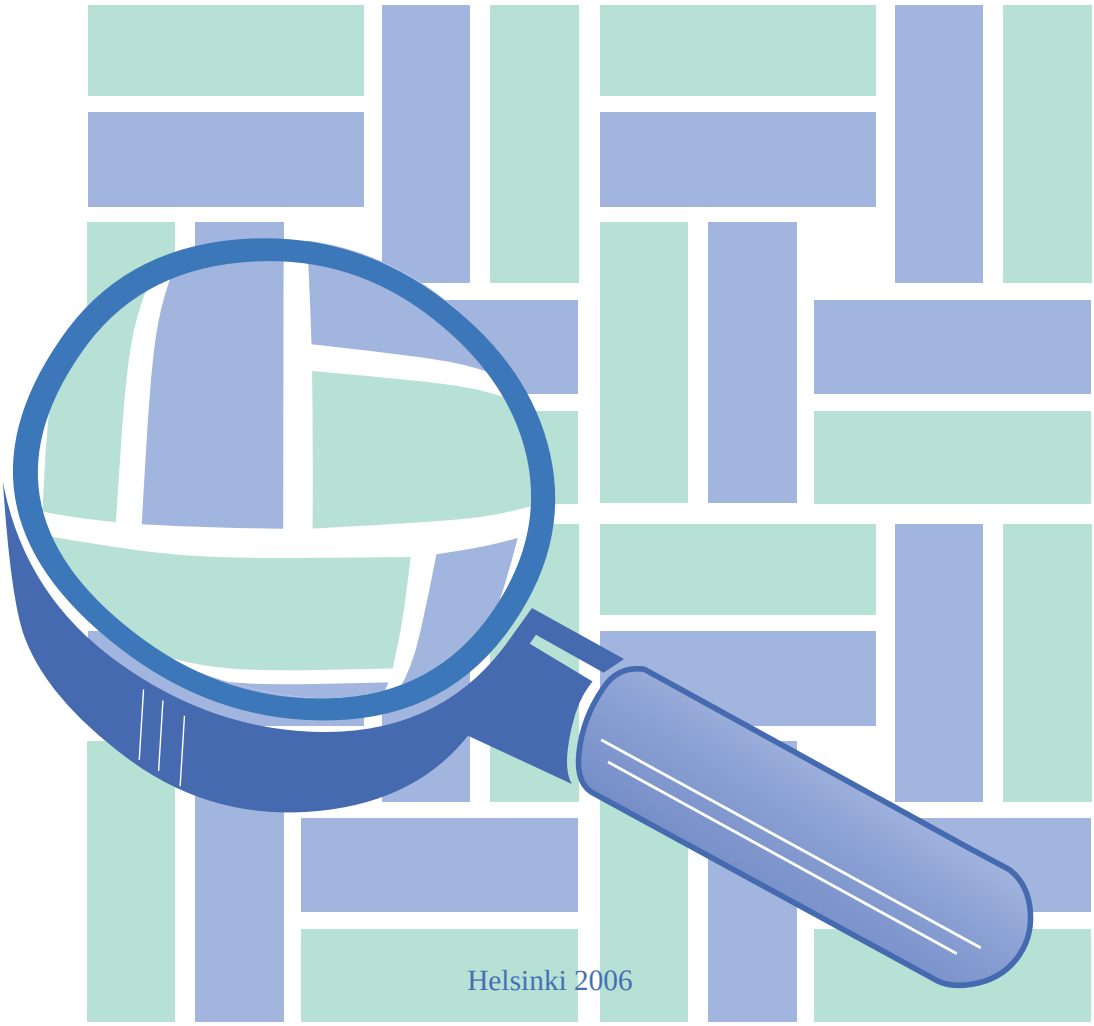
Kansanterveyslaitos
Folkhälsoinstitutet
National Public Health Institute

Kansanterveyslaitoksen julkaisuja B 4/2006
Publications of the National Public Health Institute

GOOD RESEARCH PRACTICE IN THE NATIONAL PUBLIC HEALTH INSTITUTE

Handbook



Helsinki 2006

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Editors:

Arpo Aromaa
Pentti Huovinen
Marja Leena Kantanen
Jaakko Penttinen
Matti Sarjakoski
Jari Suutari
Ritva Syrjänen
Raili Venäläinen
Jarmo Virtamo

GOOD RESEARCH PRACTICE IN THE NATIONAL PUBLIC HEALTH INSTITUTE

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Version 3.1
30.12.2005

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Kansanterveyslaitos (KTL)
Mannerheimintie 166
00300 Helsinki
Puh. vaihde (09) 47 441, telefaksi (09) 4744 8408

Folkhälsoinstitutet
Mannerheimvägen 166
00300 Helsingfors
Tel. växel (09) 47 441, telefax (09) 4744 8408

National Public Health Institute
Mannerheimintie 166
FI-00300 Helsinki, Finland
Telephone +358 9 47 441, telefax +358 9 4744 8408

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Jaakko Penttinen, Matti Sarjakoski, Jari Suutari, Ritva Syrjänen,
Raili Venäläinen ja Jarmo Virtamo

HYVÄ TUTKIMUSTAPA KANSANTERVEYSLAITOKSESSA
Käsikirja, Versio 3.1, 30.12.2004

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TIIVISTELMÄ

Käsikirja sisältää tutkimustyötä Kansanterveyslaitoksessa koskevat suositukset, ohjeet ja säädökset sekä kuvaa laitoksessa noudatettavat menettelytavat. Siihen on myös koottu tärkeimmät lääketieteellistä tutkimustoimintaa säätelevät kansainväliset säädökset ja hyvät käytännöt. Kirja opastaa tutkimussuunnitelman laatimisessa, eettisissä näkökohdissa, lupien ja suostumusten hankkimisessa sekä rahoitusasioissa. Kirjan mukaan toimittaessa voidaan ilmoittaa, että tutkimus on tehty noudattaen Kansanterveyslaitoksen hyvää tutkimustapaa.

Kirja alkaa luvulla ”Hyvä tutkimustapa tiiviisti” ja se päättyy eräiden tutkimustyyppien erityispiirteitä koskeviin katsauksiin. Ne ovat koe-eläimiä käyttävät tutkimukset, kliiniset näytetutkimukset (laboratoriotutkimukset), kliininen tutkimus, väestötasoinen tutkimus, terveyteen liittyvä käyttäytymis- ja yhteiskuntatieteellinen tutkimus sekä rekisteritutkimus.

Painetun kirjan rinnalla julkaistaan Internetissa versio, jossa on linkit ajankohtaisiin lakeihin, säädöksiin ja muihin viitteisiin. Internet-versio on virallinen ja toimituskunta pyrkii pitämään sen jatkuvasti ajan tasalla.

Asiasanat: tutkimustyö, tutkimustoiminta, säädökset, etiikka, tutkimusmenetelmät, rahoitus

Redaktionen: Arpo Aromaa, Pentti Huovinen, Marja Leena Kantanen,
Jaakko Penttinen, Matti Sarjakoski, Jari Suutari, Ritva Syrjänen, Raili Venäläinen
och Jarmo Virtamo

GOD FORSKNINGSPRAXIS I FOLKHÄLSOINSTITUTET
Handbok, version 3.1, 30.12.2004

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SAMMANDRAG

Denna handbok innehåller de rekommendationer, instruktioner och författningar som berör forskningsverksamheten vid Folkhälsoinstutet (KTL) samt beskrivningar om förfaringssätt och metoder inom KTL:s verksamhet. I publikationen har man sammanstället den internationella lagstiftningen och de överenskommelser om god forskningspraxis som reglerar medicinsk forskningverksamhet. Verket handleder vid anfattande av forskningsplanen och i etiska frågor, i förvärvandet av tillstånd och medgivanden samt i finansieringsfrågor.

Inledningen består av ett kapitel med titeln ”God forskningspraxis kortfattad” och i slutet finns översikter angående de särdrag som är karateristiska för vissa forskningstyper. Dessa kan vara t.ex. forskning som använder sig av försöksdjur, forskning av kliniska prover (laboratorieforskning), klinisk forskning, epidemiologisk och populationsbaserad forskning, hälsorelaterad forskning inom beteendevetenskap och samhällsvetenskap.

Samtidigt med boken publicerar KTL innehållet även som en Internet-version med länkar till lagar och författningar samt andra referenser. Den officiella versionen är således den som publiceras via Internet och redaktionsrådet strävar till att uppdatera innehållet kontinuerligt.

Ämnesord: forskningsarbete, forskningsverksamhet, författningar, etik, forskningsmetoder, finansiering

Editors: Arpo Aromaa, Pentti Huovinen, Marja Leena Kantanen,
Jaakko Penttinen, Matti Sarjakoski, Jari Suutari, Ritva Syrjänen, Raili Venäläinen
and Jarmo Virtamo

GOOD RESEARCH PRACTICE IN THE NATIONAL PUBLIC HEALTH INSTITUTE
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ABSTRACT

This book contains recommendations, guidelines and legislation concerning research carried out in the National Public Health Institute (KTL) and it also describes the practices to be followed. It comprises the most important international recommendations, Finnish laws and good practices to be followed in medical research. The book gives guidance on the preparation of a study plan, on ethical issues, on obtaining permits and informed consent as well as on funding issues. When a study has been performed according to this book, the researcher can state that the work has been carried out according to good research practice in KTL.

The book begins with a chapter "Good research practice summarized" and ends with reviews on the characteristics of several research types. These are animal experiments, clinical sample studies (laboratory studies), clinical research, epidemiological and other population based research, health-related behavioural and social research and register-based research.

In parallel with the printed book we publish an Internet version in Finnish, with links to current laws, decrees and other references. The Internet version is the official one and the Editorial Board makes every effort to keep it up-to-date.

Keywords: research, ethics, research - methods, funding, guidelines

PREFACE

The National Public Health Institute serves to protect and promote the health of the Finnish people. Its work is based on high-quality research and on utilising the best possible information available for promoting Finns' health and protecting them against diseases.

The importance of the National Public Health Institute's work is emphasised by the increasing value of health. Health-related issues extend to more and more areas of society. The Institute is valued as a provider and distributor of true and impartial information on health.

A high professional standard must be ensured in all work done at the Institute. The Institute's values and ethical principles must always be followed and common resources employed in an effective manner.

Due to limited resources, the Institute has to select the most promising and scientifically most interesting research topics. Research work and utilisation of the results require strong expertise as well as dialogue and co-operation within the Institute and often with national and international actors in the field.

Research carried out at the National Public Health Institute can only profit public health if Finnish society, research financiers and the academic community have trust in the high quality of the Institute's work and in its scrupulous compliance with ethical principles.

This manual describes the practices and principles that help to guarantee validity, ethics and efficient use of resources in all research conducted at the Institute.

The third Finnish version of this manual was taken into use on 1 January 2005 and the English version on 1 June 2006.

Helsinki, 31 May 2006

Director General

CONTENTS

GOOD RESEARCH PRACTICE SUMMARISED

Besides the general part A concerning all research, this handbook also contains part B describing the characteristics of several types of research. These research types are animal experiments, clinical sample studies (laboratory studies), population-based studies, health-related behavioural and social research as well as register-based research. This summary describes the main elements of the general part A.

Appendices and references are included at the end of the manual. The online versions include links to regulations and guidelines, for example.

The sections marked with ◆ in the summary are legislation and regulations that need to be strictly followed. In addition to these, the summary and the manual itself describe several recommended practices that are not mandatory.

STRATEGIC AIMS OF OUR WORK

- The National Public Health Institute promotes people's possibilities to lead a healthy life. Research is a means for achieving this aim, not a self-serving purpose.
- The Institute also provides decision-makers with the best available information to support their decisions.
- Research must be transformed into action and the population's good health.

◆ REGULATIONS AND GUIDELINES CONCERNING RESEARCH ACTIVITIES

- Some of the most important legislation that needs to be complied with includes the Medical Research Act, Personal Data Act, Act on the Medical Use of Human Organs and Tissues, Act on the National Public Health Institute, Statistics Act and the Act on the Statistical Affairs of the National Research and Development Centre for Welfare and Health.
- Several guidelines and recommendations must be taken into account. They include, among others, GCP, GLP, GEP and the National Agency for Medicines' guidelines on clinical medicine research as well as guidelines published by TUKIJA.
- Data Protection Ombudsman's opinions and decisions.
- Guidelines and regulations of various institutes and authorities.

◆ ETHICAL RESEARCH AND PROTECTION OF THE RESEARCH SUBJECTS

Evaluation of ethics

- The ethics of all KTL's medical and other research must be evaluated. Medical research must be evaluated by the ethics board of the hospital district in question. Other types of research must be evaluated by the Institute's advisory ethics board.

– The person in charge of the study shall transmit the opinions of the ethics boards to the Institute's advisory board.
– Any animal experiments must be approved by the animal experiment committee.
– The National Agency for Medicines must be notified before starting a clinical medicine study.

Protection of research subjects

– The World Medical Association's Declaration of Helsinki, the Council of Europe recommendations and legislation on medical research.
– The risks may not outweigh the benefits. If no clear benefits are foreseeable, the risks must be minimal.
– An informed consent (in writing) of the research subject is required.
– The informed consent document includes an information section and a consent section.
– Protection of privacy (data protection) must be taken care of. Any personbased registers must be protected against unauthorised use.

◆ VIOLATION OF GOOD SCIENTIFIC PRACTICE

– The National Advisory Board on Research Ethics (TENK) has prepared guidelines for good scientific practice. This practice may not be violated.
– Violations include indifference and fraud, such as gross negligence, fabrication, misrepresentation, plagiarism and misappropriation.
– Good practices must be followed also in financial matters.
– Any alleged violations must be handled without delay according to TENK's guidelines.

PLANNING AND CARRYING OUT RESEARCH

From an idea into a study

– Planning includes all phases, from an idea to a study plan including the most important aspects with regard to implementation, authorisations, and personnel resources and funding.

Study plan

– It is recommended that a brief preliminary study plan be drawn for every new research project.
◆ All research should be agreed upon with the head of the department in question, to whom the preliminary plan is presented.
◆ The head of department must accept the preliminary plan before any external funding is sought.
◆ Every study has a person in charge of the study.

- The final studyplan written by the person in charge of the study is a detailed plan including estimates for implementation, funding and resources according to what is specified in this manual. Financiers may also have additional requirements.
- The final study plan is submitted to the ethics board (or the Institute's advisory board).
– Authorisations may be required for carrying out the plan. Obtaining these authorisations may take quite some time.
- The head of department accepts the final research plan in writing.
- Departments file copies of the research plans accepted by the head of department.
- Any significant changes to a study plan shall be resubmitted to the ethics board.

SPECIFIC TYPES OF RESEARCH

– This manual deals with the characteristics of animal experiments, laboratory studies, clinical research, population-based research and register-based research.
- An authorisation is required for animal experiments.
- The use of gene technology is regulated by legislation and the detailed decisions of the Ministry of Social Affairs and Health.
- A risk assessment must be made for genetically modified organisms. The Board for Gene Technology must be notified before starting to use gene technology (for operations exceeding a certain risk limit).
- All personnel carrying out clinical research must have the appropriate education and the necessary professional skills. The person in charge of the study must be a medical doctor or a dentist.
– High-quality standards must be observed in laboratory work.
– Population-based research is usually large-scale. This means that in addition to the requirements for clinical studies, there are special requirements concerning methods, data systems, documentation and archiving.
– In register-based studies, the research material is collected from various data registers. The contents of the registers must be known in detail in order to make sure that the correct information is selected and that a proper study plan can be written.
- Carrying out register-based research requires authorisations from the register keepers and often also a large data processing capacity.

CARRYING OUT RESEARCH

General requirements

- The person in charge of a medical study must be a medical doctor or a dentist.
- Research must be carried out according to the study plan.
- The personnel must be trained and the validity and suitability of the equipment and methods must be shown.

Informed consent

- A written, voluntary informed consent is required for each research subject in medical research. No research activities may be carried out before obtaining the informed consent.
- The contents of the document for informed consent are regulated by the Medical Research Decree. Additional information can be found in this manual and in the research guidelines of the Hospital District of Helsinki and Uusimaa.
- Research material may only be used for the studies for which the subject has given consent.

Remuneration for expenses

– According to the Decree of the Ministry for Social Affairs and Health, appropriate remuneration may be paid to the research subject to cover travel expenses and loss of earnings as well as for other inconvenience, when appropriate.

Information to research subjects

– The research subject should be informed also of the results of the research.

Material management

– An information system, usually one that is computer-assisted, is required for all research.
– The information system should be planned at an early stage in co-operation with data management and statistics experts using, for example, solutions that have been employed earlier.
– The sample management unit of KTL helps in sample collection and permanent storage.

Documentation

- All studies, study plans, implementation, research material and files must be documented in detail using the KTL's research material system (in preparation).

Storage, analysis and reporting

- Original measurement results, research results and computer files shall be archived permanently.

Data protection and privacy

- Privacy refers to the protection of personal data against unauthorised use during the processing of such data. Personal data includes all information that can be used to identify a person or his or her family. It does not refer just to personal identification numbers. The use of personal data in registers should be reduced to a minimum.
- Privacy can be assured by clearly defining the user rights to materials and by only giving keys to authorised personnel, for example.
- Good data protection is the cornerstone of all research. It guarantees the usability and confidentiality of materials. Data protection includes, among other things, the placing of data on servers, regular back-ups and implementation of sufficiently strong authentication methods.
- KTL's research material may be processed and handled (including classification, sample analysis and statistical analysis) elsewhere for purposes of research cooperation. Data protection and privacy must be seen to in such situations. All co-operation projects must be agreed upon in writing. Delivery of materials and data must be approved by the head of department.

TRANSPARENCY OF RESEARCH AND RESEARCH MATERIAL

– The Institute must openly report the central content of its activities, its priorities and the research areas.
– However, disclosure of research is restricted by many confidentiality principles stated in the Act on the Openness of Government Activities, including the right to privacy, confidentiality of the study plan, confidentiality of the basic material as well as protection of the business secrets of the Institute and its partners.

- The Institute's research material and results are the property of the Institute. In contracted research, they are the property of the client.
- Due to his supervision duty, the head of department has access to all plans, documentation, materials and results.
- The topics of research programmes and studies are usually public.

Agreements

- Agreements on publicly funded research are usually public in their entirety.
- The existence of an agreement on contracted research and the name of the contract are public.

Plans

– Preliminary study plans are usually confidential.
– In connection with the ethics board proceedings, study plans are treated as confidential.
– The personal data register descriptions and data system descriptions are public.

Materials

- Original research material is confidential.
- The head of department decides who has access to research material and who is entitled to use it for research.

Results

- The person in charge of the study must notify the head of department of the main findings in advance. The results must be published in the Institute no later than when they are made public.
- All inventions made in the Institute are the property of the Institute in the capacity of employer.

PUBLISHING AND COMMUNICATION

Publishing

– All results obtained at the Institute are public. They should be published in publications of the highest possible quality.
– The researcher or the research group is responsible for the results and scientific conclusions.
– The authors of the publication should be decided upon by the research group in keeping with good research practice.
– When possible, copyright should be negotiated in such a way that the authors hold copyright to the text. This way the article can be used in the Institute's Internet services, for example.
– The Internet is also a recommended form of publication.

Communication

– The person in charge of the study takes care of communication planning. He also informs the Institute's Director General, head of department and media officer of the principal communications with the media.
– The media officers of the Institute and of the department assist in making communication plans and writing press releases.
- A communication plan shall be included in all study plans.
– As a rule, no information is released on uncompleted studies.
– The person in charge of the study discusses with the head of department and the Director General about the communication of any information that

might be relevant to the Institute's position or about any information with a major scientific or social significance.
- The Director General defines the Institute's official position.

ARCHIVING

- Materials may be stored in the department or in the unit for extended periods of time. They must, however, at some point be archived according to legislation on archiving and the Institute's archiving guidelines.
  - The obligation to archive applies to research plans, contracts, original material, the most important databases, work diaries, samples, publications, funding decisions and final reports.
- A proposal to use archived material for new research shall be made to the archivist in charge. He will then prepare the matter for submission to the Director General.

STEERING AND ADMINISTRATION OF RESEARCH

- The Director General approves the action and financial plans and provides funding for special action plans. He also makes the decisions regarding large research projects or research programmes.
- The research activities of a department are based on annual action and financial plans.
- The head of department decides about the detailed scope of research activities and the personnel resources in various projects and duties.
  - The Institute's research programmes are extensive actions carried out to achieve the Institute's strategic goals. The research programmes provide an overall picture of the direction that the actions are taking.
  - In financial reporting, also classification into special internal accounts (ESKO) is used. These are monitored per financier for all projects with external funding.
  - The responsibilities of research management are described here with emphasis on the Institute's internal responsibilities as well as on the legal responsibility of the person in charge of each research project.
  - The study group has a crucial role in planning and implementing the study. This can only be achieved by means of good co-operation.
  - The research organisations are often very complex, as they can span several departments and units or even several countries. Even though research groups may organise themselves independently, it should be noted that written agreements are the more important the more extensive and complicated the research project.
- All the Institute guidelines described in this manual must be followed in all research done at the Institute. This means that in international research projects, for example, a separate plan for the part of the study carried out at the Institute must be prepared for the approval by the head of department.

RESEARCH FUNDING

Sources of funding and research strategy

- The Institute implements its research strategy and operational plan by means of public State funding, public cost-shared projects and contracted research, financed in full by the client.

Permission to acquire funding

- When external funding is acquired, the head of department is responsible for making sure that the research strategy is not endangered.
- When working in co-operation with commercial businesses, the Institute's integrity and impartiality must be maintained. Therefore, the head of department and, when necessary, also the Director General must participate in any negotiations.
- The head of department approves the funding application made on behalf of the institute or the department's agreement to perform a particular duty in the department.
- EU and TEKES are exceptions to this rule. They require the signature of the approved signatory (the Director General).
- A research scientist or research group usually applies for funding on behalf of the Institute for research work to be carried out at the Institute.
- When a researcher applies for personal grants, he must make sure (with the head of department) that using the grant for work at the Institute is acceptable.
- The research services of the financial unit assist in all matters related to funding.

Shared-cost research

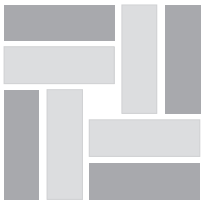
- Shared-cost research is research for the public good. The results of such research are the property of the Institute and must be published.

