TUIJA KEINONEN

Clinical Drug Trials in Finland
Quality and Characteristics

Doctoral dissertation

To be presented by permission of the Faculty of Pharmacy of the
University of Kuopio for public examination in Auditorium,
Tietoteknia building, University of Kuopio, on Friday 21st
November 2003, at 12 noon

Department of Pharmacology and Toxicology
University of Kuopio
Department of Pharmacological Sciences
University of Tampere
MedFiles Ltd.
ISBN 951-781-284-1
ISSN 1235-0478

ABSTRACT

Background: Finland has a long tradition in undertaking clinical drug research but the quality and profile of the clinical drug trials undertaken in Finland have never been investigated in detail. The barriers as well as the factors favouring (i.e. preferences) the decision to undertake a trial have not been investigated, though conducting clinical drug trials is important for Finland from scientific, healthcare, and financial standpoints. There is now international competition between countries to try to attract the pharmaceutical industry to carry out their clinical trials.

Aims of the study: The aim was to investigate the quality, regulatory compliance, and profile of clinical drug trials, with a special emphasis on paediatric patients and adult healthy volunteers, during the 1990s. The contribution of the good clinical practice (GCP) guidelines to the quality of trials was also assessed. Additionally, the aim was to explore the barriers to as well as the factors favouring trials and attitudes of the clinical investigators and the pharmaceutical industry towards conducting clinical trials in Finland. One further aim was to assess what kinds of improvements are needed in the implementation of the trials.

Data collection and methods: Applications (n=666) and notifications (n=1174) submitted to the ethics committees and the regulatory authority during 1992, 1994, 1996, and 1998 were examined. Additionally, 352 trial notifications were analysed to investigate trials in paediatric patients and adult healthy volunteers including also the year 2000. The main measurement parameters were: trials with no objection to start, number and type of questions raised, profile, phase, type, and design of trial, and regulatory compliance. A descriptive analysis was performed. In-depth semi-structured interviews were conducted with 20 clinicians working in the field of cardiovascular medicine and 18 representatives of the pharmaceutical industry with different amounts of experience of clinical trials. The interviews were audiotaped, transcribed verbatim, and analysed qualitatively.

Results: The majority of the trials were phase III (46 %), large international multicentre studies (52 %) to evaluate new chemical entities (38 %). One fourth of trials included paediatric patients and adult healthy volunteers. Both ethics committees and the regulatory authority had raised questions/comments on almost half of the trial applications/notifications submitted to them. Most questions dealt with subject information and the trial protocol. Not all trials, nor the majority of trial completions, were reported to the regulatory authority. Investigators and the pharmaceutical industry had a positive attitude towards carrying out clinical trials in Finland. The least barriers were encountered in practical conduct of trials such as subject recruitment and clinical work. The major barriers were experienced at the beginning of the trial and mostly consisted of bureaucratic obstacles. The greatest dismotiveving factors for the investigators were insufficient financial incentives, trial-related reasons, and administrative affairs/bureaucracy. The most serious disincentives from the standpoint of the pharmaceutical industry were high costs and the constraints imposed by bureaucracy. Instead, GCP training, collaboration with the mass media and other relevant parties to disseminate information about clinical research to the general public were considered as necessary and beneficial.

Conclusions: The study provided new knowledge about the quality of the clinical trials undertaken in Finland as well as the barriers to and the factors favouring their undertaking. Submitted trial documents should be prepared more carefully to achieve better GCP compliance and compliance with regulatory requirements in reporting trial commencements and completions should be improved. Furthermore, standardisation of the submission practices is needed. Financial issues and administrative management to cut through the bureaucratic red tape need urgent actions to encourage in the decisions to initiate clinical trials. Additionally, a more positive attitude from the public sector, more specific in-house rules, flexibility and support from hospitals and a more professional attitude in practical implementation were issues raised both by the investigators and by the pharmaceutical industry. Thus, investments in site management activities are needed. These quality issues, barriers to and the factors favouring trials found in this study should be taken into account in decision-making to meet the various needs of all parties involved in trials and to increase international competitiveness of Finland in the field of clinical drug research.
ACKNOWLEDGEMENTS

This work was carried out in the Department of Pharmaceutics, University of Kuopio and in the Faculty of Medicine, University of Tampere, and MedFiles Ltd. This work was financially supported by the Medical Research Fund of Tampere University Hospital, the Finnish Cultural Foundation - Ellin Turunen Fund, and MedFiles Ltd.

I express my deepest gratitude to my principal supervisor Professor Pauli Ylitalo for his kind advice, whole-hearted encouragement, and being always available whenever needed. I am indebted to my second supervisor Veijo Saano, who led me into the world of clinical trials already in 1990, for his guidance and encouragement during this work. My supervisors' enthusiasm in my work and their valuable comments during the preparation of this thesis have made this work possible. My special thanks go to the Department of Pharmacology and Toxicology and to Professor Pekka Männistö for his support and encouragement.

