

# LIF policy

*LIF's rules for non-interventional studies*

*2007:1*





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### **About LIF**

The Swedish Association of the Pharmaceutical Industry (LIF) is the trade association for the research based pharmaceutical industry in Sweden. LIF has about 70 member companies which represent approximately 92 percent of the total sales of pharmaceuticals in Sweden.

## Introduction

LIF's rules for non-interventional studies set out the criteria for pharmaceutical companies' participation in the performance of non-interventional studies. The rules promote transparency and are binding for all LIF member companies.

LIF's rules for non-interventional studies are covered by the rules in the "Agreement on forms of cooperation between pharmaceutical companies and medical professionals in the public healthcare sector" concluded between the Association of Local Authorities and Regions and the Swedish Association of the Pharmaceutical Industry (LIF). These rules apply not only to staff in the public healthcare sector but also to private healthcare sub-contractors and staff at Karolinska Institutet. The agreement on forms of collaboration also contains special rules for market studies not dealt with in this policy.


Non-interventional studies mean all studies and projects which are not clinical trials according to the Swedish Medical Products Agency. The concept of non-interventional studies thus includes quality projects, follow-up studies, prescription studies etc. The Swedish Association of the Pharmaceutical Industry [LIF] rules given below also apply to participation in or support for the establishment or operation of various registers (e.g. quality registers). For those studies and projects covered by rules on non-interventional studies, agreements must be signed by all relevant responsible authorities, if staff in the public health service are participating, or where it concerns private healthcare if the study or project may entail costs to the responsible authority (i.e. in the form of prescribing drugs).

**All studies which are not clinical trials according to the Medical Products Agency's definition are covered by these rules and classified as non-interventional studies.**

## Background

Studies are currently performed in the healthcare sector which are not clinical trials but which may be supported by pharmaceutical companies in some way. This might involve the mapping of therapeutic practice or costs, quality assurance of whether given guidelines are being followed, or a follow-up of how a drug is being used or the health economics impact of a given drug therapy. The need for information provided by such studies is considerable and is growing at both regional and national level. The Medical Products Agency may require pharmaceutical companies to follow up drug use, and the formula committees may have wishes concerning the mapping of experience of drugs in an everyday clinical context. The Pharmaceutical Benefits Board requires, for example, that Pharmaceutical companies are able to document cost-effectiveness in a Swedish therapeutic context. It is therefore necessary for pharmaceutical companies to perform studies of certain drugs in collaboration with the healthcare sector. The number of such studies has also grown in recent years.

What these studies are called and what form they take vary widely, but what they have in common is that they are not clinical drug trials and are therefore not regulated by drug



legislation. Examples of names used for these studies include observation studies, mapping studies, epidemiological studies, quality assurance projects and follow-up studies.

In this document we have chosen to refer to these studies as non-interventional studies, which means that “no additional diagnostic or monitoring procedures shall be applied to the patients, and epidemiological methods shall be used for the analysis of collected data” (Medical Products Agency guidelines LVFS 2003:6). The term “non-interventional” is hard to define, and the view of what is or is not a non-interventional study varies from body to body. However, clinical practice must always be adhered to in these studies, although this too can vary from clinic to clinic.

It is important that information from non-interventional studies is fed back to the health-care sector in order to raise the quality of drug use and ensure efficient utilisation of healthcare resources.

## **Difference between non-interventional studies and clinical trials**

The design of the study determines whether it is a clinical trial or a non-interventional study.


A clinical trial generally studies a select group of patients (patients chosen on the basis of various exclusion and inclusion criteria) in a controlled manner. Patients are normally randomised to one or more treatments. These studies are always prospective and often take quite a long time to perform.

A non-interventional study includes patients on the basis of one or more selection criteria, e.g. by diagnosis or treatment received. Data is then collected retrospectively or prospectively using forms, or obtained from existing databases or medical records. In a cross-sectional study, information is obtained about the situation at a particular point in time. No study-related intervention is made.