Budgeting and financial monitoring of research

- Contracted research is subject to value-added tax. This research is carried out at the request and according to the interests of the client. Public funding of the Institute cannot be used to support this kind of research.
- The head of department is responsible for the finances of research carried out at his department. He also nominates a person in charge of financial monitoring.

Reporting to financiers

- The financiers require a final report; some also require interim reports. These reports must be written as specified by the financier. A clear budget and concise financial monitoring facilitate reporting.



PART A.

PRINCIPLES AND PROCEDURES

1 INTRODUCTION

The research carried out at the National Public Health Institute focuses on topics significant to public health, and it must be of the highest quality. The research is carried out according to international, national and the Institute's own regulations and guidelines. The general operational principles as well as the unwritten and written guidelines of the scientific community are quite solidly established. However, national and European legislation may change at quite short notice.

This handbook serves two main purposes. Firstly, it is meant to give new researchers a general picture of the Institute's activities as well as to give them the possibility to familiarise themselves with the framework in which their research is carried out The departments and units and especially the senior research scientists continue to be responsible for training new researchers in specific areas of research and work methods. Secondly, this handbook gives all personnel the possibility to monitor the development of recommended practices and legislation. This applies in particular to the research scientists and persons in charge of the projects. We aim to update this manual annually. Links included in the manual facilitate access to the relevant documents.

This manual describes the basic principles and methods of research carried out at the Institute. It is part of a series of measures at the Institute aiming to improve the quality of work. This manual also includes guidelines and recommendations concerning research work at large and specific types of research. Detailed guidelines, however, depend on the subject and scope of research and should be prepared by individual departments and units.

The legislation, decrees and regulations guiding the functions and actions of the Institute have been observed in this manual. The handbook gives general operational guidelines for the whole Institute. Each department and unit describes their activities as necessary in detailed documentation, such as the quality manual and related guidelines. The documentation prepared in various departments and units must be in line with this manual.

The manual has a board of editors nominated by the Director General. The board reviews and updates the contents of this handbook at least once a year.

Any improvement suggestions from the employees of the Institute are welcome. The suggestions should be addressed to the quality manager of the Institute. All suggestions will be discussed at the board of editors' meetings.

This manual will be published in the Institute's internal guideline portal (http://ktlwww.ktl.fi/kirjasto/sisaiset_maaraykset/). The Finnish language version published in the internal portal is the official and applicable version. The versions of the handbook can be distinguished by the handbook date and version number.

2 GENERAL QUALITY PRINCIPLES OF THE NATIONAL PUBLIC HEALTH INSTITUTE

The Institute's quality policy is described in the quality manual. The goals of the Institute's quality policy include:

- enhancing the actions and performance of the Institute,
- ensuring that the actions and results of the Institute fulfil the requirements set out by various interest groups and legislation, and
- demonstrating the reliability of actions and results.

In order to achieve the quality goals, the management shall, at all levels:

- communicate the Institute's commitment to quality policy to the personnel,
- encourage the personnel to improve quality,
- assure that the personnel are committed to implementing the quality policy,
- see to the development of the personnel's professional skills, and
- together with the personnel, create an atmosphere that supports the achievement of the goals set out in the Institute's strategy.

3 STRATEGIC GOALS OF RESEARCH

3.1 The Institute's aim and mission

The research of the Institute fulfils the Institute's legal task: "The Institute promotes the population's health and prevents disease"[1]. The main goal of all research activities is to provide information on the causes and prevention of disease as well as on the promotion of health.

According to its mission,

- the Institute promotes people's possibilities to lead a healthy life,
- as an expert body under the Ministry of Social Affairs and Health, the Institute is responsible for providing professionals and citizens the best available information to support their choices.

The Institute's goal is to promote people's health. This means that the Institute has fulfilled its goal only once research findings have been transformed into good health and into actions supporting good health. Research is a means of promoting Finnish people's health, not a self-serving purpose. The Institute is also part of an international network whose work benefits all the peoples of the world.

3.2 The result agreement between the Ministry of Social Affairs and Health and the Institute

The Institute makes an annual result agreement with the Ministry of Social Affairs and Health, detailing the result goals for the next year. This agreement also defines the central aims of the Institute for the following calendar year and the following 4-year-period that supports the implementation of the strategy of the Ministry and of the health related goals in question.

3.3 The research strategy of the Institute

The research strategy of the Institute is based on the Act on the National Public Health Institute and the aforementioned result agreement as well as on the strategy of the Ministry of Social Affairs and Health (Strategies for Social Protection 2010 – towards a socially and economically sustainable society, Ministry of Social Affairs and Health Publications 2001:3) and the programme on research policy. The research strategy is also influenced by currently

[1] Act on the National Public Health Institute (828/1981), 1§

important scientific knowledge of public health problems, their causes and prevention.

The research activities of the Institute are directed at major public health problems. These problems are characterised by the following:

- the problem causes serious health consequences to large groups of the population,
- it is a worsening problem,
- it is estimated that the know-how and resources of the Institute can reduce or solve the problem in question,
- studying the problem at the Institute strengthens the Institute's know-how in an important area of public health and promotes training in the field,
- benefits gained by solving the problem are estimated to be large in comparison to the resources required for solving it.

The Institute's research strategy is put into practice in the departments' annual action plans as well as in the result agreements between the Director General and various departments.

4 LEGISLATION AND GUIDELINES CONCERNING RESEARCH

Legislation. The most important laws concerning the research carried out at the Institute are the Medical Research Act (488/1999, 295/2004), Personal Data Act (523/1999), Act on the Medical Use of Human Organs and Tissues (101/2001), Act on the National Public Health Institute (828/1981) as well as the Act on the Openness of Government Activities (621/1999) and the Act on the Status and Rights of Patients (785/1992). Laws of importance with regard to research employing registers include the Statistics Act (62/1994) and the Act on the Statistical Affairs of the National Research and Development Centre for Welfare and Health (409/2001). For genetic research, the Gene Technology Act (377/1995) and legislation concerning animal experiments (see chapter 13) are of importance. These laws as well as other important legislation are mentioned in the Appendix. Legislation is changing continuously and must be developed also in order to secure the legal basis for research. At present, questions of importance also for the development of legislation include the use of stem cells, long-term follow-up studies based on stored samples as well as genetic research (bio-banks, pharmaceutical research, and genetic epidemiology).

Guidelines and recommendations. Another important entity is the guidelines and recommendations concerning good research practice. They are available for laboratory studies, clinical studies and epidemiological studies, among others. Many of these guidelines are written by international organisations. Some of them are even mandatory. They share names that include the abbreviation for good practice (GP), such as GLP (laboratory), GCP (clinical), GEP (epidemiological). The National Agency for Medicines (www.nam.fi) has published its own guidelines for clinical medicine trials.

TUKIJA's reports and guidelines. A third evolving entity of research guidelines are the reports, guidebooks and instructions for the ethical review of plans written by the National Advisory Board on Health Care Ethics' (ETENE) Sub-Committee on Medical Research Ethics (TUKIJA). Also the pharmaceutical industry employs these instructions when planning medicine research. TUKIJA also gives recommendations for improving legislation. The national documents are published in the publication series of the Ministry of Social Affairs and Health, and they are available on the TUKIJA Internet site (www.etene.org/tukija).

Data Protection Ombudsman. The Data Protection Ombudsman's office is an important source of guidelines in situations where data protection is of special importance.

Institutes and authorities. Several national research institutes and authorities as well as hospitals and health centres have prepared their own complementary

regulations that are applied to research in their premises, using their personnel and performed on the clients being treated in these units. Many of them also have their own guidelines on ethics and good research practices. It should be noted that the permission of the research facility is always required in addition to other authorisations and opinions. The management of each institute will decide on the matter.

5 WHY DO WE DO RESEARCH?

The Institute's motivation for research is very clear and based directly on the Institute's legal duties. Without high-quality research, the Institute cannot produce new original information on its own or utilize information relevant to public health produced elsewhere. Sufficient expertise and research skills are also a prerequisite for using the results of own research and research carried out elsewhere for the good of public health. Naturally the Institute's reputation as a high-quality research institute and an organization promoting public health is also a necessary requirement for successful international and national co-operation and for receiving funding. This is also a prerequisite for promoting public health in Finland.

The motivations of individual research scientists vary greatly. Some researchers hope to find out and learn more, thereby increasing scientific knowledge. In time, competition becomes a part of the motivation, also driven by the funding system: one has to make inventions and publish more quickly than others. There is nothing wrong with this as long as the ethical principles (see chapter 6) are followed. For some researchers, a strong desire to build a scientific career in the Institute or elsewhere may play a role. In addition to or even instead of gaining scientific information that serves public health and one's own personal ambitions, many researchers have quite instrumental goals. Many feel that a thesis or dissertation is a necessary part of their professional education and career development. It may also be the culmination point of their scientific career. One of the Institute's important tasks is to train skilled professionals to serve the community. The Institute gains significant benefits from the work of these individuals. Some of the research scientists may also set more concrete goals and wish to work in specialist duties serving public health, somewhere in between scientific research and specialized R&D activities promoting public health. Some of these researchers then start setting higher and higher scientific objectives for themselves, including at least a dissertation, which is often considered a requirement for qualified expert work.

6 RESEARCH ETHICS

6.1 Introduction

Research has both intrinsic value and instrumental value for the person carrying out research. In medical research, the intrinsic value may be the reduction of disease and suffering, for example. The success of the researcher or the Institute could be seen as an instrumental value. If research is only approached from the viewpoint of its instrumental value, it may have ethically unacceptable consequences. Only research of a high quality is ethically acceptable. Research focused on the wrong targets or using unacceptable methods is a waste of resources and may lead later studies to a wrong track.

Unethical actions in research may clearly violate legislation or people's sense of justice, or it may be more difficult to define or prove. Examples of the first case include intentionally fraudulent research as well as gross violations of human rights. Some examples of the latter case include selfish use of other people (research subjects, fellow researchers or employees) and false research results due to incapability or negligence. Problems belonging to the first group are handled according to national guidelines[2]. The latter types of problems are addressed and prevented by means of legislation and internal guidelines, but foremost by means of adequate researcher training and by building a good team spirit. As people's ideas of good practices and fairness vary surprisingly much, it is important that the management support ethically and humanly preferred models of action and behaviour throughout the research community.

The research scientist is primarily responsible for the ethics of his research. He must consider ethical aspects when planning research and include his grounded assessments in the research plan. This responsibility cannot be transferred to others – not to the ethics board, not to superiors and not to other people involved in the research. In addition, all research carried out at the Institute must undergo an independent ethics board review.

6.2 Reviewing the ethics of a project

All research at the Institute undergoes an ethical review. The research may not be started before the ethics board or work group has approved the study plan. Medical research is reviewed by the ethics board of the hospital district. Other research projects are evaluated by the Institute's work group for research ethics.

Medical research on humans or human embryos and foetuses is regulated by the Medical Research Act (488/1999 and 295/2004) and the Medical Research

[2] The National Advisory Board on Research Ethics, 7 December 2001: Hyvä tieteellinen käytäntö ja sen loukkausten käsitteleminen (Good scientific practice and handling of any violations)

Decree (986/1999 and 313/2004). The act covers medical research involving intervention in the integrity of a person, human embryo or human foetus for the purpose of increasing knowledge of the causes, symptoms, diagnosis, treatment and prevention of diseases or the nature of disease in general. According to the preamble to the Act, it does not apply to animal experiments, questionnaire or interview studies or to certain psychological tests or tests related to physical functioning, for example.

Medical studies are evaluated by the ethics committee of the hospital district where the person in charge of the study works or where the research will mainly be carried out. Opinions on international multi-centre clinical medicine studies shall be given by the National Advisory Board on Health Care Ethics' (ETENE) Sub-Committee on Medical Research Ethics (TUKIJA), unless this task has been assigned to a regional ethics committee. TUKIJA may also handle study plans referred to it by a hospital district's ethics committee. It should be noted that the ethics committee only gives its opinion on the study plan, not a permission to carry out the study.

A favourable opinion from the Institute's research ethics work group must be obtained for other research concerning people, such as questionnaire and interview studies as well as register-based research. The research ethics work group evaluates the study plan according to the same ethical guidelines as the regional ethics committees. This work group also monitors that the Institute's instructions, regulations and practices are observed in all medical research concerning humans.

Animal experiments must be subjected to evaluation by the animal experiment committee.

The National Agency for Medicines (NAM) has published its own regulations and guidelines for clinical medicine studies. The Agency also monitors such research. It should be noted that in addition to the evaluation by the ethics committee, the National Agency for Medicines must always be notified before starting clinical medicine studies. Additional information can be obtained at the NAM Internet site at (www.nam.fi).

6.3 Protection of research subjects

The World Medical Association's Declaration of Helsinki [3], the Council of Europe recommendations [4] and the Act (488/1999, 295/2004) and Decree on (986/1999, 313/2004) Medical Research apply to research on humans.

In human research, the interest and well-being of the subject must always come before the interests of science, society and the researcher. Any risks and inconveniences to the subject must be minimized. If the research may cause inconvenience (trouble, anxiety, pain, etc.) or risks (complications from treatment or research interventions, serious or unexpected side effects), the likelihood and extent of these should be evaluated in advance. Any risks must be acceptable when compared to the benefit gained from the study. One of the most important principles of human medical studies is that the risks may not outweigh the benefits. If no clear health-related or scientific benefits are foreseeable, the health risks related to the study must be minimal. When the study concerns treatment of a serious disease, on the other hand, even a relatively high risk related to the examination or treatment may be acceptable if the patient can expect to benefit significantly from participating in the study. The benefits and risks of the study must be described to the subjects in advance.

Special attention must be paid to the benefits and risks when the research subjects are mentally handicapped, minors, pregnant or nursing women or prisoners (Act 488/1999, 295/2004 7–10 §).

6.3.1 Informed consent

Medical research on humans may not be conducted without the subject's informed, voluntary consent in writing (see 7.7.2). Where a mentally handicapped person opposes the examination, it may not be performed regardless of the consent given by the person's guardian or other legal representative. Similarly, where a minor opposes an examination or a study procedure, their opinion shall be complied with, taking into account their age and maturity.

Subjects are entitled to withdraw their consent at any point prior to the completion of the study. This may not affect their treatment. They shall be informed of this right before the start of the study. The effect that the withdrawing of consent has on the recording and saving of information already collected or on the removal of personal or other data from the study material must be assessed on a case-by-case basis.

[3] 18th World Medical Assembly, 1964: Declaration on biomedical research and the 20th World Medical Assembly, 2000: Revised Declaration of Helsinki on medical research

[4] Council recommendation No. R (90) 3 concerning medical research on human beings, 6 February 1990

6.3.2 Privacy

The right to privacy of the people participating in the study must be taken care of. According to the Act on the Openness of Government Activities, the Personal Data Act and the Act on the Status and Rights of Patients, all health-related information on the subjects known to the researcher must be handled in such a way that confidential information is not released. A person register description must be prepared of all research registers containing personal information. The regulations of the Personal Data Act (523/99) as well as the Institute's internal instructions[5] must be observed with regard to any and all data files holding information on identifiable persons. It must be made sure that only authorized personnel have access to personal data even within the Institute. In addition, personal data may only be used for the purpose they were collected for. This purpose is described in the informed consent document. Data privacy is discussed in more detail in chapter 7.12.1 of this manual.

6.3.3 Recruiting of study subjects

A common method of recruiting voluntary persons for medical studies is by means of a newspaper advertisement. The advertisement must be designed following the basic principles of patient information. The information must be accurate, it must provide information on what participation in the study means and it must include the person and institutes in charge of the study.

6.3.4 Insurance coverage

The ethics committee checks that the patients are insured. All persons participating in the Institute's research as research subjects are covered by the Institute's insurance on the basis of the Act on Patient Injuries (585/86). Any medicine-related damages are covered by the pharmaceutical injuries insurance. The client (company) of the study often also takes out a separate insurance against injuries.

6.4 Violation of good scientific practice

Research aims at scientific truthfulness. Only correct (truthful) research results can be employed for the benefit of the population's health. Good scientific practice helps to achieve these aims. The National Advisory Board on Research Ethics (http://pro.tsv.fi/tenk/) under the Ministry of Education has prepared guidelines for good scientific practice. Indifference to good scientific practice and deceitful research cause serious consequences for all research. It is therefore important that research organizations and the entire scientific community do their utmost to prevent dishonesty in research.

[5] Kansanterveyslaitoksen sisäinen määräys 3/2003: Henkilörekistereiden perustaminen ja ylläpito (Establishing and maintenance of personal data registers, internal regulation 3/2003)

Violations of good scientific practice include negligence and fraud. Indifference manifests itself as gross negligence and negligence in the performance of research, in particular. Some forms of fraud include fabrication, misrepresentation or falsification, plagiarism and misappropriation. Scientific dishonesty as defined here does not include genuine scientific disputes about interpretation or assessment or human errors that can occur during data collection.

Every research scientist, person in charge of the study, head of unit and research programme, head of department as well as the Director General are responsible for preventing dishonesty. The key stages of the research process include the objective and accurate logging and reporting of observational or experimental information as well as the verification of observations.

Any alleged violations must be handled duly and without delay in order not to endanger the legal protection of the researchers or trust in the Institute's research activities. The proceedings are carried out according to the TENK guidelines (see http://pro.tsv.fi/tenk/julkaisutohjeet.htm). The main issue here, however, is each researcher's own morally sound and responsible approach to scientific research.

The requirement of good scientific practice also applies to funding and finances. If the project has external funding, the Institute's guidelines for transferring funds to the appropriate accounts must be followed. Directing funds obtained in the name of the Institute to one's personal accounts is fraudulent. The relevance of invoices must also be checked when paying research expenses. Financial malpractices may lead to legal action.

7 PLANNING AND CARRYING OUT A PROJECT

7.1 From an idea to a scientific study

The National Public Health Institute feels that research innovation, quality and performance are best guaranteed when the research topic is selected and the study plan is prepared on the researcher's initiative.

Scientific ideas are created continuously, often simultaneously and independently. Significant ideas are the sum of several factors. Good professional skills and knowledge of previous research on the subject are a necessary requirement. The most topical ideas are often conceived independently by several people and groups at the same time. On the other hand, good ideas are more often created in groups of like-minded people than alone.

Just an idea is not enough, however. Also skills and resources for carrying out the research are needed. Research ideas and those who present them must compete for limited possibilities and resources both internationally and in Finland. Because of limited resources, also the Institute has to select the most promising ideas for implementation. This is why it is important to prepare a preliminary plan as soon as possible and to find out what are the possibilities of other researchers and personnel to participate in the implementation of the plan. After the preliminary enquiries, it is necessary to discuss the matter with the directors of department in order to make sure that fellow researchers and the department support the idea. Next, a detailed study plan is prepared. The need for resources is evaluated, an opinion is obtained from the ethics committee and additional sources of funding are explored. The head of department must approve funding applications, so for this reason too it is important to bring up the matter and discuss possibilities at the early stages of the project, both in the department and in the Institute.

The Institute has numerous comprehensive data sets including those from population studies that can be used to clarify many research issues much more quickly than without such materials. There are established rules and practices for the use of these materials in order to manage large projects, to prevent overlapping research and to protect the interests of the researchers who have participated in the previous stages of the research (including planning and field work). In order to create a successful study, it is necessary to plan the project with someone who truly knows the material in question. You can usually get started by preparing a brief study plan as discussed before, listing also the planned publications and fellow researchers. The work and publication plans of the entire project or research programme can then be updated on the basis of this document.

An idea becomes a feasible project only after several stages. Each of these stages requires sufficient knowledge and technical skills. In addition, discussions and agreements concerning the scope and framework of the project are needed with the head of the department and, in some cases, with the Institute's management. Far-reaching research projects require even more extensive negotiations with partners and possible financiers. Sometimes an idea that initially seemed good is eventually found not to be feasible, or a similar research project may already be underway in many places elsewhere. This may lead to the rejection of the idea or to major modifications. After several stages, a final study and implementation plan is made. This plan will then be followed as closely as possible.

7.2 Preliminary study plan

Each study must be based on a study plan that will be handled and approved as defined in the Institute's internal instructions[6]. A study plan is prepared for each new project. A new study plan must also be written for any research on previously collected material if the research has not been covered in the original plan. When conducting shared-cost research it is important that the Institute's researcher is responsible for planning and approving the project. The Institute's researcher is responsible for project planning and the reliability of results also in contracted research where the initiative and primary interest belong to the client outside the Institute.

All studies must be agreed upon with the head of department. A brief, one-or two-page preliminary study plan is useful when discussing the project. The resources needed should also be assessed in the plan. The need for any shared-cost funding and the planned sources of finance should be specified and justified. When necessary, the head of department will inform the Director General and the administrative director if it is likely that the project will require significant resources from outside the department (such as data management, laboratory analyses, internal financing). The head of department must also give a preliminary approval for the plan before external financing is applied for.

7.3 Information retrieval

The background of the research project must be known in sufficient detail, as it has a major effect on the planning and carrying out of the project as well as on the reliability of results. Literature sources have traditionally been highly valued when reviewing research results and their validity. Methods for the study are often selected on the basis of literature and literature is even more important in the reporting stage.

[6] Kansanterveyslaitoksen pysyväismääräys 4/2001: Tutkimussuunnitelmien käsittely ja hyväksyminen KTL:ssa (Processing and approval of research plans at the Institute, standing regulations 4/2001)

Comprehensive literature retrieval is necessary right from the beginning. The scope of information retrieval will be defined during planning and implementation. This way, the latest research results can be collected during the implementation of the project. Already in the reporting stage one should make sure that the latest literature is available. The Institute has carried out much research where data have already been gathered several years ago and collection methods can no longer be influenced. Even then, it is necessary to study the relevant literature by means of comprehensive searches.

The researcher rarely finds himself in a situation where no literature on the research problem is available. Situations where no one has worked on a similar design and with similar methods are practically nonexistent. Even when no literature is available on the precise issue in question, relevant articles may be published during the analysis and writing phases. It is, therefore, important to closely monitor publications.

Information retrieval is time-consuming even with the electronic search methods currently available. Reading and understanding the material takes just as much work as it used to. Organising materials and sorting out relevant sources also require effort. Any references once obtained (with the publications in printed or in electronic form) should be saved in such a way that they can be shared with other participants in the study and that they are available when writing the next publication. It is therefore recommended that literature be stored in a suitable electronic form that can be easily sorted by research project and/or subject matter.