I am grateful to the reviewers of the thesis, Professor Martti Marvola, Ph.D. (Pharm), and Professor Olavi Tokola, MD., Ph.D., for their valuable and constructive comments on the manuscript.

I am indebted to the co-authors of the original publications Professor Hannes Enlund, Ph.D. (Pharm.), Professor Tapani Keränen, MD., Ph.D., Docent Timo Klaukka, MD., Ph.D., Virpi Saarela, MD., Ph.D., Sakari Nieminen, MD., and Pirkko Miettinen, M.Sc. (Pharm.), I want to thank them for their help, valuable comments, and inspiring encouragement.

I express my sincere thanks to the National Agency for Medicines and the Ethics Committees of the University Hospitals in Helsinki, Kuopio, Oulu, Tampere, and Turku. Additionally, I express my special thanks to the Finnish physician-investigators and the pharmaceutical industry representatives who volunteered to be interviewed in the study. This study would not have been possible without the commitment of these parties.

I am grateful to the men behind MedFiles Ltd. Markku Jusliu, Ph.D. (Pharm), Peeteri Paavonen, Ph.D. (Pharm.), Pekka Peura, Ph.D. (Pharm.), and Jorma Pykkänen, M.Sc., and all my colleagues in MedFiles for the encouragement, understanding, and allowing me to take the time to prepare this thesis apart from the hectic work in the business. I also thank cordially all my friends and colleagues for their encouragement and support during my studies. I am indebted to them for their endless interest in my work.

I owe my warm thanks to my mother Kaija, my three sisters Sari, Heli, and Susa, and their lovely families for their support and all those happy moments I have spent with them. My warm, very special memory goes to my deceased father, Eero. I wish he had seen the completion of this thesis. Finally, my warmest thanks go to my husband Hannu who has had to suffer too much for the sake of my scientific ambition. His patience, love, and care made this work possible.

Kuopio, November 2003

[Tuira Keinonen]
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPMP</td>
<td>Committee for Proprietary Medicinal Products</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Record Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries' Associations</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Agency for the Evaluation of Medicinal Products</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCTP</td>
<td>Good Clinical Trial Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>NAM</td>
<td>National Agency for Medicines</td>
</tr>
<tr>
<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>SMO</td>
<td>Site Management Organisation</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
LIST OF THE ORIGINAL PUBLICATIONS

This work is based on the following five original studies which are referred to in the text by their Roman numerals I to V:


III Keinonen T, Miettinen P, Saano V, Ylitalo P. Clinical trials in children and healthy volunteers. Quality and characteristics of notifications reviewed by the regulatory agency in Finland. Paediatric and Perinatal Drug Therapy (submitted).


The articles are reproduced in this thesis with the kind permission of the copyright holders. This thesis also includes material that has not been published in the articles.
CONTENTS

1. INTRODUCTION .............................................................................................................. 15

2. REVIEW OF LITERATURE .............................................................................................. 19

2.1. Development of the quality principles in clinical drug research ............................... 19
    2.1.1. Development of ethical principles ................................................................... 19
    2.1.2. Development of Good Clinical Practice ............................................................ 20
    2.1.3. Progress in Finland ......................................................................................... 21

2.2. Regulations and guidance in clinical drug research ..................................................... 23
    2.2.1. International regulatory requirements and guidance .......................................... 23
    2.2.2. Regulatory requirements and guidance in Finland ............................................. 24
        2.2.2.1. Ethics committees and their review process .............................................. 24
        2.2.2.2. Regulatory authority review process ...................................................... 24

2.3. Clinical drug trials - practical implementation ............................................................ 25
    2.3.1. The parties: ethics committee, investigator, sponsor, regulatory authority, subjects ......................................................................................................................... 25
    2.3.2. International profile of clinical trials ................................................................ 27
    2.3.3. Clinical trials in Finland .................................................................................. 31
    2.3.4. Barriers to and factors favouring trials ........................................................... 32
        2.3.4.1. Barriers to and factors favouring trials from the viewpoint of investigators ......................................................................................................................... 32
        2.3.4.2. Barriers to and factors favouring trials from the viewpoint of subjects .......... 39
        2.3.4.3. Barriers to and factors favouring trials from the viewpoint of the pharmaceutical industry/sponsor ................................................................. 43
        2.3.4.4. Suggestions for improvements .................................................................. 46

2.4. Quality and regulatory compliance of clinical drug trials ........................................... 52
    2.4.1. Quality assurance and audits ........................................................................... 52
    2.4.2. Inspections ....................................................................................................... 54
    2.4.3. Quality and regulatory compliance of trials .................................................... 56