## **When are non-interventional studies performed?**

Which type of study should be chosen – clinical trial or non-interventional study – depends on its aim. Non-interventional studies are never a substitute for clinical trials, but may be a complement. We need the knowledge that is generated by both clinical trials and non-interventional studies. For example, epidemiological data cannot be studied in a clinical trial. Internationally Sweden has the advantage of being able to draw on national health data registers for epidemiological data. One example is the National Board of Health and Welfare’s Prescribed Drug Register, which collects drug data from pharmacies.

Besides providing greater knowledge about drug effects, non-interventional studies can also be a good way of further mapping risks in the real world. Post-marketing surveillance



(PMS) studies can in some cases be important in studying adverse effects after the introduction of a new pharmacological therapeutic principle.

Non-interventional studies allow information to be collected on the actual use of a particular drug. These studies can also provide epidemiological information about a particular disease, or even identify an unfulfilled medical need.

## LIF's rules

### Criteria for non-interventional studies:

1. **The study must be performed in the course of standard healthcare provision.**
  - The prescription of any drugs being studied must be clearly separated from the decision to include the patient in the study.
  - The drug must be prescribed in the normal manner and in accordance with the terms of the marketing authorisation. The contribution of the medical representative may only be administrative in character and under the supervision of the medical department, which should also ensure that the representative has the relevant training. The representative's contribution may not be associated with the prescribing of drugs.
  - The study 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.
  - Financial compensation for extra resources for implementation of non-interventional studies should only be paid in cases where the workload within the framework of the study obviously exceeds the staff's ordinary daily operational responsibility/work duties.
2. **Responsible health authority.**

An agreement must be concluded between the healthcare provider, the responsible investigator and the pharmaceutical company. This also applies to studies which the investigator carries out in his/her "spare time", i.e. outside paid working hours for the healthcare provider or private healthcare subcontractor. Where financial remuneration is payable, this must be reasonable in relation to the amount of work involved and specified in the agreement.
3. **Regional ethics Board.** The study must not be performed if the regional ethical review board is opposed to this.
4. **Study plan/protocol.** There must be a study plan/protocol which approved and monitored by the pharmaceutical company's medical department and which contains:
  - a. **Background.** Motivation for performing the study.
  - b. **Aim.** Description of what is to be studied (the scientific purpose).
  - c. **Motivation for number of patients.** Total number of patients and number of patients per investigator.
  - d. **Data collection.** How data is to be collected, patient information, questionnaires, etc.

- e. **Data processing and collation.** Who is responsible for data processing, how it will happen, and when.
- f. **Adverse event reporting.** Reporting to the Medical Products Agency/company.
- g. **Study reporting.** A summary of the report/publication should be analysed and, within a reasonable time, communicated to the pharmaceutical company's medical department. The medical department should keep a list of such reports which should be kept for a reasonable time. The report/publication is to be completed within 12 months of the end of the study and distributed to the participating clinics and, where necessary, the authority concerned. If the study indicates a result which is important from a risk or utility point of view, the summary of the report/publication should immediately be sent to the relevant authority. As with corresponding provisions in clinical trials, pharmaceutical companies should publish such information as is stated in the summary of the report/publication

**Both the study plan/protocol and study report should be made available on demand to the Pharmaceutical Industry's Information Examiner [IGM] and the Information Practices Committee [NBL] as well as LIF's Compliance Officer.**

5. **The Swedish Data Protection Act (PUL).** Patients must receive, where applicable, written information (including relevant provisions of the Personal Data Act) and give their written consent to take part in the study unless the Regional Ethical Review Board has permitted otherwise. In some cases the Regional Ethical Review Board may agree that consent need not be obtained from patients with reference to section 19 of the Personal Data Act.
6. **Ownership of data.** The agreement between the parties must cover issues such as who owns the database and who holds the publication rights.
7. **The company's internal process.** The company must have guidelines which describe the internal process for the performance of non-interventional studies. The company's medical department must approve these studies.
8. **Quality assurance.** ICH Good Clinical Practice must be applied where applicable, and standard scientific methodology must be used. Monitoring (verification of source data) or auditing need not normally be performed, but there must be a process for quality assurance.
9. **The Swedish Medical Products Agency.** An application need not normally be submitted to the Medical Products Agency. In case of uncertainty, the Medical Products Agency must be contacted.