The library and information services of the Institute acquire and deliver material needed for research. The information services help researchers in planning information search strategies and using data banks and other sources of information, and give guidance in the use of instruments for monitoring new publications and references.

7.4 Final study plan

Before starting a study, the person in charge of the study must prepare a detailed plan including plans for resources and financing.

All research carried out at the Institute must have a detailed study plan in writing, approved as appropriate. The person in charge of the study signs and dates the study plan. Departments file copies of the study plans accepted by the head of department. An accepted study plan is logged into the Institute's study plan register. The name of the project is public information.

When preparing the final study plan, besides the research problem and methods, special attention should also be paid to stating the questions carefully, preparing the study design, statistical planning and data systems. Ethical issues must be

considered and attention must be paid to securing good data protection and data privacy. The need for authorisations must be investigated. Archiving of materials should also be planned already at the beginning of the project.

Guidelines for information searches and management of literature references should be defined. When necessary, experts on these issues should be consulted either within the unit or department or at the Institute's internal services department.

The need for different types of resources cannot be assessed without making a work and implementation plan for the project. Personnel and other resources are needed and must be reserved for all activities included in the plan. Often part of the study personnel are new employees just hired for the project. It is also essential, therefore, to make a plan for training and education.

The essential parts of a study plan are as follows:

1. Name of the project, identification code and person in charge of the study in the Institute (also name of the principal investigator or project leader, if not the same)
2. Summary of the project
3. Background and previous literature
4. Goals of the study and research questions
5. Study design
6. Study material
7. Course of the project
8. Methods
9. Statistical power
10. Control of sources of error (non-response, for example) and quality assurance
11. Handling and analysing of the material and data
12. Ethical aspects
13. Data protection issues, consents, authorisations, research contracts and data file descriptions
14. Time table
15. Personnel resources, division of tasks and time management plan; resources required for facilities, equipment, licenses, etc.
16. Project organisation
17. Budget and financing plan
18. Archiving plan
19. Publishing and communications plan
20. Utilizing the results
21. Appendices.

Besides the above points, a project may also have other central elements that should be taken into account in the project plan. A description of the duties and

responsibilities of all parties is required for extensive multi-centre projects. Also, the different guidelines of each financier must be taken into account in plans for funding applications.

A study is carried out according to the final project plan and valid operating and work directions. If the final study plan is altered as the work progresses, the reason for the change, the date and the name of the person who approved the change shall be logged. Minor changes may be made by the person in charge of the study. Essential changes usually require the preparation of a new study plan. This matter is discussed in more detail in chapter 7.5.

Each department or unit should agree with the head of department on who is authorised to prepare, check and approve guidelines for operations (standard operating procedures) and work processes. These must include at least the name of the department or unit, date of publication or alteration, version, page number, total number of pages and the name of the person who prepared and accepted the instructions. The various phases of the study are logged into the work or laboratory journal. In clinical studies and field studies, a work journal is needed either for each study location or even for each point of measurement or observation. Especially any deviations from normal procedure must be recorded in the journal. After the project has ended, all work journals related to the project are archived according to the Institute's archiving guidelines.

7.5 Authorisations, opinions and contracts

The person in charge of the study must present an account of authorisations, required opinions, contracts and person register descriptions to the head of department before starting the research. The head of department will approve the final research plan after receiving this information.

Before starting the study, the person in charge of the study must make sure that the final project plan with appendices (informed consent document, recruiting advertisement, questionnaires, etc.) has received a favourable opinion from the ethics committee or from the Institute's work group for research ethics. The research plan evaluated by the ethics committee must also be sent for information to the Institute's work group for research ethics. If the project comprises several hospital districts, it is recommended that the evaluation done by the hospital district's ethics committee is sent for information to the ethics committees of the other hospital districts participating in the study.

If a major change is implemented in the research plan after starting the study, the change must receive a favourable opinion from the ethics committee that reviewed the original study plan before starting activities according to the revised plan. If the ethics committee gives a negative opinion, the project may be continued according to the original plan. This does not apply to situations where the change is due to safety risks that prevent the implementation of the project according to the original plan.

Any research deploying register data or archived samples also needs permission to use those materials from the holder of the material. In some cases, these permissions are obtained from authorities, such as the Social Insurance Institution of Finland, the Population Register Centre, the National Research and Development Centre for Welfare and Health (Stakes) or the Ministry for Social Affairs and Health. Obtaining permissions may take several months. Difficulties in defining the design and the necessary information may result in an exceptionally long process to obtain the permission. Data privacy issues may also cause problems. When planning research based on registers, it is useful to contact the experts in charge of the information already in the early stages of planning.

Costs due to the delivery of data may be charged from the researcher or research institute using the information. The calculated and invoiced processing costs of large registers may be very high. This must be taken into account in the cost estimates included in the study plan. Negotiations with the register keeper for invoicing at a lower cost are also recommended.

If a research project is done in co-operation with another organisation, using the facilities, equipment or personnel of a hospital, health centre or day care centre, for example, an authorisation must be obtained also from the organisation in question. When the co-operation is essential or when it includes major financial commitments, all operations and funding should be agreed upon in writing before starting the work. When long-term co-operation in several research projects is in question, a permanent framework agreement can also be made.

If the research is done outside the Institute, all the necessary authorisations must be obtained for using the Institute's resources outside the Institute[7]. An authorisation for using the Institute's servers for remote access must be obtained[8].

In special circumstances and especially with complex and extensive research projects, it may be necessary to make written agreements also on the duties of the Institute's various departments.

7.6 Specific research types and methods

7.6.1 The most important research types and sources of information

For further descriptions, the research conducted at the Institute is divided into several groups and research types, mainly based on the material and methods used for solving the research problem. These groups are biomedical research,

[7] Sitoumus ja lupa KTL:n resurssien käyttämisestä laitoksen ulkopuolella (Commitment and authorisation to use the Institute's resources outside the Institute)

[8] Käyttölupahakemus KTL:n palvelinkoneiden etäkäyttöä varten (Application to use the Institute's servers by remote access)

clinical research and population-based (epidemiological) research. Biomedical research refers to laboratory studies where material usually of biological, sometimes of human, origin or its known properties are used but where the results are not linked to identified persons. As a rule, the Medical Research Act does not apply to biomedical research. Some materials, such as tissue samples or microbe strains originally collected in connection with clinical research, can be used, however. Animal experiments are subject to different legislation altogether. Clinical research typically refers to medical research as specified in the legislation. Actions violating a person's physical integrity may be performed. A review by an ethics committee is always required before starting a clinical study. Population-based research deals with many similar issues as clinical research. Both of them may include clinical sample studies conducted in laboratories using the same methods as in biomedical research, ranging from gene technology to immunology, microbiology and biochemistry.

On the other hand, the same basic topics (such as the effect of the genes on health or factors affecting the risk of disease) can be approached using different methods. The various research types may use similar approaches, research subtypes with different names, although the implementation and methods resemble one another.

Finland has exceptionally good national registers on diseases and the related use of health services and medication. In discussions during the past few years the term register-based research has become to be used both in the original meaning of research using one or several registers and to describe clinical and epidemiological studies where part of the data are drawn from registers. The national health research institutes founded the support centre for register-based research in 2003 with funding from the Academy of Finland. This centre is located in Stakes.

7.6.2 Animal experiments: ethical evaluation and authorisations

The basic principle of animal protection legislation states that it is prohibited to cause pain, stress, agony or suffering to animals. Animal experiments can, however, be approved when they are necessary for scientific research, for human or animal health care or for teaching, and when certain conditions are met. The 3R principle serves as a general guideline for animal experiment ethics: reduction, refinement, replacement[9]. This means that only as few animals as are necessary to ensure the validity of results are used and that as little pain or inconvenience as possible is caused.

Authorisations are needed for all animal experiments. An institute has to have an authorisation to conduct animal experiments. Applying for an animal experiment authorisation and conducting or supervising animal experiments

[9] Russell, W.M.S and Burch, R, The principles of humane experimental technique (1959)

requires that the researcher meet certain criteria for competence. Each scientific animal experiment requires an approved research plan as well as authorisation to conduct the experiment from the animal experiment committee or the county administrative board. In order to apply for an authorisation, the (competent) researcher fills out the form "Study protocol and application for an authorisation" [10]. Instructions are available for filling out the form [11].

When assessing whether an experiment is acceptable or not, the pain and inconvenience caused to animals must be evaluated against the benefits of the experiment. No official method for assessing the benefits and risks is used in Finland so far. The EU is planning to include such a method in a new directive, and a task force of the Finnish Ministry of Education is already preparing such a method. When evaluating an application for an animal experiment authorisation, mainly the following factors are assessed:

- The fundamental purpose of the project and the necessity of the proposed animal experiments.
- Appropriate grounds for the choice of animal species and population; experiments should be made on species on the lowest possible level of development.
- If alternative methods, such as cell or tissue cultures, can be used instead of animals, the animal experiment is not acceptable.
- Grounds for the number of animals to be used. As few animals should be used as possible; yet there should be enough test animals to guarantee the validity of results.
- Use of animals of a specified genetic and microbiological quality.
- Caging conditions and appropriate care (size of the cage, bedding, feeding, stimuli, caging alone or in a group).
- Test arrangements and conducting the experiments: have the operations, such as dosage and sample collection, been arranged in a way that takes the well-being of animals into account as well as possible.
- When assessing the amount of pain and other inconvenience, the primary concern should be for the inconvenience experienced by each animal: if the pain experienced by one animal can be decreased by means of increasing the amount of test animals, this should be done.
- The appropriateness of anaesthesia, pain medication and euthanasia methods.
- Appropriate definition of the most humane moment to euthanize the animal. This refers to the time when the animal must immediately be euthanized in order to prevent pain, stress, suffering or agony.

[10] Kansanterveyslaitoksen koe-eläintoimikunta Eläinkoesuunnitelma ja lupahakemus (Animal experiment committee of the Institute; Animal experiment plan and application)

[11] Eläinkoesuunnitelmalomakkeen täyttöohje (Filling instructions for the animal experiment form)

7.6.3 Use of gene technology in research

The use of gene technology in research is regulated by the Gene Technology Act (377/1995) and the Act amending the Gene Technology Act (490/2000), the Gene Technology Decree (821/1995) and the decree amending the latter (491/2000), as well as detailed decisions of the Ministry of Social Affairs and Health. The law requires that a risk assessment of all genetically modified organisms be made by the researcher. This assessment applies to risks to human health or the environment as well as to precautions for controlling this risk. The Board of Gene Technology must be notified before starting to use gene technology in laboratories as well as when certain operations above the specified risk limit are undertaken. Practical guidelines (Board for Gene Technology recommendations) for working with genetically modified organisms as well as notification forms with filling instructions are available on the Board's Internet site (www.geenitekniikanlautakunta.fi). The department of the Institute using gene technology shall notify the Gene Technology Board before starting to use gene technology. A notification must be made also when the unit moves to new facilities or when changes affecting the risk are carried out in the facilities. In spite of the amendment of the Act, no new notification is required if the unit already has notified its facilities and none of the changes mentioned above have been made.

The notification includes information on the facilities, security measures and the gene technology activities that are being carried out in the unit at the time of the notification. Based on the risks involved, gene technology operations are divided into four classes. Class 1 operations may be started right after notification, Class 2 operations 45 days after notification and Class 3 and 4 operations only after the Board has accepted the notification. New operations of Class 1 need no longer be notified to the Board. A risk assessment must be carried out and recorded, and all operations must be recorded (detailed work journals are sufficient). On the other hand, all other new operations must be notified to the Board. A new notification must be made for new facilities and for operations of a higher risk class than mentioned in the previous notification.

Every department using gene technology appoints persons in charge of the safety of operations and of supervising and recording the use of gene technology. Deputies are also appointed. These persons are also responsible for the notification procedure as well as amended notifications due to changes in the facilities or operations. A project-specific risk assessment is made for all actions. It is recorded and updated annually or always when any changes affecting the risk are made to functions or facilities. The risk assessment is carried out by the persons in charge of projects (group managers) together with the person in charge of gene technology. Special emphasis is on teaching appropriate and safe work methods to all employees using gene technology. The person in charge of the project and the director of the unit are responsible for safety[12].

[12] Government Decision on the protection of employees against biological hazard at the workplace No. 1155, 1993

7.6.4 Biomedical research

The purpose of biomedical research is to study mechanisms through which pathogenic microbes, other external risk factors and the person's genotype influence the probability of disease in individuals and various population groups, as well as to identify possibilities for identifying new targets for intervention. Microbe strains, cell cultures or animal experiments can be used for research, as can samples collected from humans ex vivo or post mortem. The use of these materials always requires an ethical assessment in advance. Biomedical research refers here also to disease surveillance and to the development and evaluation of laboratory methods for clinical and population-based research. Environmental health research at the Institute is also classified as biomedical research.

Often the results of biomedical research can be employed to promote health only in the long term, and often indirectly or even in surprising fields of application. Because of this, only internationally valued research that is to be published in well-known journals and that creates new valid information can be justified. Previous studies in the field and other existing knowledge must be examined before commencing a research project. As the amount of available information is increasing rapidly, it must be easy to monitor literature and search for information also as the project progresses in order to guarantee that the research issues remain up-to-date. The laboratory methods used in biomedical research are often expensive and require much work. In order to optimise the use of resources, the research projects should always be planned carefully. Only valid and reliable methods should be used, and co-operation with other groups both in methodology and in the purchase of equipment and reagents should be considered.

Biomedical research may be descriptive or it may test hypotheses. Nonetheless, surprising observations may be made during the project, giving grounds for changing the focus of the research. When this happens, all events leading to the change and the grounds for changing the line of study must be documented in sufficient detail.

7.6.5 Clinical research

All personnel carrying out clinical research must have appropriate training and the necessary professional skills. The person in charge of the study must be a doctor or a dentist. The examinations and treatments used in clinical research often affect the physical integrity of the research subject. Some of them may also cause a risk or nuisance that must be acceptable when compared with the benefits. Some small-scale studies as well as some larger population-based studies examine the efficacy of a treatment or a health-promoting activity. Typical research at the Institute includes studies on vaccinations, the effect of medication or health promotion by means of changing one's lifestyle. The requirements of privacy and data security are emphasised. Clinical research will be discussed in more detail in chapter 15.

7.6.6 Clinical sample studies

Studies carried out in various laboratories are an important part of all clinical and population-based research at the Institute. In addition, laboratory-level scientific research is carried out in several laboratories. Laboratory research ranges from biochemistry to molecular biology and bacteriological and virological studies. Before planning a study, every researcher of the Institute should familiarize themselves with the possibilities of the laboratories as well as gain sufficient knowledge of the requirements of the various methods. Laboratory studies are discussed in chapter 14. The importance of good quality in all laboratory work is emphasised. A central requirement is the safe handling and storage of samples of human origin in such a way that also privacy can be guaranteed.

7.6.7 Population-based research

Population-based projects (epidemiological research, health care research) are usually extensive, including thousands or tens of thousands of research subjects. The physical integrity of the research subject may be violated also in this research type. All prerequisites and requirements concerning clinical research also apply to population-based research. The requirement of no risk or very low risk research is emphasised even more. Privacy and data security are very important. The specific requirements linked to these studies arise from the need to master a wide variety of clinical and laboratory research methods and register data, on the one hand, and from the sheer scale of the research, on the other. The extensive scale also places special requirements on data systems and archiving. Population-based research is discussed in chapter 16.

The Institute regularly carries out research serving health monitoring. The research subject is often a large sample of Finns that represents the whole population. The health habits of adults have been studied by means of questionnaires since the 1970s. Every five years, FinRisk-studies are carried out, including some health examination elements. The Institute aims to implement national surveys including a comprehensive health examination every 10 to 15 years. The first of these studies was the Health 2000 study carried out in 2000 and 2001.

The Institute has also performed large vaccination and medicine trials to study the efficacy of preventive and therapeutic measures. An example of these is the ATBP study of cancer prevention. The research subjects of this study have later been followed up in order to identify the risk of disease. In the 1990s, a very large follow-up study material was transferred to the Institute from the Social Insurance Institution of Finland. Follow-up of this material has since been continued. The material includes the so-called Mobile Clinic Health Examination Survey and the Mini-Finland Health Survey.

7.6.8 Health-related behavioural and social research

The Institute also carries out research using the approaches and methods of behavioural and social sciences. This may concern population-based research, and also other methods are often used. The Institute also carries out studies of social and behavioural health determinants, for example, and of the ways to influence these factors. Behavioural and social research is discussed in more detail in chapter 17.

7.6.9 Register-based research

Register-based projects draw their data from registers or by combining several registers. In some cases, also research combining register data with data received from clinical or population-based research is called register-based research. Some of the central aspects in register-based projects are the need to fully understand the contents of the register, the validity of the research design as well as to ensure privacy. Register-based research is discussed in chapter 18.

Information included in registers is worth using, although regulations and discussions on the subject may sometimes lead one to think that using registers is somehow dubious. The various register holders apply instructions and restrictions that derive from legislation or their own guidelines and concern procedures for cases where identifiable personal information is needed. Sensitive information about individuals and especially about their health is almost always needed for medical research.

The researcher must familiarise himself profoundly with the data source and show the intended use of the data by means of a project plan. After that, the researcher needs to apply for a permission to obtain the specified data on specified people. When the purpose is to combine the data with the researcher's own research material, a usual procedure is to provide the register holder with personal identity numbers. The amount of material can be very large in research based only on registers, and combining registers may be technically very demanding. Because of this, a project plan should always be made before starting the actual work. Cost of handling large registers varies by register keeper. It can sometimes be unreasonably high for a research scientist or even for the Institute unless the register keeper is not willing to apply lower pricing. The Information 2005 (Tieto 2005) work group of the Ministry of Social Affairs and Health has suggested that in the future, all information for research should as a rule be made available free of charge.

7.7 Carrying out a project

7.7.1 General requirements

Medical research may only be undertaken when the person in charge is a professionally and scientifically qualified doctor or dentist. In other types of research, also other professionals can be in charge of research.

All medical procedures or treatments of patients must be based on the decisions of a doctor or a dentist.

The project must be carried out according to the project plan and applicable work instructions. The duties of every person working in the project are specified in writing.

If temporary new staff is hired to work on the study, even for a short period of time, or if the project is carried out using resources of another organisation, sufficient training must be provided and appropriate confidentiality agreements [13] must be signed.

It must be shown that the equipment and personnel can perform reliably. The functioning of the equipment and the validity of the results are monitored and the results are documented. The calibrations, maintenance and repairs of equipment are recorded in a traceable manner. Each piece of equipment is nominated a person in charge, who is thoroughly trained in the use of the device and monitors its use and condition. Equipment that has to be verified this way includes all field work equipment, such as laboratory instruments, sphygmomanometers, EKG equipment, spirometers and equipment used to measure functional capacity. The high quality of work of people working as field researchers is ensured by means of training, guidelines, comparative measurements and interviews and by monitoring their performance. All information used in the research is recorded, handled and saved so that it can be reported, interpreted and verified again even after a long period of time.

7.7.2 Informed consent

A voluntary informed consent is required for each research subject in medical research. If the subject is not able to write, he may give his consent orally in the presence of at least one independent witness. The requirement for a written consent can also be waived when giving personal data might be against the best interest of the research subject and the study only causes him minor inconvenience and does not harm his health. An example of this kind of situation is when a person participates anonymously in a survey of infectious diseases at a health centre or other, concerning, for example, HIV infection, including sample collection for studying the prevalence of an infectious disease. The ethics committee must approve these kinds of methods.

[13] Vaitiolositoumus-lomake (Confidentiality Agreement form)

No examinations may be carried out before obtaining the informed consent. Exceptions are only allowed when the consent cannot be obtained because of the patient's poor state of health, the matter is urgent and the examination or treatment is likely to benefit the patient's health. Only temporary measures are allowed without an appropriate consent. The informed consent must be obtained as soon as possible. If a person is incapable of giving his consent to clinical medicine research, he cannot be a research subject unless his next of kin or other person close to him or his legal representative has given consent to participation before the beginning of the study.

The document for informed consent includes an information section for the subject as well as a consent section to be signed. These sections must be printed, laid out and identified in a way that unambiguously connects them to one another. If the consent is given for several purposes, all purposes must be clearly identified in both the information section and the consent section (including possible use in further research). The consent document must also include information on the Institute's role in the research as well as the person in charge of the study and any contact persons.

The information section must include all information that the research subject needs in order to give an informed consent. It must be written in a way that is easy to understand. A good information section is short, matter-of-fact and clearly written. The same information must also be given orally to each research subject. The subject must have the opportunity to ask questions to gain more information. Whenever possible, the information should be given in the subject's mother tongue. According to the legislation, this requirement only applies to persons whose mother tongue is Finnish or Swedish. Whenever possible, other languages should also be taken into account. The research subject must have enough time to decide. This should be taken into account in the study arrangements.

The information section of the consent document provides all the relevant information that the subject needs in order to give an informed consent. The information section also mentions what results the subject will receive himself and what personal results are not given, specifying the reasons for this.

The consent section is usually just one page long. It must, however, include all aspects of measures that are of importance to the subject. As the study is described in the information section, no details need to be repeated. The consent section, too, must be clear and easy to understand. When subjects are mentally handicapped, minors, pregnant or nursing women or prisoners, this should be taken into account in the consent document. Additional information on writing the information section and on details to be included in the consent is available in the research guidelines of the Hospital District of Helsinki and Uusimaa, for example (http://www.hus.fi -> tutkimus ja opetus -> eettiset toimikunnat).

Experience has shown that the information given to study subjects is often too difficult to understand.

