies that are initiated and in its totality are conducted by the county council with remuneration from pharmaceutical companies (investigator- initiated trial/study)

1. The company and the county council shall be the contracting parties. The investigator shall support and sign the agreement. No agreements can be made solely between the company and employees within the healthcare sector.

2. The county council is responsible for the conduction of the trial/study and that current legislation is applied.

3. The county council has an obligation to report both ongoing clinical trials and results of completed clinical trials to a publicly available database, for example through http://clinicaltrials.ifpma.org . The county council is urged to correspondingly report non-interventional studies.

Consultation body

Through this main agreement a special consultation body is formed for clinical trials/non-interventional studies, named "*SKLs och LIFs samrådsgrupp, klinisk läkemedelsprövning/icke-interventionsstudie*". The parties each appoint two representatives to the group.

The work in the consultation body aims primarily to give the parties the possibility to continuously follow up this agreement, and to when necessary prepare proposals for revisions of the agreement.

Information

It is incumbent on the contracting parties to submit information about this agreement to concerned members, and recommend and actively work for concerned members to apply the same.

Other

Läkemedelsindustriföreningens Service AB, a by LIF wholly owned service company, does work for the pharmaceutical industry in Sweden on for the pharmaceutical industry common interest, i.a. through promoting the development of and the compliance with ethical principles within the pharmaceutical sector. SKL has been informed that LIF will commission to the service company to implement LIFs obligations according to this agreement.

Period of validity

This main agreement applies from March 1, 2009 up to and including February 28, 2011. If the agreement is not canceled in writing by one party at least six months before the end of the period of validity, the agreement is extended for two years and the same six months' period of notice will apply for the next period.

Signing

The agreement is established in two copies, of which the contracting parties received one each.

Stockholm, December 12, 2008

Sveriges Kommuner och Landsting

Läkemedelsindustriföreningen, LIF