# Financial support for the National Quality Register within the health service

## Background

The National Quality Register holds data collected by healthcare personnel from various clinics around Sweden. The register contains individual data on problems or diagnoses, treatment interventions and outcomes. The fact that the register is National means that data may be compiled for all patients and analysed on a patient, operational and national level.

County councils have overall register responsibility, but healthcare personnel within the county council manage the register. Those managing the register have principal responsibility for its development and content and guarantee that participating units follow the provisions of the Swedish Data Act/Data Protection Act on consultation and patient information etc.

The Swedish National Board of Health and Welfare and Swedish Association of Local Authorities and Regions (SALAR) are collaborating to support development and use of the National Quality Register and, during 2007, 55 registers received financial support from them. There is a quality review system for registers which require annual reports, including annual statements describing how the register's activity has contributed to local quality development.

A majority of National Quality Registers are currently receiving financial support from pharmaceutical companies. One recommendation is that the supporting pharmaceutical company from the register in question should have access to depersonalise and compiled registered data on that companies and products.

## Conditions for financial support to a National Quality Register:

1. There should be a written partnership agreement between the parties (authority, register manager and company) stating the parties' rights and liabilities as well as the duration of the partnership.
2. The contents of the partnership agreement should be open and clarified in all contexts where the register is presented. E.g. via websites, publications annual reports etc.

## References

### **Medical Products Agency**

*www.lakemedelsverket.se*

#### Clinical trial (LVFS 2003:6):

“Any investigation in human subjects intended to discover or verify the clinical, Pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State.”

#### Non-interventional trial (LVFS 2003:6):

“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.”

### **Pharmaceutical Benefits Board**

*www.lfn.se*

The board’s role is to decide whether a drug or other items covered by the pharmaceutical benefits scheme should be subsidised. The board’s decisions may be conditional upon companies performing non-interventional studies to document cost-effectiveness in a Swedish therapeutic context.

### **Personal Data Act (1998:204)**

*www.datainspektionen.se*

Personal data are defined as all information which can be traced directly or indirectly back to a living person. Sensitive personal data include information about a person’s health.

Section 19 reads: “Sensitive personal data may be processed for research purposes, provided the processing has been approved in accordance with the Act concerning the Ethical Review of Research Involving Humans (2003:460).”



## **Regional ethical review boards**

*www.forskningsetikprovning.se*

The concept of “research” is narrowly defined in the Ethical Review Act (2003:460), which means that the regional ethical review boards may reject applications which they consider to be more about quality assurance than research. The Ethical Review Commission’s report “The Ethical Review Act – proposed changes” (SOU 2005-78) recommends that the concept of “research” be extended, with the effect that non-interventional studies may also be included and so undergo ethical review. The report is currently being considered by the government.

## **National Board of Health and Welfare**

*www.socialstyrelsen.se*

The Centre for Epidemiology at the National Board Of Health And Welfare is responsible for the national health data registers, including the Prescribed Drug Register.

## **National Quality Register**

*www.kvalitetsregister.se*

All National Quality Registers include personally identifiable information on problems/diagnoses, treatments and outcomes. The Swedish Association of Local Authorities and Regions is collaborating with the Swedish Board of Health and Welfare at central level to support development and use of the register and sustain these financially.



**Läkemedelsindustriföreningen, LIF**  
*The Swedish Association of the Pharmaceutical Industry*