According to the Medical Research Act (313/2004), the document of consent shall include:

1. the research subject's name, personal identity number or date of birth, and address,
2. that the information referred to in section 6 (2) of the Act has been given to the research subject ("Research subjects shall have their rights, the purpose and nature of the research and the procedures it involves explained to them properly. The potential risks and harm shall also be explained to them properly. This information shall be given in a way that permits research subjects to give their informed consent regarding issues that are connected with the research and have a bearing on their decision-making."), and data about the provider of the information,
3. the other sources from which information concerning the research subject will be gathered,
4. an explanation on to whom the information gathered can be delivered to and on how the confidentiality of the information is protected,
5. the research subject's voluntary consent,
6. a mention of the right to withdraw the consent without it affecting the research subject's right to receive the care he needs,
7. the document of consent shall be dated, and it shall be signed by both the person who gives and the person who receives the consent. A copy of the document shall be given to the research subject. If the study subject has given his consent orally, an independent witness must sign the document of consent. The witness's signature must be accompanied by his name in print and contact information. When the ethics committee has deemed that the study can be carried out without requiring written consents, the data in section 1 is omitted from the consent document. Obviously, the study subject does not have to sign the document if he forbids the recording of information and refuses to sign the document. All relevant information on the study subject relevant to the research must, however, be recorded in the document of consent. Such information may include the age and gender of the subject, for example. A copy of the document shall be given to the provider of the consent.

Research material may only be used for the purposes to which the subject has consented. If someone wants to use the study material later for other research, a new consent must be obtained.

Similar principles must be followed also in research that does not fall under the Medical Research Act. Naturally, the privacy of all study subjects must be respected in this case, too.

The Act on the National Public Health Institute (327/2001) gives permission to use in the Institute's research all information and blood and tissue sample collections that were collected before May 2001. An extension is in preparation. This is on condition that the use of the information or samples for research does not violate any specific consent given by the provider of information or sample at the time the information or sample was given.

7.7.3 Remuneration of expenses and other remunerations to research subjects

The Ministry of Social Affairs and Health has issued a decision concerning remunerations to research subjects (1394/2003). An appropriate remuneration may be paid to the research subject, his guardian, next of kin, other person closely connected to him or his legal representative to cover actual travel expenses and loss of earnings. Also remuneration for any other inconvenience may be paid for participating in research that does not directly benefit the subject's health. The remuneration for other inconvenience (strain, inconvenience and hindrance to daily duties) can vary from 50–170 euros, depending on the degree of inconvenience.

7.7.4 Information to study subjects

The research subject should be informed about the results of the study. It is important to consider how the participants are informed of the main results of the project. In the case of long-term research requiring active participation, such as a clinical medicine trial, it may be necessary to give interim information on the progress of the project in order to enhance motivation to participate. This also applies to the final results of medicine and vaccination trials. In the case of observational studies, the information to be given to the subjects is not as obvious. With regard to health examinations or functional capacity measurements it is, as a general rule, good to release information that is generally used in health care and therefore known to most people. In such studies, the results of a few laboratory tests have often been given, risk scores may have been calculated or information provided regarding the subject's performance and health when compared to the general population.

7.8 Tests and opinions obtained elsewhere

If data collected in the study will be used elsewhere for producing data for the study, special care must be taken of the data security and the quality of the information produced elsewhere. If possible, all materials to be sent elsewhere, such as blood samples, EKG recordings, x-ray images and electronically transferred graphs and images should be equipped only with the code numbers of the research subjects. This way the identity of the subjects will not be exposed when data is processed outside the Institute.

Data security must be ensured by means of contracts and confidentiality commitments.

7.9 Management of the research material

7.9.1 Data management

Every project needs an information system guiding the collection of material, quality control, analysing, publishing and archiving. The system may be based on manually updated lists, card files or similar, but usually the information systems are at least partially computer-assisted.

A good information system efficiently uses the data recorded to guide the project. At best, this may reduce the amount of manual work required and enhance the quality of the research material collected.

It is important to plan early on and in co-operation with other experts the implementation and progress of the project and the information system. A data management expert as well as a statistician should participate already in the early planning phase. In practice, this means that the department's principal systems analyst or a representative of the Institute's data system unit should participate in the early phases of planning of the study schedule and concepts. This process also helps to evaluate how material, programmes, methods and knowledge gained in the Institute's previous projects can be utilised. The starting of a new project can be sped up significantly if existing experience and solutions can be put to use.

During implementation, one does not usually spend time thinking of the end of the project and the need to archive the results and documents of the project. Even if the publications have already been produced as planned, the material may be useful for later research and even grow in importance along the years. All material should be saved so that it can easily be used again later. A good data system records the progress of the project in a database and creates archive-ready materials at the end of the project. This reduces the amount of work needed later. This can be achieved by using the uniform data management methods generally used in the Institute and by maintaining the material documentation up-to-date.

The most important principles of good data management are the following:

Material must be collected and maintained in such a way that study results can be proven based on the original material even several years later. The contents of the material may not be changed by removing even erroneous values. All fixes should be recorded as additions to the data. When changes are implemented, a new version is created and the versions are recorded. Results are published at

different times; making it important to know which version they are based on. Each update needed (the addition of new data) is only made in one place.

The objects (persons, examination visits, samples, etc.) are equipped with unique codes containing no other information and therefore requiring no alterations. As these codes link the various research objects to one another, the accuracy of the codes must be managed carefully by means of check numbers and characters, for example.

The research material is the property of the Institute, not the personal property of the researcher. They are not to be saved in personal directories or on local drives of workstations. The data processing unit helps in the selection of a storage location and in the definition of data protections. Consultation with the unit is important also in order to give the unit a possibility to select appropriate backup and archiving methods. It also needs some preparation time to be able to provide centralised data processing resources.

7.9.2 Sample management

Samples must be collected carefully, and the Institute's sample management methods and tools must be used. Co-operation with the unit responsible for sample management (ABIL in Helsinki) is needed during the planning of the project. The Institute's sample management is responsible, among other things, for the methods needed for appropriate handling, storage and archiving of samples. There are still differences in the practical implementation between various cities and departments, but procedures are being unified. The following describes the planning stages of sample collection:

The need for samples depends naturally on the issues addressed in the project. Usually only some tests are carried out at the beginning of the project. Most samples are used in later cross-sectional and follow-up studies.

It is necessary to define:

- what types of and how many samples are needed: serum, plasma, nail, etc.
- what the samples are used for (analyses, quantity for storage)
- how to take the samples correctly; are there any special requirements such as fasting, time of day or prevention of contamination?
- any other special requirements, such as: cold collection, freezing temperature, conditions for transportation
- how long the samples will be stored and at what temperature.

Appropriate storage space must be reserved in co-operation with the laboratory in charge of sample management. Nowadays, this means the purchase of freezers and acquiring space in which to place them. These matters must be taken care of well before starting the project. The Institute aims to develop sample storage towards a more centralised system.

When samples are collected, all necessary information about the sample is recorded on a sample form. It is therefore necessary to define the issues specified below.

- The sample collection data that should be recorded, such as the time of sample collection, duration of fasting, degree of haemolysis.
- The need for unique sample numbers and reserving these numbers from the Institute's sample number space. The amount of collected samples, test tubes and storage tubes should be taken into account.
- The printing of bar code stickers for the sample tubes. A unique sample management number is printed as bar codes on the stickers. The sticker printer of the sample management unit is available for this.
- The transfer of the samples and sample data to the sample management system. Information related to the use of the sample may be saved in the system, such as sample location, sample quantity, number of thawings, etc. The location of samples in the box is recorded by means of a box reading programme.

Support for sample collection and other planning issues are available at the sample management unit (TTO/ABIL) as well as other laboratories familiar with the issue.

7.10 Documentation

Although the study plan is a necessary basic document, the actual implementation of the project must be documented as well. This is the only way to assess and ensure the validity and reliability of results. Documentation must cover all phases of research, from the preliminary research plan to the final research report and archiving of materials. Documentation makes it possible to trace the different stages of the research also once the project is over.

Every research project is given a unique name and a code (such as a combination of letters and numbers). This code is used to identify all material related to the research (such as paper and computer documents, samples, etc.). Each unit or department maintains a log of its projects as well as codes currently or previously in use. The Institute employs a register of project plans where all future plans shall be recorded. The data system unit and library and information service unit are responsible for the project plan register. Codes for the plans can be obtained from the project plan register.

If the original material is altered or corrected, the fix implemented, reason of the fix, person implementing it and the date must be recorded in the material or related documents. The original material (first recording of results) of a study or an accurate copy of it is stored and archived according to the Institute's archiving guidelines. The material or related documents must show the time of

data collection and person who collected it (by marking the person's signature or initials and the date, for example). After the corrections are done, a copy of the project's data file is saved in the archive.

Original study results include all original data, such as gel photographs, x-ray images, chromatography and scintillation counter printouts, immunological, chemical and bacteriological analysis results, plotter graphs, clinical-physiological measurement results, answers obtained from interview forms and questionnaires or logged directly on a computer, sound and video tapes, etc. The original results marked with dates and author names are stored permanently in the Institute. All other material relevant to the interpretation or understanding of the study must also be saved and archived.

Computer files containing research results are likewise documented and stored permanently. All data processing systems and programs must be documented carefully as well. File access rights and rights to implement changes and corrections must be defined in written guidelines. These guidelines can be written specifically for each department, unit or study, for example.

7.11 Storage, analysis and reporting

Information must be saved into files either as it is accrued or after all parts of the project have been completed. A well-designed data system (see chapter 7.9.1) helps one to save data correctly. When the study material has been collected and saved in electronic form, it is necessary to make sure that there are no formal errors. Only permitted values may be included in the material, and the structure of the material should be logical. Checking small materials is quick, but very much time may be required in large population-based research projects.

Statistical methods suitable for the research design should be used for analysing the results. When necessary, a suitable expert, usually a statistician, should be consulted. Analyses should be started with simple descriptive basic methods that give a good idea of the validity and properties of the material. Any unexpected observations can often be explained by errors in the data. Errors in the statements guiding the analysis are also common. It is therefore necessary to check all results carefully and determine how they have been obtained.

Analysed data can be used for one or several articles to be published in an international publication of the highest possible quality and using peer reviewing (see chapter 9.1). All observations published originally in an international scientific publication should usually also be published in a Finnish journal.

In the case of contracted research, only a technical report needs to be written for the client.

7.11.1 Utilisation of the Internet in data dissemination and processing

Some researchers of the Institute work in other cities and also in cities where the Institute does not operate. Not all of them are employees of the Institute. The situation is similar in research carried out as international co-operation. Data processing is often handled centrally by one party to the research. This solution is well suited in many cases, but not very well suited to the current decentralised ways of working and remote work.

Data processing can be done flexibly via the Internet. A popular method is to provide all persons involved in data processing with access rights and connections. This way the files can remain in the Institute's computers. Many of the parties only need a small part of the entire data file. A traditional solution is delivery by email or on a disc. In some cases, using the Internet requires secure data transfer and data encryption. In research co-operation, anonymous data can often be transferred to known recipients applying less advanced precautions. However, there are situations, such as contracted research or patent-related matters requiring very strong encryption for all data. Group work software can be used in long-term co-operation projects. Good experiences also exist of arrangements where research material stripped of personal identity numbers is ordered and sent via email.

7.12 Privacy and data security

7.12.1 Privacy

Privacy is regulated in the Personal Data Act (523/1999). Privacy refers to the protection of personal data against unauthorised use during handling of the research material. Privacy means that the individual's information is protected. Data security refers to the protection of data against alteration and deletion. Data security procedures also help to ensure privacy.

Personal data refers to information that can be identified as belonging to a certain person or his family. A personal data register is a collection of personal data. The register keeper is a person or institute maintaining such a register. In the Institute, this refers to the whole Institute, not an individual person, unit or department. Personal data may be processed with the consent of the registered person. A personal data register may be processed only according to its purpose, and only used for research purposes. The personal identity number may also be used for research purposes.

Privacy covers the protection of people's private lives and other related rights when processing personal data. In practice, privacy means that all material is protected against unauthorised use. Only authorised persons are allowed to read and update the contents of the data file.

Confidentiality must be ensured concerning the right of use of any materials.

The right to use material and data must be specified clearly. It is updated as the employees' duties change. Material is protected in such a way that only authorised persons are allowed to read and update the information contents of the material. Technically, this is achieved by means of locking the premises and data systems. Keys – either traditional keys or software keys – are only given to authorised employees. The keys may not be passed on. The Institute's archiving guidelines, waste management guidelines and data security guidelines regulate the destruction of material. This way we can be sure that the destroyed material does not end up in the wrong hands.

Another aspect is related to personal data registers. Respect of privacy means that personal data are used as little as possible and that they are protected as well as possible. The entire research process and data collection must be planned in a way that prevents unnecessary collection and recording of personal data. A general aim is that no personal data be included in forms or samples and especially not in the data files to be analysed. The data system guiding research logistics helps to achieve this aim. Research subjects are identified by means of artificial codes. The connection between these codes and personal data is recorded in a separate list that should be protected especially carefully.

In general, the field study personnel need the personal data of the subjects when collecting samples and data. When possible, personal data should be separated from the actual research forms into work or call lists or folders that will be destroyed after the storage period as specified in the archiving plan. If the data cannot be destroyed, the key lists (and files) must be stored separately from the actual study forms. No actual research data or any sensitive information may be recorded in the lists.

7.12.2 Data security

According to the decision on information security in public administration, several areas are included in data security:

- administrative data security (management and organisation of information security operations)
- personnel security (management of data security risks related to the personnel)
- physical security (physical safeguarding of materials and data processing systems)
- data communications security (ensuring the security and functioning of communications used for processing materials and data)
- software security (ensuring the functioning and correctness of software used for processing data)

– information material security (ensuring the confidentiality, integrity and usability of materials)
– functional security (supporting the use of IT technology and ensuring continuity).

Data security refers to the aim of protecting information material, data systems and services in such a way that threats to their confidentiality, integrity or usability do not cause significant harm to people, research, the Institute or society. Confidentiality requires that only authorised personnel are allowed to use the materials. This is particularly important when processing personal data. Confidentiality is supported by controlling access to the data system where user rights and methods of use (such as reading data or modifying data) can be restricted as appropriate. The simplest form of access control is a personal user name. A system employing shared user names or where all users have the same access rights does not usually meet the confidentiality requirement. At the same time, it is important to remember that there should be no unnecessary obstacles to the use of information requiring no specific privacy or data security.

As confidentiality requirements become stricter, stronger authentication methods can be used for identifying users and for confirming the non-repudiation of a message or operation. However, no system is ever more reliable than its users, developers and administrators. The computer and data system units give guidance and aid in the planning and implementation of data system access control.

Research material must be available always when needed. Availability is affected by the implementation of the whole data system and the operation platform. The material must remain usable regardless of involuntary or voluntary human errors or physical damage and functional errors. Backups are always required. Electronic materials must be stored on a server. This way the IT unit can automatically make backups of the data. If the material has to be processed on computers without a connection to the Institute's servers, backups must be made as soon as possible and saved on the Institute's servers.

With regard to material management, data security requirements must be taken into account from the very beginning. In addition to the chief data analyst or person in charge of your own department, you can always consult the Institute's data security manager or the computer and data system units in matters related to data security.

7.12.3 Delivery of research material

The Institute's materials may be processed outside the Institute in the context of research co-operation. Typical examples include reading, interpreting and classification of material, sample analysis and statistical data analysis. It should be made sure that the original material stays at the Institute (by means of

copying, for example). When this is not possible, original material should always be returned to the Institute. All material for analysis or interpretation should usually be delivered without personal information. All results and remaining samples should be returned to the Institute.

The best way to take care of these issues is by signing a co-operation contract. The department head accepts the co-operation contract and delivery of materials at the suggestion of the person in charge of the project. All information on deliveries shall be stored centrally at the department.

8 TRANSPARENCY OF RESEARCH AND RESEARCH MATERIAL

A basic principle of the Act on the Openness of Government Activities (621/99) is that the documents of all authorities, the Institute included, should be publicly available. In Finnish society, everyone has the right to information about the activities of authorities.

For the research carried out at the Institute, this principle of openness means that the Institute must actively and openly report the central contents of its activities, the topics of its work and the topics of research. Several confidentiality principles of Section 24 of the Act limit the transparency of research. These are discussed in more detail in the memorandum of 1 December 1999[14]. The most important principles limiting openness are the right to privacy, confidentiality of the research plan, confidentiality of the basic research material as well as the Institute's and its partners' right to business secrets.

All materials and research results are the property of the Institute, unless otherwise agreed or specified. The results and materials of contracted research, on the other hand, are usually the property of the client.

The head of department controls all activities of the department as well as the Institute's rights to results and materials. He is also entitled to receive all necessary information on all research. In addition to the person in charge of the project and other members of the research team, also the head of department has the right to study research journals and logbooks, materials and results and use them as necessary.

8.1 Research topics

All the topics of research programmes and projects accepted for implementation at the Institute are usually public and available in the plans of action of departments and units. Even the topic of research may be confidential in some contracted research.

8.2 Agreements on research funding

The financing agreements of publicly funded research are usually public in their entirety. Some parts of the funding agreement may, in some cases, be made confidential because of the financier's right to business secrecy.

[14] Hallintojohtaja J. Penttisen muistio julkisuusperiaatteesta Kansanterveyslaitoksessa, December 1, 1999 (Administrative Director J. Penttinen's memorandum on the principle of openness at the Institute)

The existence of an agreement on contracted research and the name of the contract are public. It is therefore important that the client's business secret does not appear in the name of the contracted research project. The contract is often confidential because of the client's confidential business information included in it.

8.3 Study plans

The preliminary plans prior to the acceptance of a project are confidential and usually only available to the researcher or research group as well as the heads of departments in question.

The study plans of accepted projects are usually confidential. They are stored in a centralised location within the department. The head of department may, having heard the researcher in question, decide on a case-by-case basis when information regarding the research plan may be released in spite of confidentiality. The head of department must always consider all aspects affecting confidentiality at the Institute, such as the possibility of patenting or protection of other intellectual property rights as well as the contract partner's right to business secrecy.

The study plan is usually considered confidential in the ethics committee process.

8.4 Research materials

The personal data register descriptions or data system descriptions concerning research materials and files are public documents.

The original research material is confidential.

However, in line with the principle of openness, the Institute may provide other researchers with research materials after removing any confidential information. This usually refers to personal identification numbers.

The person in charge of the study is responsible for organising the storage and archiving of research material according to the procedures defined by the head of department.

The original research material, measurement data and other results and files containing these are not public. The owner of such material is the Institute, not an individual researcher or group of researchers. In research, they are generally only available for use by the researcher or research group of the project in question. In addition to them, the head of department and any other superior nominated by him is entitled to study the material.

Having consulted the person in charge of the study and the person in charge of the research programme, the head of department decides about any other

persons entitled to access the research material and results and to use them in their own work. A list of such people is stored in a centralised location in the department together with the study plan and as a separate file. Access rights as specified in the list may also be controlled by technical means. This applies in particular to the right to use data files.

8.5 Results and observations

Results and observations are public after they have been published in a scientific journal or in a similar forum. Research contracts or similar matters may, however, restrict the publication and release of results and observations.

8.6 The researchers' copyright, and protecting the immaterial rights to research results

Issues related to protecting immaterial rights, such as patenting, must be considered and any applications sent well before publishing the results.

As in other state research institutes all inventions made at the Institute are the Institute's property in its capacity as employer. An internal regulation concerning the protection of immaterial rights is available. [15]

[15] Kansanterveyslaitoksen pysyväismääräys 2/2001: Keksinnöt ja tekijänoikeudet sekä tutkimustulosten kaupallinen hyödyntäminen Kansanterveyslaitoksessa (Inventions and copyright and commercial utilisation of research results at the Institute, standing regulations 2/2001)

9 PUBLICATION AND COMMUNICATIONS

9.1 Publication in a scientific publication

The researcher or the research group decides on the publication of results and observations. The person in charge of the project must inform the head of department of all observations of importance to the department or the Institute before submitting the manuscript for first publication.

Research methods and results must be subjected to scientific critique. All results obtained in the Institute's scientific research are public – including any results that the researcher or the financing agency may find unexpected or unpleasant. A researcher rarely decides alone on the publication of results, but he must always feel responsible for the use of the results. The researcher's and research group's as well as the Institute's rights to the results and benefits of the research are defined in chapter 12. Any conflicts of interest are primarily resolved by the common superior and as the last resort by the Director General.

The researcher and the research group must ensure that the results and observations made will be published in a publication of the highest possible quality. They are also responsible for the scientific conclusions. Any results published internationally should also be published in a national scientific or professional publication as appropriate.

Before publishing an article, the publisher makes a contract with the author regarding the transfer of copyright to the publisher. The author should be aware of the copyright issues and at least read the contract text written by the publisher before signing the contract. When possible, the author should try to reserve the right to publish a copy of the article on his own Internet site or on the Institute's site. Many publishers allow an archiving practice enabling such open access. The situation still remains very unstable, however. Up-to-date information on publishers' policies can be checked at the SHERPA Internet service site, for example, (http://www.sherpa.ac.uk/romeo.php).

The authors of a study to be published must be agreed upon in the project group according to good research practice and taking into account the recommendations of the Medical Journals Editors (ICMJE).[16] In general, all persons who have done significant scientific work in the project are included as authors. Each author mentioned must have played an important role in the process leading to the study in question (idea, planning, implementation, analysis and interpretation, writing or editing the article and approving the final version for publication).

[16] International Committee of Medical Journals Editors. Uniform requirements for manuscripts submitted to biomedical journals. New England Journal of Medicine 1997; 336: 309–15

The authors and their role in the process are mentioned in the reports in various ways, which are understandably different when publishing the results of large co-operation studies and in small projects. It is good to agree on the publication principles at an early stage, usually already in the study plan.

9.2 Internet as a publishing channel

It is likely that an increasing part of scientific publishing will transfer to the Internet. It is worthwhile to keep up with this development. Besides printed scientific publications, also plans, reports and other products (such as publications and databases) are produced in extensive domestic research projects and especially in international projects. These materials have to be available even though they are not suitable for publishing in traditional scientific journals. The most important of those materials should also be published in print in the Institute's publication series or in other suitable series. The primary method of publication is, however, the Internet. Attention should be paid to giving information concerning the publication of these materials and to their easy availability on the Institute's Internet site.

9.3 Communication

Communication and giving information is a part of a researcher's work. The researchers tell about the study on their own initiative to the academic community, financiers, personnel, interest groups, the press, research subjects and other possible target groups.

In the case of significant research projects, information is given already when starting the project and possibly also during it. Information regarding results that are of importance to health monitoring and surveillance are given in various phases of the project. This requires that the validity of the observations has been ensured by means of internal methods. Research results and observations are usually released only after they have been published in scientific publications. The person in charge of the project is responsible for planning communications. A communications plan must be included in all study plans. In addition to publishing in a scientific publication, this plan also addresses the utilisation of results to benefit health, the importance of research for the users and applications, as well as the contribution of the project to the discussion on matters of social and health policy. Any restrictions due to funding agreements or other contracts must be taken into account in the plan. The media officers of the department and of the Institute assist in preparing the communications plan.

The media are important partners for the Institute in scientific communications. Personal contacts and press releases are used for maintaining contact with the

media. A press conference is organised for especially important projects. The press releases are written by the person in charge of the study or by an expert authorised by him.

The media officers of the Institute and of the department assist in writing press releases and organising press conferences. The person in charge of the study must inform the Director General, the head of department as well as the media officers of the Institute and of the department of the most important communications to the media.

Every research scientist involved in the project is an expert in his field and may give interviews and make statements. If the media ask for information on unfinished, still unpublished research, the superior of the person in charge of study will decide on any information to be released. As a general rule, no information concerning unfinished research is released.

Information about the publication of results is given or the results themselves are released in the department or unit in question or in the Institute in general usually no later than at the time of publication in a scientific journal or other publication or in the media. In practice, the most suitable method is to publish them in the Institute's internal network when the person in charge considers it appropriate. If the results are deemed to be so extensive and important that they will attract general interest, the Director General and the media officer must be informed before releasing the information.

The person in charge of the study discusses with the head of department and the Director General about the communication of any information that might be relevant to the Institute's position or any information that is expected to have major scientific, practical or social significance.

The Director General states the Institute's official position.

The Institute's own research information channels – the intranet, the public Internet site of the Institute, Kansanterveyslehti magazine and information leaflet distribution – are utilised for communicating results.

10 ARCHIVING

10.1 General

The purpose of archiving is to guarantee the permanent preservation and usability of documents and to ensure that the needs of information services related to the documents can be met. Using archived documents, the life span of a research project can be reconstructed later and it can be shown that the research was carried out according to the instructions and quality systems applicable at the time. All original research material generated at the Institute will be stored permanently, unless a decision to destroy material that is no longer needed is specifically made with the permission of the National Archives. Even though materials may be stored in a department or in a unit for extended periods of time, they must at some point be archived according to the Institute's archiving guidelines[17]. A copy of the research material (data) is archived after any necessary corrections have been made to the data file.

Besides usual written material, the term document also refers to maps, drawings, images and films as well as electronic recordings or recordings made by other means that can be read, heard or otherwise understood by means of technical equipment. In the Institute, archiving also concerns the tissues, sera, environmental and other samples owned by the Institute.

The Archives Act (831/94) and the Institute's archiving guidelines[18] apply to archiving. The Institute's archiving guidelines include an archiving plan detailing the storage periods of materials, for example. The reports containing the basic observations made during research as well as the primary scientific reports are archived together with other documents generated during research. Work journals are archived after they are full and no longer needed for research. Removing work journals from the Institute is forbidden. Besides the electronic files, also paper printouts are archived when possible, as well as original research contracts and opinions, documents related to the acquisition of equipment.

The Senior Archivist nominated by the Director General is responsible for the management, development and control of archiving. The person in charge of the study is responsible for archiving the materials of his research project. All material to be placed in the final archives shall be delivered to the archivist, who must have the opportunity to inspect the materials. Some time should also be reserved for correcting any flaws detected in the inspection.

The archiving guidelines and data security guidelines applicable at the time apply to the destruction of archived material and to the protection of data.

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[17] Kansanterveyslaitoksen pysyväismääräys 4/1999: Kansanterveyslaitoksen arkistosääntö (The Institute's archiving guidelines, standing regulations 4/99)

[18] Kansanterveyslaitoksen pysyväismääräys 4/1999: Kansanterveyslaitoksen arkistosääntö (The Institute's archiving guidelines, standing regulations 4/99)

At least the following documents are archived for each project:

1. Abstract (what was studied, how, why and when)
2. Study plan and any modifications to it
3. Research contracts
4. Original material
5. Major databases of the research project and corresponding paper printouts, if possible
6. Work journals
7. Information on the archived samples related to the project and the location of these samples
8. Publications (at least the main publications)
9. Funding decisions
10. Final report.

All materials generated at the Institute are the property of the Institute, unless otherwise agreed. No original data may be removed from the Institute without permission. If delivering original material outside the Institute is necessary, a specific permission procedure must be followed[19]. When original or other material is delivered outside the Institute, the delivery must fulfil all the requirements set out in this manual and in other guidelines on data protection and data security as well as in legislation.

10.2 Using archived material

Archived material may be used for new studies. The same requirements apply to using the material later as they did to original use (original permissions, consents as well as principles and legislation on data protection). It should be noted that if the purpose of use is considered to have changed, a new consent is needed from the study subject. A study plan must be written for research based on archived material. The plan must be processed and approved before starting the project, just as for the original project (see chapters 7.2 and 7.4).

A proposal concerning the use of archived material in new research shall be made to the Senior Archivist of the Institute. He shall then prepare the matter for submission to the Director General.

[19] Menettelyohje alkuperäisaineiston luovuttamisesta (Instructions for transferring original material)

11 STEERING AND ADMINISTRATION OF RESEARCH

The research activities are governed by the annual plan of action and budget of the department as well as by the Institute's research and action plans based on targeted funding. The Director General approves the plan of action and the budget and grants funding for the plan of action. Targeted funding was given in 2004 to the allergy programme, to the programme to reduce health inequities and to the research programme on healthy aging, among others.

Available external funding also affects the areas of research selected. Because of this, it is emphasised in this manual that external funding should preferentially be applied for projects and studies that are in line with the Institute's strategy.

11.1 Steering and administration of research at the department

The research activities of each department are based on the Institute's research strategy, on the department's annual plan of action and budget approved by the Director General and on the result agreement based on these. The plan of action details the goals and contents of research carried out at the department. Details of the most important projects, subprojects and studies in the various units are also included.

The head of department decides on the exact contents of research activities and on the assignment of researchers and other personnel to various projects and other duties in his department.

11.1.1 Research programmes

The division into research programmes reflects the strategic goals set for the Institute's research activities. Research programmes are extensive action packages designed to achieve the Institute's strategic goals. Research programmes are also used as a means for financial planning and monitoring in the department and the entire Institute. The Director General approves research programmes based on a suggestion made by the head of department.

Research programmes help to guide the research activities of the Institute and to improve research quality and co-operation between research groups. The head of department decides on the research activities conducted in the various programmes. The progress of research programmes, projects and individual studies is monitored at each department.

When a research programme is started, the head of the department appoints a person in charge of the research programme.

All research programmes are listed in a list by the Institute's financial unit.

11.1.2 Internal project accounts (ESKO)

The classification into internal project accounts is used in financial monitoring. An internal account is formed of each research or funding contract so that financing and costs can be monitored for each contract. This is necessary also because many financiers require a separate report about the use of the allocated funds according to the official bookkeeping system. An internal project account (ESKO) is formed always when external funding is received for the research. Internal accounts include funding from the Academy of Finland, TEKES, the Finnish Work Environment Fund, the EU and various foundations usually covering part of the costs of a study.

The appropriate person in charge in the internal services decides on the creation of an internal account following a proposal made by a department or a unit.

11.1.3 Administrative authority

The Director General decides on the Institute's organisation (departments and units) in connection with the approval of the rules of procedure. The Director General decides on the research programmes based on the suggestion made by the head of department and on the action plans for targeted funding. The head of department decides on the beginning and ending of projects and of studies related to a research programme. The decision to start or end a project or a study must, however, be subjected to the Director General's approval in the following cases:

1) if the study or project places extensive demands on the Institute's own resources for a long period of time,
2) if the research plan or other central issues of a research or project covering several departments cannot be agreed upon by the departments,
3) if the action requires significant additional budget funding for the department, or
4) if the action is otherwise significant financially or in principle, for example, it expands the department's area of activity specified in the plan of action.

11.2 Responsibilities in research management

11.2.1 Director General

The Director General allocates the available resources to the departments.

In regard of co-financed research and contracted research, the Director General decides on the issues included in the financing agreement.

11.2.2 Head of department

The head of department decides on issues related to the management and financing of research programmes and studies to the extent that they do not fall under the Director General's authority. The head of department approves the plans and their modifications for all research carried out at the department. The head of department also decides on the internal organisation of the department. The head of department signs and decides on contracts related to the practical implementation of studies, concerning the receipt or delivery of materials. Exceptions to this rule are extensive agreements that should be approved by the Director General. The head of department makes sure that a written study plan has been prepared for all projects, including archiving, data management and communications plans. The head of department is also responsible for ensuring the adequacy of quality assurance.

The head of department is responsible for the strategy, actions and finances of the department. Therefore, he is also responsible for the work environment, work safety, training and development of personnel as well as for data privacy and data security.

11.2.3 Person in charge of a research programme

The person in charge of a research programme nominated by the head of department is responsible for the scientific leadership of the programme. The person in charge makes sure that the programme advances as planned. The persons in charge of studies in the programme are responsible for financial and personnel issues. However, they must report to the person in charge of the research programme also about the progress of work and about the resources. The person in charge of the research programme reports annually to the head of department on how the goals set for the project and the related individual studies have been achieved and how resources have been used.

The person in charge of the research programme should also, in co-operation with the project and line organisations, enhance co-operation within the programme and the training and developing of the personnel carrying out the programme.

11.2.4 Person in charge of an internal account

The person in charge of an internal project account is appointed by the head of department or unit that suggested that the account in question should be created. The person in charge of an internal account is usually the person in charge of the study related to the internal account in question.

11.2.5 Person in charge of a study

The Medical Research Act requires that a person in charge of the study be appointed for all medical studies. This condition is also applied in this Manual. Comparable suitable titles often used include principal investigator, researcher in charge and co-director. Multi-centre projects often have several principal investigators (or co-principal investigators). Extensive studies and multi-centre projects often have a steering group or core group for the whole project with full authority, as well as other work groups. The Act or our own regulations do not affect the internal organisation of a study. A person in charge of a study should, however, be appointed for all studies carried out at the Institute, not only those for medical research. It is recommended that the principal investigator is also the person in charge of the study, as the duties of the person in charge cover most duties of the principal investigator.

The head of department appoints a person in charge of the study for all projects. This person is responsible for the implementation of the project including quality and ethical issues. He is also responsible for making sure that every individual working in the project receives adequate initiation to and training for his research duties before starting the study. The person in charge of the study must also consider data privacy and data security aspects in the collection and processing of research material. He is responsible for budget administration and the data management, archiving and statistical validity of the entire project. If the study or parts of it are outsourced, the person in charge must also make sure that the quality of work provided by the vendor or other co-operation partner is sufficient.

The Medical Research Act (488/1999) requires that the person in charge of medical research is a professionally and scientifically qualified medical doctor or dentist. In other types of research, also other professionals can function as the person in charge of the study.

The person in charge of the project shall ensure that there are competent staff and suitable tools and equipment available for the study and that the study is also conducted under safe conditions. The person in charge shall also ensure that the research is conducted in accordance with the provisions of the Medical Research Act, the international obligations covering the status of research subjects and the rules and guidelines that govern research. The person in charge shall stop the study immediately where required for the safety of the research subjects. If new information is received that is of importance to the safety of the research subjects, the person in charge and the client shall immediately take all precautions necessary to protect the subjects and, in the case of clinical medicine trials, also notify the ethics committee and the National Agency for Medicines as soon as possible.

The person in charge operates as an official with legal responsibility. According to the Medical Research Act, any person conducting medical research without the consent of the research subject, without the favourable opinion of the ethics committee, or in violation of the conditions laid down in sections 5–10 of the Act, shall be fined for a breach of the Medical Research Act.

11.2.6 Research group

Carrying out a study successfully requires an expert research group taking responsibility for its duties and for achieving high-quality results. No one can carry out all stages of a research project by himself. A good atmosphere and open co-operation are key factors in successful research.

The researchers and other staff participating in the research form the research team. Internal communication should be agreed upon before starting the study. This way all members of the team are aware of the various phases of the project.

Research groups often comprise members from outside the Institute, both Finnish and foreign. The research group has autonomy in its scientific work, interpretation of observations and in its internal organization. The heads of departments and units or other superiors can influence the scientific conclusions of the research groups only as members of the groups or as scientific experts in a comparable position.

High-quality research work can be ensured by means of seamless co-operation between the researchers and other staff, starting with the planning of research and ending with the archiving of materials. The person in charge of the study must make sure that all staff are familiarised with the research duties and, when necessary, receive adequate training in new research methods. Every member of the staff is responsible for his own schedules and results, for recording the results and for observing the quality principles and work instructions.

11.3 Research co-operation

Extensive projects are carried out in co-operation with several people and organisations. It is usual at the Institute that the people belonging to the project organisation and to the line organisation (departments, units) co-operate in the various phases of the study, often forming complex matrix organisations crossing departmental borders. In extensive field studies, most employees may be temporary research personnel.

Many projects are carried out in co-operation between various departments or jointly with the Institute and other research organisations. Many of these projects are also managed from outside the Institute. The Institute's policies must be followed also in these cases. The approval of the head of department

must be obtained before starting the part of research that is the Institute's responsibility.

The implementation of research and the duties of each party must be agreed upon with all the parties involved. These issues are also recorded in the study plan. Written contracts concerning the implementation of the project should always be made for extensive undertakings. Contracts should also be made always whenever one of the parties invests substantial resources (equipment, personnel, money) into the project. These contracts define the goals based on the research plan, the duties and responsibilities of each party, the administration and transfers of research materials generated as well as the publication of results. Also the privacy and data security aspects mentioned in the research plan must be taken into account.

Jointly financed studies and contracted studies are a special entity of projects that always require a separate contract defining the funding, deliverables and other issues (see chapters 12.3 and 12.4).

11.4 Safety at work

The employer has a legal responsibility to take care of the employees' safety at work. Labour protection aims to guarantee safe and healthy working conditions and to support the maintenance of working capacity. The labour safety programme of the Institute[20] describes how labour protection is implemented in the Institute and what the goals are for the development of work conditions.

The head of department is responsible for work safety at his department. The heads of units and other superiors must be familiar with the safety regulations and instructions. If the head of the unit observes or learns of any shortcomings in safety, he must see to it that these are repaired and removed. The employer must intervene in any undesirable behaviour, if it harms or is a risk to the health of an employee. Also, the employees must be aware of their duties and responsibilities with regard to labour protection. The head of department must report all occupational injuries and close calls in writing to the occupational safety manager.

Work safety requires co-operation between the employer and employees. The Institute has an occupational safety manager, a labour protection delegate is elected and there is a labour protection board in the Institute. The employer is represented in this co-operation by the occupational safety manager. He must be familiar with labour protection and occupational safety regulations. The employees select a labour protection delegate and two substitutes who represent the employees before the employer and the labour protection officials. All

[20] Kansanterveyslaitoksen sisäinen määräys 4/2003: Työsuojelun toimintaohjelma (Operational plan for labour protection, internal regulations 4/2003)

personnel groups work together on the labour protection board responsible for promoting safe and healthy working conditions. In addition, representatives may be elected to the labour protection organisation. The Institute has two separate labour protection organisations. The organisation of the Helsinki offices also covers the departments and units located in Turku and Oulu. The Institute's department located in Kuopio is a separate workplace in terms of labour protection.

The best way to prevent accidents is to familiarise all employees properly with their duties and with the protection and rescue instructions of the Institute.

Some of the risks related to the work at the Institute include allergy risks in animal experiments, the risk of infection due to exposure to biological factors during sample collection and sample processing (HIV, hepatitis), needle stick injuries, working with carcinogenic substances and dangerous chemicals, working with radioactive materials, risk of explosion and fire in laboratories where gases and solvents are used, inadequate electrical safety of equipment and ergonomic risks in laboratory and computer work. According to studies, psychological stress is caused by hurry and external schedules, unclear division of duties and work descriptions, temporary employment, poor leadership and management as well as discord and pressure among colleagues, for example. All of these factors are present also in the Institute, but probably not more than elsewhere. Some problems related to the facilities include poor indoor air quality, lack of space and disorder adding to the risk of accidents. The perceived poor indoor air quality is a most difficult problem since the basic reasons for this can often not be identified even in the most thorough studies.

12 RESEARCH FUNDING

12.1 Sources of funding and research strategy

The Institute implements its research strategy and plan of action by means of both public funding and cost-sharing. In addition, the Institute may, under certain conditions, carry out contracted research for clients.

External funding covers approximately 40% of all of the Institute's costs. External funding is usually necessary in order to carry out research. The Institute's policy is to secure as much external funding as possible to guarantee the implementation of its action plans. The Institute encourages its researchers to apply for external public utility funding. Success in the competition for securing funding is also a good indication of the quality of research. Some of the drawbacks of external funding are that it is often only available for the short term, and securing funding and reporting on it take up an increasing part of the senior researchers' working hours.

When applying for external research funding, the head of department is responsible for making sure that the implementation of the action plans is not endangered. When applying for funding, one must make sure that the activities of the financier do not conflict with the goals of the Institute, thereby endangering the Institute's credibility and reliability. The Institute considers that co-operation with businesses is essential. When working with industrial or commercial companies, the integrity and impartiality of the Institute must remain intact. The head of department and, when necessary, the Director General must therefore participate already in the early preparations for co-operation projects.

12.2 Permission to acquire financing, signing of the financing application and research contract

External financing can expand the actions of the Institute and tie up the Institute's resources for extended periods of time. Therefore, the permission of the head of department must be obtained before starting to apply for external financing in order to guarantee that the project has enough support within the Institute.

According to the Institute's rules of procedure, the head of department shall approve funding applications and commitments to perform a task at the Institute, made on behalf of the Institute. Funding applications made to the European Union or TEKES are an exception to this (both require the signature of the approved signatory of the Institute), as do matters concerning far-reaching and significant funding that have to be resolved by the Director General. The

internal regulations on external funding and contracts[21] give more detailed instructions on the applicable procedure.

A researcher or research group usually applies for funding on behalf of the Institute. Funds are granted to the Institute, not to an individual department or researcher. External financiers usually grant funding to the researcher or research group mentioned in the research plan under the assumption that the person or group works in the Institute.

If, under special circumstances, a researcher applies for a personal grant in his own name, he must make sure that the Institute does not object to using the grant for work carried out at the Institute. An internal regulation on personal grants is available 4/2000[22].

Funding is applied for research of significance to the strategy of the Institute. Funding is usually only available for causes that the funding organisation in question considers important. Some financiers (including the Academy of Finland and TEKES) have in recent years started to focus their funding on specific research programmes. Funding can be applied from these programmes provided that the programme supports research in accordance with the Institute's research strategy.

The funding application, abstract of the project plan and the project plan should be as clear as possible. All information must be accurate, the subject matter must be important and the relevant literature must be covered. The expertise of the research group should be communicated convincingly. As a good presentation style takes years to develop, one should ask for help and guidance from colleagues with more experience in this respect.

Most financiers pay particular attention to the hiring of research staff and to supporting further education. Funding should therefore be applied especially to these purposes. On top of the salary expenses, the implementation of every research project causes approximately 40–45% of additional costs that should be taken into account in the calculations. Theseinclude the cost of facilities, goods and services as well as the salary costs of other personnel, and they should be included in the funding applications. The Academy of Finland does nowadays grant some funding for overhead costs (12.5%), but many other public-utility organisations do not. They do, however, fund the specified salary costs of other staff. When budgeting for research partly funded by a private company, the Social Insurance Institution of Finland (Kela) or the Ministry of Social Affairs and Health, these costs should be included in full.

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[21] Kansanterveyslaitoksen pysyväismääräys 6/2001: Ulkopuolinen rahoitus ja sopimukset (External funding and contracts, standing regulations 6/2001)

[22] Kansanterveyslaitoksen sisäinen määräys 4/2000: Kansanterveyslaitoksessa noudatettava politiikka henkilökohtaisten stipendien tai muun rahoituksen vastaanottamisessa ja seuraamisessa (The Institute's policy for receiving and monitoring personal scholarships or other personal funding, internal regulations 4/2000)

The Institute's project tax, or administration fee, (15%) should be taken into account. It usually applies to funding received from other sources than the Academy of Finland.

The funding contract is signed by the Director General on the basis of the written favourable opinion or presentation of the head of the department in question.

12.3 Shared-cost research

Shared-cost research has the following characteristics:

- the goal of the research is of general interest,
- the research results are the property of the Institute, they are public and the funding organisation receives no special rights to them,
- the direct goal of the research is not to develop a product or method for commercial use, although financing from TEKES, for example, can be an exception to this rule,
- the research is a part of the Institute's own research programme;
- significant amounts of the Institute's own budget financing is also used for the project, and
- the results are published.

The Institute only accepts research funding granted to it. This means that the Institute must be marked as the recipient of funds in the decision to grant the funds and a party or member of the research consortium as the recipient in funding contracts.

12.4 Contracted research

Contracted research is a business transaction between the Institute and the client, made at the initiative of the client and based on its interests. For the Institute, contracted research is work that cannot be supported by means of budget funding. Value-added tax applies to contracted research. Contracted research, too, often includes use of the Institute's expertise in the work carried out according to the requirements of the contract. Contracted research must be in line with the Institute's research strategy. A specific instruction is available for contracted research at the Institute[23].

[23] Kansanterveyslaitoksen pysyväismääräys 6/2001: Ulkopuolinen rahoitus ja sopimukset (External funding and contracts, standing regulations 6/2001)

12.5 Budgeting and financial monitoring of research

The head of department is responsible for the finances of research activities at his department at unit- and research programme -level as well as for the finances of individual studies as part of the department's finances.

A separate budget must be prepared for the funding applications or funding contracts for external funding as well as for targeted funding granted by the Director General. Both the type of research and the funding organisation define how the budget should be prepared.

The Institute's internal regulations on external funding and contracts (6/2001) give detailed instructions on how the relevant cost items should be calculated. Attached are cost estimate sheets for shared-cost contracts [24] and for contracted research [25]. The methods for calculating direct and indirect labour cost and overhead costs, for example, are different in these sheets. Also the Institute's project tax, or administration fee, and VAT charged by the state are calculated in different ways in these research types. All the costs of each research project should, in any case, be taken into account in total, not just the cost of hiring a researcher for the work.

Depending on the financier a detailed budget calculation according to the financier's guidelines may be required for the funding application or agreement. Separate internal regulations (6/2001) are available for procedures concerning the Academy of Finland and TEKES. Separate regulations are also available for the cost calculation of EU-funded projects. EU (Dg Sanco) grants for R&D projects use a different method of cost calculation than for research projects. It should be kept in mind that many funding organisations change their own guidelines often, sometimes annually. It is important that the funding organisation's currently applicable guidelines are adhered to. Personal grants transferred to be managed by the Institute can be accepted as shared-cost financing [26].

The research services of the financial unit assist in matters related to grant applications.

The head of department appoints the person in charge of monitoring the budget of the project.

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[24] Kansanterveyslaitoksen pysyväismääräys 6/2001: Liite 1: Yhteisrahoitteinen rahoitussopimus (Standing regulations 6/2001, Appendix 1: Shared-cost funding agreement)

[25] Kansanterveyslaitoksen pysyväismääräys 6/2001: Liite 2: Maksullinen tilaustutkimus (Standing regulations 6/2001, Appendix 2: Contracted research)

[26] Kansanterveyslaitoksen pysyväismääräys 4/2000: Kansanterveyslaitoksessa noudatettava politiikka henkilökohtaisten stipendien tai muun rahoituksen vastaanottamisessa ja seuraamisessa (The Institute's policy for receiving and monitoring personal scholarships or other personal funding, standing regulations 4/2000)

Depending on the sources of financing, all studies usually have several internal project accounts (ESKO), either belonging to an existing larger research programme or to a programme founded for the research in question. When the funding for the project has been cleared (research or funding agreement with a pharmaceutical company, the Academy of Finland, the EU or other source), the secretary in charge of monitoring the research budget announces the name of the project to the financial unit for opening an ESKO for the project. The budget of the ESKO equals the sums paid by the financiers. The study budget is monitored by means of reports generated by the Institute's financial monitoring software. The sums mentioned in the contracts are charged from the financing organisations as specified in the invoicing schedule. Some organisations require interim reporting before the payment of each batch. Their guidelines must be followed.

12.6 Reporting to financiers

The financing organisations have various requirements for reporting. Some require interim reporting, while others only require final reports. In any case, the report should describe the progress of the project, the results achieved and how the funds have been used. Information on the usage of funds is available in the ESKO bookkeeping unless the financier requires even more detailed information.

PART B.

CHARACTERISTICS OF SOME RESEARCH TYPES

13 CHARACTERISTICS OF ANIMAL EXPERIMENTS

13.1 General

The National Public Health Institute uses animal experiments in several types of research, including research of infectious diseases, chronic diseases and the Finnish disease inheritance as well as research into alcohol and drug dependence and the effects of the environment on health. Animal experiments are only used for obtaining information that is important for the promotion of the population's health.

Animal experiments are managed from a centralized location (animal experiment unit). These services can also be delivered as internal animal services of a department such as the facilities of the Department of Environmental Health. The services comprise the acquisition of animals for research purposes, either as own production or by purchasing of animals, basic care of animals, carrying out the experiments as agreed, veterinary care of the animals and reporting the use of animal experiments to the provincial government as specified by EU. The animal experiment unit also takes care of the administration of the work of the statutory animal experiment committee.

13.2 Supervision of animal experiments

Animal experiments are regulated by legislation and the regulations of various authorities. Furthermore, also EU legislation is binding on Finland. Finland has also agreed by decree to comply with the animal experiment agreement of the European Council. The Ministry of Agriculture and Forestry and provincial governments are responsible for the supervision. The legislation and regulations apply to the use of all vertebrates in scientific research. In addition to rodents and rabbits, supervision covers livestock and wild animals, among others. The provisions of the Gene Technology Act and the Gene Technology Decree must be taken into account when using genetically modified animals.

Animal experiments are regulated by the following acts, decrees and guidelines:

- Animal Protection Act 274/1996, amendments 1194/1996, 954/1998, 662/1999, 891/2001 and 220/2003,
- Decree on Animal Experiments 1076/1985, amendment 395/1996,
- Decree on the Implementation of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, No. 85/90. The European Convention of the Council is published in the Statutes of Finland under number 1360/1990,

– The OECD guidelines concerning the investigation of the safety of chemicals and GLP activities 92/69/EEC, 87/18/EEC and 88/320/EEC, as approved by the European Union,
– Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes,
– Gene Technology Act 377/1995, amendment 490/2000,
– Gene Technology Decree 821/1995, amendment 491/2000.

Authorisations are needed for all animal experiments. The following authorisations are required: 1) authorisation for the Institute, 2) authorisation pertaining to the competence of the researcher, 3) animal experiment authorisation.

Authorisation for the Institute

The Institute has to have an authorisation to conduct animal experiments. The animal experiment unit applies for these authorisations. Authorisation for the Institute is applied from the provincial government. Authorisation is conditional on the appropriate facilities and equipment, competent people in charge of animal experiments and the availability of veterinary services. The animal experiment unit of the Institute operates under authorisation number 1068/712–86. The facilities of the animal experiment unit have been notified to the Board for Gene Technology.

Competence

In order to be able to apply for an animal experiment authorisation and conduct or supervise animal experiments, the researcher must have certain qualifications. These include a medical or veterinary degree or some other appropriate university degree and successful completion of an animal experiment course. Animal experiment courses are included in the curriculum of university studies. They can also be given as postgraduate or continuing education. The contents of animal experiment courses follow the recommendations of the Federation of European Laboratory Animal Science Associations FELASA. The animal experiment committee verifies the competence of the researcher. Therefore, in connection with his first application, he must present information on his competence using a special form[27]. The person applying for animal experiment authorisation is responsible for the animal experiment. He must make sure that everyone participating in the testing has appropriate training and experience in the field. The place of work and the position of the person who applies for an authorisation must be such that they allow him to carry out and supervise the animal experiment.

[27] Kelpoisuus suorittaa eläinkokeita Kansanterveyslaitoksessa -lomake (Competence to perform animal experiments at the Institute)

Animal experiment authorisation

An authorisation must be applied for each animal experiment from the animal experiment committee of the Institute using a form [28] that is sent to the secretary of the committee. Instructions [29] for filling out the form are available at the animal experiment unit's Internet site at http://ktlwww.ktl.fi/kely/. In addition to researchers, veterinaries and animal attendants, there are also representatives of animal protection organisations and laymen on the animal experiment committee. The nomination policy and work methods of the animal experiment committee are described in the committee's regulations [30]. The Institute's animal experiment committee meets approximately once a month. The meeting dates and application deadlines are posted on the animal experiment unit's Internet site.

The animal experiment plan and application is an official document. Based on the information given in the application, the members of the committee and the authorities must be able to form a general picture of the purpose and necessity of the experiment, the detailed progress of the experiment, the animal species and number of animals needed as well as what happens to the animals during the experiment and how the applicant has taken into account the well-being of the animals.

The application is processed by the animal experiment committee supervising the area where the animal experiment is carried out. Animal experiment authorisation applications of the Institute are handled by the following animal experiment committees:

- applications of the departments located in Helsinki are handled by the Institute's animal experiment committee,
- applications of the Department of Environmental Health are handled by the animal experiment committee of the University of Kuopio,
- applications for animal experiments carried out in Turku are handled by the animal experiment committee of the University of Turku.

The animal experiment committee classifies the experiments mentioned in the applications. Any animal experiments that can cause the animal only minor pain, stress, agony or suffering of a short duration are classified as belonging to class 2. All animal experiments that may cause more severe pain or other inconvenience for a longer duration are classified as belonging to class 1. The animal experiment committee approves applications for animal experiments of class 2. In the case of animal experiments of class 1, the committee gives its opinion to the provincial government, which makes the decision on granting the authorisation.

[28] Kansanterveyslaitoksen koe-eläintoimikunta, Eläinkoesuunnitelma ja lupahakemus (Animal experiment committee of the Institute; animal experiment plan and application)

[29] Eläinkoesuunnitelmalomakkeen täyttöohje (Filling instructions for the animal experiment form)

[30] Koe-eläintoimikunnan ohjesääntö (Regulations of the animal experiment committee)

An animal experiment may not be started before receiving authorisation. The experiment must be carried out as specified in the authorisation. It is possible to apply for minor changes to an existing animal experiment authorisation, such as continuation of the authorisation or permission to use a larger number of animals [31].

The procedure for applying for changes is detailed in the animal experiment committee's regulations [32].

The animal experiment committee monitors compliance with animal experiment authorisations by requiring a final report from the researcher in charge after the experiments have been carried out or after the authorisation has expired [33].

13.3 Quality system of animal experiments

The animal experiment unit utilises a quality system including instructions concerning measures performed on animals and operational guidelines (KELY.T.) on the production and care of laboratory animals as well as on working in animal laboratory facilities. These instructions can be found on the animal experiment unit's Internet site. In addition to the regulations of the authorities, also the international recommendations of laboratory animal and science organisations concerning the arrangement and carrying out of animal experiments are observed in the instructions.

13.3.1 Working in the animal laboratory facilities

The animal laboratories of the Institute are structurally tight with pressure ventilation or negative pressure ventilation. The animals are kept in a controlled environment. The protection of animals and people from disease-causing microbes requires that all movements of persons and goods are subjected to strict hygiene.

The animal laboratory facilities are always locked. A personal pass must be obtained for entering and working in the facilities of the animal experiment unit [34]. The head of the animal experiment unit issues this pass. A pass can be given to a person who is familiar with moving about and working in the animal laboratory and uses protective clothing (KELY. T10). The movement of persons is also restricted by quarantine, meaning that a person may not enter the animal laboratory for 2–5 days after visiting the animal laboratory of another institute.

[31] Eläinkoeluvan muutosesitys (Application for an amendment to the animal experiment authorisation)

[32] Koe-eläintoimikunnan ohjesääntö (Regulations of the animal experiment committee)

[33] Raportti eläinkoeluvan toteutumisesta (Report on the implementation of the animal experiment authorisation)

[34] Kulkulupahakemus (Pass application)

People working with laboratory animals must take into account that they are exposed to animal allergens in spite of efficient air-conditioning, a high level of hygiene and the use of protective clothing and a face-mask.

13.3.2 Quality of laboratory animals

The reliability of animal experiments requires that the animals meet certain general quality criteria. The laboratory animals are kept in facilities where the temperature, air-conditioning, relative humidity and lighting rhythm are standardised. The composition and purity of the feed given to the animals are controlled. The equipment in the cages must be such that the animals have enough space (as recommended) as well as the possibility to engage in species-typical behaviour (shelves, hiding places, chewing sticks, etc.). The production of laboratory animals must be adequate as it influences the genetic quality of the animals. The health and microbiological quality of the animals are controlled on a regular basis. The monitoring results of laboratory animal populations bred in the animal experiment unit can be found on the unit's Internet site. Special attention must be paid to not using any animals known to carry a pathogenic microbe. This might have a negative influence on the reliability of the experiment.

13.3.3 Ordering of laboratory animals and compilation of statistics on the use of animals

The need for laboratory animals is met by means of production in the Institute's own facilities or by buying the animals from a breeder. The researcher sends a written animal order form to the animal experiment unit[35]. Also animals purchased from third parties must always be ordered via the animal experiment unit regardless of whether the supplier is a commercial company or a partner in another research institute. The veterinary service of the animal experiment unit controls the microbiological quality of the animals by requiring appropriate health monitoring reports from the supplier.

The animal experiment unit uses the animal order forms to compile EU statistics on the use of laboratory animals for the provincial government. In the animal experiment unit, all information regarding the use of laboratory animals is recorded in the Ketku data system. This system classifies the use of laboratory animals according to the country of origin of the species, EU classification of use, animal experiment authorisation and animal experiment class, for example. The animal experiment unit also keeps a register of the genetically modified animal populations kept in its facilities. For this purpose, the researcher must notify the animal experiment unit of the animal population being tested, using the form "Report on the use and keeping of GM animals" available at the animal experiment unit.

[35] Eläintilauslomake (Animal order form)

14 CHARACTERISTICS OF CLINICAL SAMPLE STUDIES

14.1 General

Clinical sample studies (laboratory studies) are needed in various types of research and expert tasks, in the Institute as well as in biomedical research and population-based research. Scientific laboratory studies and methodological research are carried out in many areas of laboratory research. The research and analysis subjects may include humans, animals, tissues, cells and genes, bacteria, viruses, other organisms, antibodies and various substances borne by or found in the air, water and soil. According to the methods used, research can be divided into chemical, biochemical, toxicological, microbiological, immunological, molecular biological and physiological as well as clinical-physiological research. All laboratory activities share many characteristics, but they also have differences due to the research subjects and methods. In the following, special emphasis is placed on sample collection and storage, procedures increasing the validity of laboratory results as well as sample management.

The senior researchers guiding research and working as colleagues take care of training for scientific work done at the laboratory.

Many of the Institute's laboratories are national, and some are also international reference laboratories, working at the forefront of science. Accordingly, special requirements apply to the Institute's laboratories. The best possible competence and exceptional care are required from them. The best possible competence is only achieved by maintaining and developing one's professional skills and continuously keeping up with progress in one's own research area, as well as by applying new information to one's work. Customer service and advice are also a part of laboratory work.

Successful research requires that the researchers of the Institute are familiar with the possibilities of laboratory studies at the Institute.

When planning a study, one should review the experience and skills of all participating researchers and other staff also as they pertain to laboratory research. The plan must naturally include the results sought for, the laboratory methods and the areas of responsibility of the persons involved. If the research team does not have enough expertise, guidance should be obtained from elsewhere, such as from the laboratories participating in the project. Before starting the actual work, the person in charge of the study is responsible for familiarising all employees with the methods used.

14.2 Quality assurance

The quality assurance of the laboratories was previously largely based on the methods that the laboratories had developed for their own use over the years and on generally required scientific control methods. Consequently, the level of quality assurance varied greatly between the various units. We have now moved on to standardised quality assurance or accreditation.

Good Laboratory Practice (GLP) is a quality system followed in research other than clinical and environmental safety research. The OECD GLP principles (OECD Principles of Good Laboratory Practice, Paris, 1997) are observed in studies whose results are used in the registration or approval of medicines, pesticides, food and feed additives, cosmetics and veterinary products as well as in the monitoring of industrial chemicals.

In Finland a laboratory following the GLP principles may apply from the National Product Control Agency for Welfare and Health (www.sttv.fi) for approval as an authorised testing laboratory if the laboratory studies the safety of chemicals or medicines (Chemicals Act 744/1989, as amended). The GLP controls of test laboratories conducting safety research on medicines are done by the National Agency for Medicine.

The International Organization for Standardization (ISO) has written several guidelines for laboratories, such as "ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories." This international standard has been approved as a European standard as well as a Finnish national standard (SFS-EN ISO/IEC 17025). National accreditation bodies, FINAS in Finland, evaluate the competence of laboratories to operate and produce accurate test results according to the principles set out in this international standard. The operational principles of laboratory studies are described in more detail in the quality manual located on the document server. All laboratories of the Institute must develop their functions according to the quality manual. The laboratories of the Department of Environmental Health use their own quality manual.

The quality management system of a certified organisation must meet the criteria of standard SFS-EN ISO 9001 "Quality management systems. Requirements". Certification according to ISO 9001 does not as such prove that the organisation is able to produce technically valid and reliable data and results. The focus of an independent third-party evaluation is on compliance with the standard-based quality management system.

14.3 Requirements for valid and reliable laboratory work

14.3.1 Personnel

The management is responsible for the following:
- specification of the laboratory's quality level,
- writing the document describing the functioning of the laboratory as a supplement to the quality manual,
- compliance with the quality assurance and steering rules,
- writing and following written instructions that are important for the functions,
- hiring competent staff and providing sufficient training and education;
- giving clear information on the responsibilities and rights of the employees and implementing them,
- participation by staff in the development of functions.

The technical person in charge or the researcher in charge of the study is responsible for the following:

- that the studies are based on the study plans,
- that detailed written instructions are available for the functions and that the instructions are followed,
- that the employees understand their duties and are competent to do them,
- that the regulations concerning sample collection, sample receipt, recording and storage are followed,
- that regulations on safety at the workplace are followed,
- that there is sufficient internal quality control,
- that the team participates sufficiently in external quality assessment,
- that research results are always reported, that all results are recorded and that the results are archived,
- that the requirements and wishes of partners and clients are known, specified in writing and followed.

The persons carrying out the tasks are responsible for:

- following the instructions, using specified analysis methods and generally accepted methods of operation,
- recording the laboratory operations as agreed,
- observing the work safety regulations,
- reporting any special issues they have noticed in their work.

14.3.2 Equipment

All equipment must be suitable and sufficient for the tasks.

A person in charge of the device and a substitute when needed are nominated for each device that is essential to the testing.

The person in charge of the device and the substitute must be familiar with the principle of operation and the use of the device. They make sure that

– all maintenance tasks and calibrations of the device are carried out according to the agreed schedule,
– a defective device is not used and that the defects are repaired.

A device folder is written for every piece of equipment and stored near the device. The device folder includes instructions concerning

– how to take the device into use,
– using it,
– calibration,
– performance monitoring,
– maintenance,
– defect repair,
– and files concerning these matters.

Only persons who have been successfully trained in the use of the device and agree to work as specified in the device folder are allowed to use a device.

14.3.3 Facilities and environment

The laboratory must have suitable facilities that may only be used for the agreed purpose. Access surveillance must be organised in a way that guarantees the confidentiality of personal data and the integrity of samples and results.

Variations in the environmental conditions must not affect the measurement results. Incompatible operations are not carried out in the same laboratory room. The environmental conditions are monitored and controlled. When necessary, the surveillance results are documented.

14.3.4 Methods, validation of methods and traceability of measurements

Accurate and suitable testing methods are used for analyses.

Clearly identified written instructions are given for all methods. The instructions describe

– the kind of circumstances where the method is used,
– the determinations to be made as well as the measuring ranges,
– the necessary equipment and requirements for technical performance,
– the necessary reference norms and reference materials,
– the requirements concerning the environmental conditions, the time needed for settling,
– the procedures used, including the marking of objects, handling, transportation, storage and preparation,

– the check-ups to be done before starting the work,
– the controlling of the equipment and, when necessary, calibration and tuning of the equipment before each use,
– the methods used for recording the results and observations,
– all applicable safety measures,
– the criteria and the requirements for approving or rejecting the results,
– the data to be saved as well as methods for data handling and presentation,
– the uncertainty of measurement results or the factors affecting the validity of the results.

The suitability of the method must always be validated before use. The extent of validation depends on whether the method is

– an international standard method,
– a self-developed method,
– a method taken into use based on a scientific publication produced elsewhere or
– a commercial method.

The measurements are validated according to national or international measurement standards by means of suitable calibration of the equipment.

Traceability to national or international measurement standards is ensured for equipment that directly measures base quantities such as mass, length, temperature and time, or simple derived quantities, such as area, volume and pressure.

The traceability of chemical analyses is shown by means of reference substances. The reference substances are used for proving the accuracy of results, for the calibration of equipment and methods, for the monitoring of the laboratory's performance and for the validation of methods. The use of reference substances as transfer standards enables the comparison of various methods. Reference substances should be used whenever possible.

14.3.5 The sample

Sample collection is the decisive step in the analysis chain. Sample collection and handling and sample analysis are independent events. Therefore, the variations due to these factors are cumulative. If, for example, the relative standard deviation of sample collection is 5% and that of analytical assay is 2%, the total relative standard deviation equals 5.4%. In this example, the reliability of the end result can be enhanced significantly only by developing the sample collection method.

A plan and instructions for sample collection and sample sending should be made in writing before starting research. The following factors should be taken into account:

– the goal and purpose of the analyses to be made using the samples,
– circumstances of sample collection (including fasting),
– the technical solution and method for obtaining a suitable sample,
– choice of sample collection sites,
– size/quantity of samples,
– separate or composite samples,
– sampling frequency,
– sampling times,
– whether there is any information available from previous research that could be used as a basis for planning (such as unit costs, variances between the various stages of work).

The sample collection plan and sample collection programme ensure, among others, the responsible use and technically correct application of general sample collection instructions. It is also important to evaluate the error sources of sample collection and their effect on test results.

The following data are documented concerning sample collection:

– sample identification data,
– research subject and sample collector,
– sample collection and sending instructions,
– the customer and recipient of the sample,
– sample collection date and time with the necessary precision,
– the purpose of the sample,
– sample handling operations that took place,
– sample handlers (organisation and/or person),
– number of samples,
– specifics of the sample collection environment, if necessary,
– sample handling times and delivery times, ambient temperature and/or humidity if necessary (during transportation, handling and storage),
– packaging method,
– archiving time of the samples.

All information related to the sample and needed for the analyses and measurements should be documented. Depending on the test, they may include the pre-analytical data of clinical sample collection describing the patient's status at the time of sample collection, such as the following:

– information concerning analyses that require fasting,
– information concerning forbidden foods and medication,
– restrictions on the use of substances (such as smoking, alcohol),

– the effect of other examinations (such as isotopic examinations),
– use of medication before the analysis of medicine levels,
– the time of sample collection (when the time of day has an effect on the result), and
– the position of the patient and the effect of physical exercise. The sample is sent and stored in such a way that,
– there is no contamination or leakage from the storage container,
– the sample container can be handled without the danger of chemical or microbiological hazard,
– the integrity of the sample is not at risk.

14.3.6 Evaluation of the validity and reliability of test results

The validity of the test result is affected by the methods, the equipment, the procedures, the competence of the staff and internal quality management as well as feedback from quality assurance. An estimate of the uncertainties related to the measurement process should accompany the result.

Regular and comprehensive quality assurance is used to monitor the accuracy of the tests. Quality assurance includes, among other things:

– the regular use of validated reference substances,
– the use of own validated reference substances,
– the use of control cards (see below),
– yield tests (the effect of sample matrices on the total quantity of the substance examined),
– the repetition of tests,
– the re-testing of samples, and
– participating in comparisons between laboratories.

The purpose of the quality assurance methods is to remove all major and systematic errors from the results and to enhance their repeatability by means of enhanced detection of random errors and by selecting efficacious corrective measures that prevent the recurrence of the same error.

Control cards are important in the laboratory's internal quality control. A control card is a statistical device for monitoring methods used for recurring analyses. A control card is based on the random variation of results according to the standard normal distribution. A set of control samples is analysed with each sample set and the results are plotted on the control card. If the results fall within the set limits, the method is under control in this respect. If the limits are exceeded, the reasons for this are investigated and removed. The control card is designed to give a quick indication of disturbances. A Shewhart-type control card is commonly used in laboratories. In this type of card, the values of control samples are plotted as a function of time. The following general rules are followed:

1) The result of the control sample falls within ± 2 s of the alarm limits. The analysis is under control in this respect.
2) The result of the control sample exceeds the alarm limit by ±2 s. There are possibly disturbances in the analysis. This requires preventive measures.
3) The result of the control sample exceeds either alarm limit by ±3 s. This refers to a random error. If possible, the analysis should be stopped and the source of error should be tracked down. The results are not reported. The analyses are repeated after correcting the error.
4) Four successive results of control samples exceed the same alarm limit by ± 2 s or successive results exceed various alarm limits by + 2 s and – 2 s. If possible, the analysis should be stopped and the source of error should be tracked down. The results are not reported. The analyses are repeated after correcting the error.
5) Ten successive results fall on the same side of the average value. This is an indication of a systematic error. If possible, the analyses should be stopped and the source of error should be tracked down. The results are not reported. The analyses are repeated after correcting the error. When done correctly, the quality monitoring of results will with high probability give an indication of the validity and reliability of the results.

14.3.7 Maintaining the quality of test results over time

The validity (level) of test results must be maintained in long-term or repeated clinical and population-based research. At the Institute, this typically applies to the population health monitoring done every 5–10 years. The customary internal quality assurance methods are of little use. The most reliable way is to compare your own results with the analysis results of an external laboratory using a reference method. At the Institute, an example of this is to include the serum cholesterol analyses in the US CDC quality monitoring system. If no such system is available, participating in an external quality assurance system is useful.

14.3.8 The use of IT in the laboratories

The quality assurance system of the laboratory utilises computer programs and systems. The validity of all functions of a new computer program should be checked by comparing them with results obtained from a similar manual method (or a suitable previously used program) before starting to use the program. An error-free transfer of manual data into the computer should be assured by means of proofreading, for example.

14.3.9 Documentation and reporting

The documentation must be extensive enough to allow the tracking down of the stages of work. This way, the tests can be repeated in a similar way, and error sources can be tracked down easily when necessary.

The documentation and reporting include, among others:

- a description of the operational principles,
- a description of the analysis method,
- job descriptions of the staff,
- detailed descriptions of the stages of the work entered in the laboratory work log,
- coding and registration of incoming samples,
- the primary results and their processing in the laboratory,
- descriptions and results of internal quality control and external quality assurance,
- the reporting and publishing of results, and
- the archiving of samples and documents.

15 CHARACTERISTICS OF CLINICAL RESEARCH

15.1 General

Clinical research is conducted on humans. It often involves an intervention affecting the integrity of a person through sample collection, a surgical operation or by giving vaccinations and medication, for example. Observational studies in connection with normal treatment are an important group of clinical studies. The majority of clinical research concerns medicine studies, vaccination studies and studies on health promotion. Studies on the use of medical devices and equipment are also included in clinical research.

Clinical research is nowadays strictly regulated by legislation and the authorities. In addition, the International Congress of Harmonisation (ICH) has approved the principles of clinical research.

15.2 Good clinical research practice

All clinical studies must be planned, carried out and reported according to the ethical guidelines which are in accordance with the World Medical Association's Declaration of Helsinki, good clinical research practice (GCP) and the applicable national legislation and regulations.

Clinical research must be scientifically justified and each study must be described in a clear, detailed study plan.

The medical treatment or examinations of patients and research subjects as well as any other medical procedures must always be based on the decisions of a doctor or a dentist.

The Act amending the Medical Research Act (295/2004) also contains regulations concerning the specific requirements of clinical medicine trials. In the Act, clinical research refers to interventional research on humans in order to study the effects of a medicine as well as the absorption, distribution, metabolism or secretion of the medicine in the human body. In the Medicines Act, a medicine is defined as a preparation or a substance that is designed for healing, alleviating or preventing a disease or its symptoms when used internally or externally. Preparations or substances designed for the examination of health or the cause of disease, or for the restoration, reparation or adjustment of vital functions when used internally or externally are also considered medicines.

Sufficient pre-clinical and clinical data supporting the decision to begin the study must be available concerning the investigational product. The investigational products should be produced according to good manufacturing practice (GMP). The products may only be used as described in the approved research plan and for the purpose described in the plan.

Voluntary informed consent should be obtained in writing from every patient or subject prior to clinical trial participation. No examinations may be carried out before obtaining the informed consent, including stopping of regular medication before starting the investigational medication (wash-out period) and all, even the most minor, laboratory sample collections included in the research plan.

An exception applies to critically ill patients when no consent can be obtained due to the urgency of the situation and the health status of the patient. In such cases, the examination must be medically necessary and it must be of immediate benefit to the patient's health. Only temporary measures are allowed without an appropriate consent. The informed consent must be obtained as soon as possible. If a person participating in a clinical medicine trial is unable to give his consent to clinical medicine research, he cannot be a research subject unless his next of kin or other person close to him or his legal representative has given consent to participate before the beginning of the study after receiving information on the nature, purpose, consequences and risks of the clinical trial in question. The consent must follow the assumed will of the research subject. This means that a clinical medicine trial may not be carried out as a so-called emergency study unless the patient or his next of kin or another person close to him or his legal representative has given consent to participate before the beginning of the study.

More detailed instructions for clinical medicine trials done in Finland are given in the National Agency for Medicines' regulations "Clinical Trials on Medical Products in Human Subjects" (http://www.nam.fi/). EU directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use gives instructions concerning clinical medicine trials.

15.3 Authorisations, contracts and notifications concerning clinical research

In addition to the authorisations described in chapter 7.5, various special authorisations and notifications are needed for clinical research, depending on the research topic.

A clinical medicine trial may only begin after the National Agency for Medicines has given the authorisation required in the Medicines Act or has not announced any obstacle to the beginning of the trial within 60 days after receiving an appropriate prior notification. Relevant changes to the study plan must also be notified to the National Agency for Medicines. The trial may not be continued according to the adjusted plan before it has received a favourable opinion. The client of the clinical medicine trial must ensure that there is a valid insurance or other form of security covering the client and the researcher.

The client must notify the National Agency of Medicine and the ethics committee also when a clinical medicine trial is cancelled, interrupted (within 15 days of the interruption, giving reasons for the premature ending) and terminated (within 90 days), as well as of the results of the trial (within one year of the trial's end). During the clinical medicine trial, the client must notify the National Agency for Medicines and the ethics committee of all unexpected serious adverse drug reactions to the investigational product within the specified period. It must also provide once a year a list of all suspected serious adverse drug reactions and a declaration concerning the safety of the research subjects.

Instructions for making these notifications can be found in the National Agency for Medicines' regulations 2/2004[36]. The report forms can be found on the EudraCT database Internet site. The plan is to record in the near future the most relevant information in the European EudraCT database used by the authorities. The notifications to the National Agency for Medicines are done by the client, unless the researcher and the client have specifically agreed on another arrangement. In this case the National Agency for Medicines must be informed briefly of the new distribution of tasks.

Every batch of vaccines used for clinical vaccine trials must be approved by the National Surveillance Unit of Vaccines and Sera (ROVA) before using the batch. The National Agency for Medicines also does batch monitoring of plasma-based blood products.

Clinical trials of medical devices and equipment must be notified to the National Agency for Medicines before starting the trial, if the purpose of the trial is to show the conformity of the device or equipment before introducing it to the market or taking it into use, or if the device or equipment or its use has been changed and insufficient research data is available on the effects of the change. In certain cases, the notification must be given 60 days before starting the trial. Relevant changes to the research plan, cancellation, interruption and results of the trial as well as any serious risks observed during the trial must be reported to the National Agency for Medicines. At the end of the trial, the client must supply the National Agency for Medicines with a final report signed by all researchers who participated in the trial.

Instructions for reporting are available in the National Agency for Medicines' regulations 1/2001[37]. A report sheet[38] available in electronic form from the

[36] Lääkelaitoksen määräys 2/2004: Ihmiseen kohdistuvat kliiniset lääketutkimukset (National Agency for Medicines' regulation 2/2004: Clinical trials of medicinal products in human subjects)

[37] Lääkelaitoksen ohje 1/2001: Terveydenhuollon laitteiden ja tarvikkeiden kliiniset tutkimukset (Clinical trials of medical devices and equipment, National Agency for Medicines' guideline 1/2001)

[38] Lääkelaitoksen lomake Ilmoitus kliinisestä laitetutkimuksesta (Report of a clinical device trial, National Agency for Medicines form)

Agency must be used. The report must be signed by the person responsible for starting and carrying out the clinical trial. The client shall send it with appendices to the Agency.

If x-ray imaging is used in clinical research, safety authorisation[39] of the Radiation and Nuclear Safety Authority of Finland must be obtained as specified in the Radiation Act and Radiation Decree.

15.4 Insurance coverage

All therapeutic trials on patients and healthy volunteers are covered on the basis of the Act on Patient Injuries (585/86) and by pharmaceutical injuries insurance.

[39] Säteilyturvakeskuksen lomake STUK 32.01 Hakemus turvallisuuslupaa varten (The Radiation and Nuclear Safety Authority of Finland form STUK 32.01; Application for safety authorisation)

16 CHARACTERISTICS OF POPULATION-BASED RESEARCH

16.1 General

Population-based research refers here to all research concerning a large group of people or data on a large group of people. Based on the research methods and areas, they can be classified as medical, social or behavioural research, for example, and based on the general research approach, as epidemiological, health economical or health care research. The largest research groups at the Institute are epidemiological studies and health monitoring studies.

The characteristics of epidemiological and other comparable population-based research are connected to the research designs and practices, sources of data and methods. These studies are often very extensive and last a long time. Typically, information is gathered on disease and on personal and environmental factors that predispose one to disease.

Information is often collected from the research subjects themselves. In these cases, the same approaches and regulations apply as with clinical research (see chapter 15, Characteristics of clinical research). Some studies are based on personal data received from other sources. In those cases, also other aspects of data security must be taken into account when obtaining and using the data.

Several guidelines supporting this manual are available on Good Epidemiology Practices (GEP), including Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research[40], Guidelines for Good Epidemiology Practices for Drug, Device and Vaccine Research in the United States, International Society for Pharmacoepidemiology 1996[41], Good Epidemiological Practice: Proper Conduct in Epidemiologic Research, IEA[42].

16.2 General principles of population-based research

All principles described in the various chapters of this manual also apply to population-based research. The following principles, for example, should be followed:

– the staff must have sufficient training and experience,

[40] Journal of Occupational Medicine 1991;33:122

[41] http://www.hsph.harvard.edu/organizations/ddil/gep.html

[42] http://www.Dundee.ac.uk/iea/GoodPract.htm

– the facilities, equipment, methods, support systems, staff and other resources must be suitable and sufficient for the research task,
– the study plan and the implementation plan based on it must be detailed and accurate. They should be the more detailed the more extensive the study is and the longer it lasts. The plan must be updated by recording all changes, the study must be carried out according to the plan and any deviations from it must be recorded. All factors concerning ethical issues, the safety of the research subjects and data protection should be recorded during the implementation stage. Also, the data collection, handling and checking stages and operational guidelines as well as the analyses of the study material must be recorded and a final report must be written.

During the active phase of the project it should be made sure that all documents and files are stored appropriately, taking into account the requirements of privacy and data security. After the end of the active phase, they should be archived as appropriate (see chapter 10, Archiving).

16.3 Ethical aspects

Ethical aspects play a special role in situations where the study subjects are so-called healthy subjects and the significance of the examinations, preventive actions, screenings or treatments to the healthy subjects or persons belonging to risk groups is not yet known. Careful consideration is needed when the purpose of the study is to examine the efficacy and side effects of early detection, disease prevention and actions directed at risk groups.

Careful ethical consideration is also needed when deciding on how to report the results of customary observational studies to the subjects. An example of a very demanding situation is the interruption of a large population-based intervention project for some reason.

16.4 Privacy issues

Research projects where the material is not classified per person but rather per group and compiled into a multidimensional table normally cause no problems to the privacy of private persons. In the case of very small subgroups (cells) consisting of less than five or ten people, it may be possible to identify a person even from the tabulated data. In such cases, privacy should be taken care of in a similar way as for personal data.

Most of the Institute's epidemiological research is based on the utilisation of data on individuals. In a large part of the studies, it is necessary to be able to identify a person also later, so that it is possible to combine data for follow-up studies, for example. A unique identification number is usually used instead of

easily recognisable personal data in order to improve people's privacy in study files used on a daily basis. A separate restricted access file is used as a key containing the identification numbers and the personal data. Also anonymous research material must be used, stored and transferred carefully, as a person can be identified even without the actual personal data, if enough other information is available.

Seroepidemiological studies and other studies based on blood samples are also carried out in population-based research. They play a crucial role in the surveillance and research of infectious disease, for example. If such samples can be identified as samples from a specific person, the same privacy principles apply as in the case of other sensitive personal data. It is especially important to inform the research subjects of what the material and samples are used for and how they are used. In communicable disease epidemiology, also anonymous samples are used for surveillance of the disease status.

16.5 Methods of obtaining data, data sources and research methods

16.5.1 Data sources, consents and authorisations

Personal data is typically obtained from the research subjects themselves or from other informants (including surveys, interviews, samples, measurements and data obtained from relatives) or from other sources, such as registers or case histories or by means of combining several sources.

An informed consent is needed when obtaining information from the research subject himself or from another informant (see chapter 6.3.1, Informed consent). The consent should also give authorisation for the linkage and use of data obtained from other sources.

Both consents and authorisations are needed in research based partially on register data and partially on data received from the subjects themselves. This applies to cohort and intervention studies, in which a part of the follow-up data is obtained from various registers, as well as to case-control studies where the cases are identified from registers or hospital records, controls are selected for them and new data is obtained by means of surveys, interviews or clinical examinations. Even when the consent of the subject himself authorises the use of data concerning him, also a supplementary authorisation from the holder of the information is often needed. Research based only on register data requires the holders' authorisations for use.

Extensive follow-up study materials collected in Finland in the 1990s or earlier are an exception. The subjects are considered to have actually consented to the use of the data for research even when no actual consent form has been used. The conditions for the use of material that has been under the Institute's

control before 2005 has been regulated through legislation. When using patients identified from registers and their controls, a suitable method of obtaining consent is for the holder of the register data to send the first letter or otherwise make the first contact.

16.5.2 Methods

In addition to general quality considerations of the methods, also other aspects similar as in clinical research exist. The research methods may not endanger the subject's health and any inconvenience possibly resulting from the methods must be reasonable when compared with the benefits. Appropriate medical competence is required when using most clinical research methods. The same ethical and safety considerations apply to the therapeutic and preventive measures carried out in large intervention studies as in the case of clinical research.

A large part of the methods are made up of interviews and questionnaires. In order to make sure that the methods are adequate and commensurate, it is useful to get thoroughly acquainted with other Finnish and international studies at the planning stage of one's own study. The contents of national health surveys and health examinations of European and several other OECD countries can be found in the HIS/HES database (http://www.iph.fgov.be/hishes/)

16.5.3 Feedback to research subjects

Population-based research often utilises measurements and analyses having clinical importance or in which the research subjects have an understandable interest for other reasons. Every research subject must receive clear personal feedback.

If the feedback includes a suggestion for further examinations or a referral, it must also include enough information for the receiving doctor or institute, and good clinical practice must be followed. When necessary, the health centres and hospitals receiving referrals must be informed in advance.

16.6 Large materials and studies of long duration

Large materials and the long duration of a study create special requirements for methods and quality maintenance, data management systems, documentation and preparedness for staff changes. The resources of an organisation requiring a large staff for a long time must be ensured even more carefully than usual.

16.6.1 Large materials

Large register data materials and large population study materials both set special requirements for data collection, checking, recording, handling, storage

and archiving. In population-based studies extensive material often means that a large quantity of data has been obtained in several stages. This requires good control of the entire material and of the details and careful planning and documentation of these phases of work, as well as a sufficiently competent staff. Population-based studies often require more data processing capacity than other research types.

16.6.2 The extent and duration of data collection in population-based research

When possible, achieving the required quality (validity and reliability) should be ensured in population-based research already before starting the actual field study. Maintaining the measurement level should be possible during the entire data gathering stage. Carrying out one or several pilot studies may be useful.

In addition to the quality of other methods, special attention should be paid to the differences between the observers and interviewers and reducing these differences, documenting them, maintaining the quality of measurements and documenting any changes in the quality. The quality of the final data also depends on validity checks before and after recording and on the validity of any classifications. Instructions, guidance and monitoring are needed.

A separate preliminary study phase, instructions, training, standardisation and recording of circumstances, calibration of equipment, parallel and repeated measurements and repeated standard measurements as well as alarms triggered by deviations are methods that should be used for the quality maintenance and monitoring of all methods as applicable. The accuracy and suitability of methods should be examined when selecting and developing them. This also includes the adjustment of questions and question series according to the purpose, environment and cultural factors.

Special attention is needed in the case of a research design based on field studies repeated on a regular basis, such as every five years. The research group may be either the same population or a new sample. The purpose is to obtain a valid picture of changes in the events under observation. The maintenance of measurement quality is a necessary prerequisite here. Sometimes this is easily done by means of standardisation of the methods, equipment and implementation instructions and by using calibrations and external standards, but often it is very difficult to maintain the quality. It may even be difficult to verify whether the original quality has been maintained or whether there are deviations.

16.6.3 Follow-up studies

Studies of incidence and causes based on the follow-up approach as well as population-based intervention studies measuring the efficacy of preventive measures and treatments usually last a long time, generally at least 5 years and

often 10–20 years or even longer. In addition to careful planning, implementation and documenting, suitable personnel arrangements are also necessary to make sure that the research project can be carried out regardless of personnel changes.

16.6.4 Non-response

Non-response has increased in population-based research also in Finland to an extent where it may compromise the validity of results. In prevalence studies the minimising of non-response and the lack of bias in non-response are very important. The goal should be set at 90–100% participation, although smaller percentages often have to be accepted. In any case, the non-response should be analysed and its effect on the results assessed. Even a non-response slightly higher than in the aforementioned goal doesn't usually cause too much harm in case-control or intervention studies, but it gravely reduces the accuracy of studies concerning the occurrence of risk factors, disease and functional limitations.

16.6.5 Multi-centre studies

Carrying out research simultaneously in several places or even in several countries sets very high demands on the organisation, plan, methods, instructions and operations. They must ensure comparability by making sure that similar methods and operations are used at all the sites. The procedures aimed at achieving and maintaining comparability and high quality and documenting related issues are especially important. If the project is carried out in several countries, there is an additional requirement concerning the equivalence of questions, interviews and other results. This requires that they are adjusted according to the circumstances and culture of each country. Unlike in other cases, clinical medicine trials carried out as international multi-site studies are evaluated centrally by the National Advisory Board on Health Care Ethics' appropriate Sub-Committee (TUKIJA).

16.7 Special features in the various stages of epidemiological research

16.7.1 Generating ideas and problem setting

The information needed must be identified during the phase of idea generation and preliminary planning. Also, the best approaches for obtaining this information should be determined. Several population study materials and many registers are available in Finland. Population-based research can be carried out more easily than in many other countries by carefully utilising these materials. During preliminary planning, the research method to be used and the materials to be utilised must be decided. Assessment should also be made of the requirements and schedule for obtaining materials from various sources.

16.7.2 Study planning

The preliminary research plan and the final study plan are written as described in this manual.

It is often useful to draft a separate implementation plan and instructions in addition to the study plan proper. This plan or a series of work and operational instructions based on the plan are the guidelines for carrying out the various stages of the project.

If an extensive project includes several sub-studies, it is a good idea to attach a separate plan of each sub-study to the study plan proper.

16.7.3 Study journal

It is recommended that a study journal be kept in projects of a long duration, for the purpose of logging the progress of the project and especially any changes to the study plan or methods, changes in personnel, equipment malfunctions, observed deviations from the plan and instructions as well as significant events influencing the project. The person in charge of the study shall organise the keeping of the journal.

16.7.4 Authorisations

The same authorisation and consent procedures apply to epidemiological research on humans as to every other type of research, but authorisations may be required from several parties for the use and combination of different data.

16.7.5 Storage and archiving of the materials

Population-based research differs from other types of research only because the materials that are collected and computer files that are compiled are very extensive and usually unique. It is rarely possible to correct errors by repeating the entire project.

16.7.6 Utilisation of data in later research

The materials used in extensive population-based studies often also form a good starting point for studying problems that were not mentioned at all or were mentioned only generally in the original study plan. It is important that the study materials can be utilised for research needs arising at a later stage. Material already collected can often provide answers also to new research problems more quickly, more easily and more economically than by carrying out a completely new study. Research work is also made more efficient when previous investments into research materials can be utilised.

In Finland, the original research group has traditionally had priority for such further research, the director of the project in question being the key decision-

maker on this issue. There are, however, examples from other countries where the materials of publicly funded projects become available to all researchers after a certain period of time. The Finnish practice may also be changing.

The principles described in this manual can also be applied to such further research. Supplementary instructions suitable for such situations are needed in order to develop practices. It may, for example, be unclear whether the situation concerns a new study that requires a complete new study plan and appropriate decisions. The head of department will decide on the interpretation after discussing the matter with the researcher and, when necessary, with the persons in charge of the unit, of the project and of the study.

It may also be open to interpretation whether or not the consent obtained originally also covers further use.

Problems may arise when defining the researchers and authors of such later research. When an extensive project lasts long, a large group of researchers usually participates in the various stages of the projects, some leaving and others joining during the project. The research organisation may also undergo changes. In any further research on the materials, however, any previous substantial work should be taken into account in a fair manner.

In addition to the possible person in charge of the new study and the persons who feel that they are members of the research group of the sub-study in question or authors of the report, also the director of the study and, when necessary, the person in charge of the research programme and the head of department should participate in the assessment in any unclear situations, in order to define the participation of each person and their right to be included as authors of the reports

17 HEALTH-RELATED BEHAVIOURAL AND SOCIAL RESEARCH

17.1 General

Central research types at the Institute include the monitoring of health behaviour, studies concerning knowledge and attitudes, studies concerning health policy as well as interventional studies on health and health behaviour. Many of these are strongly based on social and behavioural sciences, others mainly on the epidemiological research approach. The study material can be collected by means of surveys, interviews and observations, or it can be obtained from texts, documents and images. These materials may be used in connection with other observational materials.

The same quality requirements apply to behavioural and social health research as to the population-based research described earlier. The tradition of behavioural and social research includes the idea that information is based on theories, in other words that our picture of reality depends on the theories and concepts used. The theories and concepts and the methods based on them are defined already in the plan. The research project should be designed in co-operation with experts of this field.

There are recommendations and established methods for handling the material, including the handling of missing data or the rating and interpretation of scales, for example. Many of the statistical methods used are the same as in population-based research. The research questions and materials, on the other hand, may lead to using methods such as multi-level analysis or structural equation models.

The characteristics of behavioural and social research are described in more detail in the instructions finalized in the beginning of 2005 (Good research practice in health-related behavioural and social research), available in the Institute's Internet site.

17.2 Monitoring studies

The monitoring of public health, health behaviour and factors affecting them is partly based on the population samples studied annually and can be used for monitoring the trends or changes in health behaviour in the population and in population subgroups. Health Behaviour among the Finnish Adult Population (AVTK) and Health Behaviour of the Finnish Elderly (EVTK) are established monitoring studies (www.ktl.fi/eteo/avtk) utilizing mail surveys. The purpose is to produce information on the development of health and its determinants and on variation between population groups for the needs of planning and

assessing health policy. Special attention must be paid to the repeatability and comparability of the questions (with regard to different years and areas, for example). In order to reach the entire target population of the monitoring, the questions must be based on actual and continuously developing information on the habits, culture and health problems of the target population.

17.3 Studies concerning knowledge and attitudes

Health knowledge, perceptions and behaviour or the use of health services can be studied in a sample representing the entire population or a subgroup of the population. This kind of research may concern new social phenomena. Knowledge, perceptions, practices or changes in these may need to be studied (such as drug abuse or attitudes towards genetics).

17.4 Experimental research

Experimental research aiming to promote health is used to develop and evaluate suitable methods for various uses. The goal may be to change the health, the behaviour or the health-related knowledge and perceptions of the entire population or a specific subgroup. The primary target of intervention may be the entire population or a specific subgroup, a certain risk or patient group or professionals in health care.

The Institute may be the planner of the intervention, the expert in a certain field, or the party carrying out or evaluating the intervention. The effect of other environmental factors is especially difficult to isolate when studying the effects of community intervention. An example of extensive community intervention is the Ikihyvä project (www.palmenia.helsinki.fi/ikihyva).

17.5 Studies concerning health policy

Research concerning health policy can utilise social theories as a basis and apply the research methods described earlier. On the other hand, its theory and methods may also be based on the tradition of population-based epidemiological and health care research that partially draws on behavioural and social sciences. In addition to surveys and interviews, also documentation and register data are used for collecting the research materials. The results of research are used especially for analysing the effects of health policy and health care as well as other actions affecting health. Such studies carried out at the Institute include evaluating the effect of changes in tobacco legislation and related actions. A health policy evaluation of the effects of changes in the subsidies to dental care is currently in progress based on the tradition of population-based research.

18 CHARACTERISTICS OF REGISTER-BASED RESEARCH

18.1 General

Register-based research refers to research entirely based on data available in (national or regional) registers; either in just one register or by combining research data from several registers. The registers may include the identification data of persons as well, but register-based research can also be done by means of anonymous personal data or tabulated data. The combination of personal clinical data or population-based material with the data of one or several registers is sometimes also referred to as register-based research. This is also true when persons are identified from a register and additional data is obtained by means of interviews or clinical studies.

The Finnish Social Science Data Archive in Tampere has a number of registers that contain no personal identification data. A joint support centre for register research of the state's health research institutes has operated in Stakes since 2003 supported first by funding from the Academy of Finland and later by the sector research institutes and SII. Its purpose is to enhance the utilisation of registers in health research.

The possibilities for doing register-based research in Finland are basically good, as many national registers are extensive and contain information on health and disease, incapacity for work, social factors or the use of health and social services. In addition to the information from population censuses (such as education data) currently carried out entirely on the basis of registers, also tax records are available for estimating income levels, for example.

National registers are administered by various organisations. Some of the most important registers for health research include the Social Insurance Institution of Finland (SII) registers (purchases of medication, free or nearly free specially reimbursed medicines, incapacity to work, services refunded from health insurance), the National Research and Development Centre for Welfare and Health (Stakes) registers (treatment reports, malformations, cancer), the Statistics of Finland registers (population census, causes of death), the Central Pension Institute's registers (pensions for incapacity to work) as well as the registers of the National Public Health Institute and the Finnish Institute of Occupational Health.

The use of registers for research is governed by legislation and the regulations of the holders of the registers.

18.2 Characteristics of register-based research

The most important characteristics are related to the special requirements that the competent utilisation of register data sets for the researcher and to the regulation of the use of registers. Certain characteristics also derive from the large size of national registers.

18.2.1 Knowing the register

The planning of a competent research design requires that the researcher knows the contents of the register well and especially knows how to define and collect information contained in the register. Naturally, a basic requirement is that he is familiar with the methods of clinical, epidemiological or health care research. The information contents of many registers have undergone at least some changes over the years. This makes it more difficult to define information and increases the amount of computer time needed. The researcher must form an idea of how persons have been selected for a certain register, in other words what concept of health or disease the register depicts and how comprehensive it is. Sufficient familiarity with the contents can often only be obtained through long experience or by including an expert of the register keeper in the planning of the study. Based on experience, major problems in drawing up the research design and selecting the right information are caused by third-party researchers' poor knowledge of the register.

18.2.2 Regulating the use of registers

The use of registers for research and the linkage of registers for research purposes are regulated by legislation. There are obstacles due to regulations only when the legislation concerning the organisation in question sets such obstacles. The transfer of identifiable personal data is restricted especially in the legislation concerning Statistics of Finland and Stakes. In the first case, the prohibition to transfer data applies to most data, excluding data on the causes of death or on education, for example that have separately been defined as transferable data. In Stakes, strict restrictions and prohibitions apply to the use of information on social services. When the transferring of certain information is restricted, some studies can be carried out by having them done by the register keepers or by transferring combined data to the researchers where no individual persons can be identified. This method is well suited to one-time studies but less suited to situations where the risk of disease in the study population (either a sample or the entire population) should be studied by means of registers.

Although the regulations concerning the transferring of data vary between organisations, they focus around the possibility to transfer personal data for a specified purpose. At the same time, the researchers are not allowed to make contact with the persons in question based on the information they receive.

If the persons need to be contacted, the first letter will be sent by the register keeper in question.

An obstacle especially to repeated studies and follow-up studies is that the keeper of a particular register (such as a register on treatment reports) may not transfer the maintenance of the register to a third party except under special conditions as stated in legislation. This means that according to the current interpretation, the Institute can use one-time combined registers or even carry out one-time combinations of registers, but it is not allowed to establish permanent national registers that can be updated. An exception to this rule at the Institute according to legislation is the infectious disease register. From the viewpoint of the Institute and the monitoring of health in Finland, legislation should allow the Institute to maintain permanent registers that are completely or partially based on data received from the registers of other register keepers. This issue has currently been solved by entering into co-operation agreements with the register keepers in question.

Tabulated register data is also employed in research and in health monitoring. Such use does not involve any privacy issues.

18.2.3 The size of registers and the extent of data processing

National registers are large and will continue to increase if information covering several years is needed for research. The large size in itself causes high data processing costs and even problems in allocating computer time for the research. Large internal costs may also result in a large invoice to the researcher. The costs may often be so high that no sufficient funding can be found.

18.2.4 Asking for advice

The Institute has much experience in the register-based monitoring and record-linkage of population samples (AVTK, Finriski, Mobile clinic, Mini-Finland, Health 2000, ATBP), and health monitoring (monitoring the incidence of coronary heart disease and strokes, UHOTA=health and need for care in the Uusimaa region). Advice on and guidance in the use of external registers should be requested especially from the senior researchers at ETEO and TTO. When using the Institute's own registers, units studying and monitoring infectious disease and vaccinations should be consulted as well.

19 REFERENCES AND APPENDICES

19.1 Internal regulations, guidelines, manuals and forms of the Institute

Portal of the Institute's internal regulations http://ktlwww.ktl.fi/kirjasto/sisaiset_ maaraykset/:

Kansanterveyslaitoksen tutkimusstrategia (The research strategy of the Institute)

Kansanterveyslaitoksen ja sosiaali- ja terveysministeriön välinen tulossopimus (The result agreement between the Ministry of Social Affairs and Health and the Institute)

Henkilörekistereiden perustaminen ja ylläpito, Sisäinen määräys 3/2003 (Establishing and maintenance of personal data registers, internal regulation 3/2003)

Internet site of the animal experiment unit http://ktlwww.ktl.fi/kely/

Kelpoisuus suorittaa eläinkokeita Kansanterveyslaitoksessa (Competence to perform animal experiments at the Institute)

Eläinkoesuunnitelma ja lupahakemus (Animal experiment plan and application)

Kansanterveyslaitoksen koe-eläintoimikunta (The Institute's animal experiment committee)

Eläinkoesuunnitelmalomakkeen täyttöohje (Instructions for filling out the animal experiment plan)

Koe-eläintoimikunnan ohjesääntö (Regulations of the animal experiment committee)

Eläinkoeluvan muutosesitys (Application for an amendment to an animal experiment authorisation)

Raportti eläinkoeluvan toteutumisesta (Report on implementing the animal experiment authorisation)

KELY:n menetelmäohjeet eläimiin kohdistuvista toimenpiteistä (KELY instructions on measures directed at animals)

KELY:n toimintaohjeet (KELY.T.) koe-eläinten tuotannosta ja ylläpidosta sekä koe-eläintiloissa työskentelystä (KELY instructions (KELY.T) on the production and care of laboratory animals as well as on working in the animal laboratory facilities)

Eläintilauslomake (Animal order form)

GM-eläinten käyttö- ja ylläpitoilmoitus (Report on the use and keeping of GM animals) (available at the animal experiment unit)

Kansanterveyslaitoksen arkistosääntö, Pysyväismääräys 4/99 (the Institute's archiving guidelines, standing regulations 4/99)

Menettelyohje alkuperäisaineiston luovuttamisesta (Instructions for transferring original material)

Kansanterveyslaitoksen tietoturvapolitiikka, Pysyväismääräys 7/94 (Data security policy of the Institute, standing regulations 7/94)

Vaitiolositoumus (Confidentiality agreement)

Kansanterveyslaitoksessa noudatettava politiikka henkilökohtaisten stipendien tai muun henkilökohtaisen rahoituksen vastaanottamisessa ja seuraamisessa, Pysyväismääräys 4/2000 (The Institute's policy for receiving and monitoring personal scholarships or other personal funding, standing regulations 4/2000)

Julkisuusperiaatteeseen liittyvä muistio 1.12.1999 (Memorandum on the principle of openness, dated 1 December 1999)

Keksinnöt ja tekijänoikeudet sekä tutkimustulosten kaupallinen hyödyntäminen Kansanterveyslaitoksessa, Pysyväismääräys 2/2001 (Inventions and copyright, and commercial utilisation of research results at the Institute, standing regulations 2/2001)

Uuden työntekijän perehdyttämislomake (Training form for new employees)

Tutkimussuunnitelmien käsittely ja hyväksyminen KTL:ssa Pysyväismääräys 4/2001 (Processing and approval of research plans at the Institute, standing regulations 4/2001)

Kansanterveyslaitoksen tutkimuseettinen työryhmä (The Institute's research ethics work group)

Kansanterveyslaitoksen aineistorekisteri = aineistokartoitus (The Institute's materials register or materials evaluation)

Kansanterveyslaitoksen tutkimussuunnitelmarekisteri (The Institute's research plan register)

Kansanterveyslaitoksen EU:n V puiteohjelman cost statement -lomakkeet (The cost statement forms for the EU's Fifth framework programme at the Institute)

Työsuojelun toimintaohjelma. Sisäinen määräys 4/2003 (Operational plan for labour protection, internal regulations 4/2003)

Kulkulupahakemus (Pass application)

Ulkopuolinen rahoitus ja sopimukset. Pysyväismääräys 6/2001 (External funding and contracts, standing regulations 6/2001)

Sitoumus ja lupa Kansanterveyslaitoksen resurssien käyttämisestä laitoksen ulkopuolella (Commitment and authorisation to use the Institute's resources outside the Institute)

Käyttölupahakemus Kansanterveyslaitoksen palvelinkoneiden etäkäyttöä varten (Application for the authorisation to use the Institute's servers for remote access)

Yhteisrahoitteinen rahoitussopimus: kustannusarviolomake (Contracted research agreement: cost estimate sheet)

Maksullinen tilaussopimus: kustannusarviolomake (Contracted research agreement: cost estimate sheet)

Kansanterveyslaitoksen työjärjestys (Working order of the Institute)

Kansanterveyslaitoksen jätehuolto-ohje. Pysyväismääräys 6/95 (Waste disposal instructions of the Institute, standing regulations 6/95)

Kansanterveyslaitoksen laatukäsikirja (Quality manual of the Institute)

19.2 Laws and decrees

The acts and decrees are available free of charge via the public legislation portal (www.finlex.fi). The database can be searched by regulation name (such as the Personal Data Act) or number (523/1999) or with text from the regulation.

Medical Research Act (488/1999)

Act Amending the Medical Research Act (295/2004)

Medical Research Decree (986/1999)

The government's decree amending Sections 2 and 3 of the Medical Research

Decree (313/2004)

Act on the Openness of Government Activities (621/1999)

Personal Data Act (523/1999)

Act on the Status and Rights of Patients (785/1992)

Act on Patient Injuries (585/1986)

Act on the National Public Health Institute (828/1981)

Decree on the National Public Health Institute (374/1998)

Archives Act (831/94)

Act on the Protection of Privacy and Data Security in Telecommunications (565/1999)

Radiation Act (592/1991)

Radiation Decree (1512/1991)

Chemicals Act (744/1989)

Animal Protection Act (274/1996)

Decree on Animal Experiments (1076/1985)

Decree on the Implementation of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, N:o 85/90 The European Convention of the Council is published in the Statutes of Finland under number 1360/1990. Appendices A and B to the Convention are treated as recommendations.

Gene Technology Act (377/1995)

Gene Technology Decree (821/1995)

The Ministry of Social Affairs and Health decision on the remunerations to research subjects (1394/2003)

Statistics Act (62/2001). Act on the Statistics of the National Research and Development Centre for Welfare and Health (409/2001)

Act on the Medical Use of Human Organs and Tissues (101/2001).

19.3 Ethical recommendations and instructions

The Declaration of Helsinki on Biomedical Research, 18th World Medical Assembly, 1964

Revised Declaration of Helsinki on medical research, 20th World Medical Assembly, 2000. The Finnish version can be found on the Finnish Medical Association site at http://www.laakariliitto.fi/etiikka/helsinginjulistus.html

Vancouver guidelines International Committee of Medical Journals Editors. Uniform requirements for manuscripts submitted to biomedical journals. New England Journal of Medicine 1997; 336: 309–15

International Congress of Harmonisation Internet site

Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research. J Occup Med 1991; 33: 122

Guidelines for Good Epidemiology Practices for Drug, Device and Vaccine Research in the United States. International Society for Pharmacoepidemiology 1996. www.hsph.harvard.edu/organizations/ddil/gep.html

Good Epidemiological Practice: Proper Conduct in Epidemiologic Research, IEA. www.Dundee.ac.uk/iea/GoodPract.htm

EU Council recommendation No R(90)3 concerning medical research on human beings, 6 February 1990

The European Convention of the Council is published in the Statutes of Finland under number 1360/1990. Appendices A and B to the Convention are treated as recommendations.

Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

The OECD guidelines concerning the investigation of safety of chemicals and GLP activities 92/69/EEC, 87/18/EEC and 88/320/EEC, as accepted by the European Union.

Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes

19.4 National instructions and regulations of the National Agency for Medicines and other authorities

Clinical trials on medicinal products in human subjects, National Agency for

Medicines' regulation 2/2004. Reporting adverse drug reactions, National Agency for Medicines' normative guideline 4/2001

Clinical trials on medical devices and equipment, National Agency for Medicines' guideline 1/2001 Radiation safety guidelines Data security guidelines of the state

Council of State Decision on the protection of employees against biological hazard at the workplace No. 1155, 1993

19.5 Internet sites of institutes

The Internet site of the National Advisory Board on Health Care Ethics' (ETENE) Sub-Committee on Medical Research Ethics (TUKIJA)

The Finnish Pharmaceutical Insurance Pool Internet site The Board for Gene Technology Internet site

The Hospital District of Helsinki and Uusimaa guidelines for ethics committees (http://www.hus.fi -> tutkimus ja opetus)

The Radiation and Nuclear Safety Authority of Finland Internet site The Data Protection Ombudman's Internet site

19.6 Quality systems

SFS-EN ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" ISO/IEC/7025/41/57 ISO9000

Other forms and instructions:

Etene form

Further processing request form 5b of the ethics committees of the Hospital District of Helsinki and Uusimaa

The Ministry for Social Affairs and Health research authorisation form

GCP guidelines

Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Official Journal of the European Communities

20 DEFINITIONS AND ABBREVIATIONS

Original material. The first recording of results.

Accreditation. A process in which a competent body officially states that a body is competent to carry out certain tasks. An accredited laboratory must meet the criteria defined in the international standard SFS-EN ISO/IEC 17025.

Sensitive information. Information concerning an individual or an organisation, the registration and use of which are restricted due to legal requirements or at the specific request of the party in question.

Document. A set of information and storage media, such as a record specification, operational instructions, a drawing, a report or a standard. The medium may be paper, a magnetic tape, an electronic or optical disc, a photograph or a sample or a combination of these. A set of several documents, such as specifications and records, is often referred to as "documentation". (ISO 9000)

Audit. A systematic, independent and documented process to objectively evaluate observable audit material in order to determine to what extent the specified audit criteria have been met. (ISO 9000)

EMEA. The European Medicines Agency

ESKO (internal project account). A classification sublevel used for the financial monitoring of a project.

FDA. Food and Drug Administration of the United States

GCP. Good Clinical Practice

GEP. Good Epidemiology Practice

GLP. Good Laboratory Practice; OECD guidelines for the general organisation of laboratory activities and the planning, carrying out, controlling, documentation and reporting of laboratory research. The European Community has ratified the OECD guidelines on the basis of directives applying to the testing of chemical, pharmaceutical and veterinary products. GLP is not the same as accreditation.

Research programme. In the management of the Institute's finances and actions a research programme typically refers to an entity larger than just one study. The common basis may be a health or research problem, material or a research method, for example.

Personal data. Personal data refers to all information concerning natural persons or their properties or living conditions that can be identified as concerning the person in question, his family or persons in the same household. (Personal Data Act 523/1999)

Traceability. The possibility to trace the previous stages, purposes or locations of the observation target. (ISO 9000)

Calibration. The measures to determine the interconnection between the measurements of the measuring device, measuring system or material measure and the corresponding measurement quantities.

Quality management system. A management system designed to guide the organisation in matters related to quality. (ISO 9000)

Quality assurance. That part of quality management that focuses on creating confidence in the fact that the quality requirements will be met. (ISO 9000)

Quality. The extent to which the natural properties meet the requirements. "Natural", as opposed to "given", refers to an existing, especially permanent property. (ISO 9000)

Quality policy. The general objective and direction stated by the management with regard to quality. (ISO 9000)

Study. A piece of research defined by a study or project plan. Used here interchangeably with project.

Research project or project. A piece of research defined by a project plan. Used alone project describes any defined action based on a plan.

Research programme. Defíned here as a broad and long-term research activity defined mainly by its goals. A research programme comprises many simultaneous and consecutive projects or studies.

Person in charge of the project / the study. Used here interchangeably to denote in medical studies the legally prescribed person responsible for all aspects of the study.

Method instruction. A document describing the principle and various stages of a test carried out in a laboratory.

Procedure. The defined implementation of an operation or a process. (ISO 9000)

Department. A profit centre; in this manual department and profit centre have the same meaning.

Funding agreement. A contract on shared-cost research between an external financier and the Institute as the party carrying out the research. The purpose of the contract is to agree on additional funding for the Institute's research that is of public interest.

Certification. A procedure in which a third party gives a written certificate that the product, method or service meets the requirements as defined.

SOP. Standard Operating Procedure.

Standard. A normative document based on a consensus accepted by an acknowledged body, presenting the rules, instructions or characteristics for general and repeated use for operations or their results in order to achieve an optimal structure in a certain situation.

Record. A document presenting the results obtained or containing evidence of the operations carried out. Records can be used for the documenting of traceability as well as for presenting evidence of verication, preventive actions and corrective actions. (ISO 9000)

Data search. Data search may refer to the search for an answer to a certain question or to the collection of more or less extensive data material concerning a certain subject.

Data risk. The risk of a damage-causing event concerning data or the use and handling of data.

Privacy. That part of data security that is aimed at the prevention of unauthorised use, handling and possession of data.

Data security. The methods for minimising data risks in order to guarantee the confidentiality, accessibility, usability and maintenance of data.

Data safety. That part of data security that describes a state with minimal data risks. In practice, data safety and data security are often used as synonyms.

Contracted research. Research where the Institute carries out an assignment that is in the interest of a third party (the client). In terms of its financial conditions, contracted research can be equated with paid services. The results of contracted research are the property of the client.

Operating procedure. A document describing the defined procedure for carrying out an operation or a process.

Result agreement. An annual agreement between the Ministry of Social Affairs and Health and the Institute detailing the results to be obtained each calendar year and the resources available for this, or the agreement between the Director General and a profit centre on the results to be obtained each calendar year and there sources available for this.

Profit centre. A separate operational unit directly under the Director General. The departments of the Institute and internal services (SIPA, comparable to the departments) are the profit centres of the Institute.

Person in charge of a study. A person in charge of a study must be nominated for all studies. In medical research, this person must be a medical doctor or a dentist with the appropriate professional and scientific competence. In other types of research, also other professionals can be nominated as the person in charge of research.

Research contract. A contract on the terms of the research work. The parties of the contract may be the persons carrying out the research or the financiers or both.

Validation. Ensuring, based on objective evidence, that specific requirements for a specific use have been met. (ISO 9000)

Shared-cost research. Research of general interest, funded by one or several parties in addition to the Institute. The results of such research are public.

Unit. A laboratory or other operational unit inside a department or a profit centre. Sometimes used as a general reference to different levels of the organisation (the laboratory, the office).