3. AIMS OF THE STUDY ...................................................................................................... 58
4. DATA AND METHODS ........................................................................................................59
4.1. Data and study progress .........................................................................................59
   4.1.1. Stages of the study .........................................................................................59
   4.1.2. Data to study profile, regulatory compliance, and quality of clinical
drug trials ......................................................................................................................60
   4.1.3. Data to assess barriers to and factors favouring trials from the viewpoint
   of investigators and the pharmaceutical industry ......................................................60
4.2. Data collection ........................................................................................................61
   4.2.1. Profile, regulatory compliance, and quality of clinical drug trials ..............61
   4.2.2. Barriers to and factors favouring trials from the viewpoint of
   investigators and the pharmaceutical industry .........................................................62
4.3. Analysis of data ......................................................................................................62
   4.3.1. Profile, regulatory compliance, and quality of clinical drug trials ..............62
   4.3.2. Barriers to and factors favouring trials from the viewpoint of
   investigators and the pharmaceutical industry .........................................................63
4.4. Ethical and confidentiality aspects .........................................................................63

5. RESULTS ...................................................................................................................65
5.1. Profile of clinical drug trials in Finland (II, III) ....................................................65
   5.1.1. Number of clinical trials ...............................................................................65
   5.1.2. Characteristics of clinical trials .....................................................................65
       5.1.2.1. Trial phases, design, and object .................................................................65
       5.1.2.2. Trial participants, centres, and sponsors ..................................................67
5.2. Quality and regulatory compliance of clinical drug trials in Finland (I, II, III) ...70
   5.2.1. Acceptability by ethics committees .................................................................70
   5.2.2. Acceptability by regulatory authority ...............................................................70
5.3. Barriers to and factors favouring clinical drug trials in Finland (IV, V) ..........71
   5.3.1. Investigators' perspective ...............................................................................71
   5.3.2. Pharmaceutical industry's perspective .............................................................72
   5.3.3. Similarities and differences in the responses of the investigators
   and the pharmaceutical industry ..............................................................................73

6. DISCUSSION ..............................................................................................................76
6.1. Methodological considerations ................................................................. 76
6.2. Clinical drug trials in Finland ................................................................. 78
6.3. Quality and regulatory compliance of clinical drug trials .................. 78
6.4. Barriers to and factors favouring clinical drug trials ......................... 81
6.5. Recommendations and future aspects conducting clinical drug trials in Finland ................................................................. 82

7. SUMMARY AND CONCLUSIONS ......................................................... 85

8. REFERENCES ......................................................................................... 88

ORIGINAL PUBLICATIONS
1. INTRODUCTION

The final step in the drug development process is the study of the drug in human beings, i.e. so-called clinical drug trials. The aim of any clinical trial is to obtain a true answer to a relevant medical question, and a scientific purpose is a prerequisite for any clinical trial to be started (Pocock 1983). Apart from purely scientific reasons, there are various other aims that clinical trials are anticipated to address. These include improvements in medical care and public health, and furthermore a major economic commitment by the pharmaceutical industry and financial benefit to the community as a whole. Since the trials are carried out in human beings, ethical aspects are of special importance. Tragic experiences of medical experiments on human beings, such as experiments in concentration camp inmates conducted by the Nazis during the Second World War and the Tuskegee Syphilis Study are well-known (Allen 1996, Freimuth et al. 2001). Subsequently, other serious incidents have occurred thereafter, such as death of trial subjects participating in clinical trials, unethical or unprofessional activity of researchers or the pharmaceutical industry (Lurie and Wolfe 1997, Thompson 2000, Järvi 2002, Steinbrook 2002) and raise questions about the ethical and scientific conduct of clinical trials even today despite the existence of strict national and international regulations and guidelines. Flaws in the drug development processes have serious economical, ethical, and legal consequences not only to the pharmaceutical companies and researchers but widely to the community, not to mention the medical and other consequences to the individual drug user. This is exemplified by the notorious experiences of thalidomide in the late 1950s and early 1960s, a drug which caused severe birth defects in thousands of children even though it was deemed to be safe since animal experiments had showed extremely low acute toxicity (von Moos et al. 2003).

The drugs have to be safe, effective, and of high quality. Safety and efficacy in human beings can ultimately be demonstrated only in clinical trials. These are customarily divided into four phases according to the clinical information accrued and the size of a trial (Pocock 1983). Most of the clinical drug trials are carried out to obtain a marketing authorisation for a new medicinal product. Figure 1 presents the drug development process from discovery to clinical phase, and finally, if successful, to the pharmaceutical market. Research and development (R&D) of a new drug is a costly, lengthy, and uncertain process and clinical
trials are the most expensive and time-consuming part of this process. Today, it takes on average 10 to 15 years and over 800 million euros to bring a new drug onto the market (EFPIA 2002, PhRMA 2003). The complexity and number of clinical drug trials needed for a marketing authorisation application have dramatically increased. From the point of view of the pharmaceutical industry, the increased R&D costs, overall competition, reduced and concentrated development objectives are major stimuli to find ways to carry out trials more rapidly, with higher quality and better cost-efficiency.

Figure 1. Drug development process from discovery to different clinical phases, to pharmaceutical market, and to patent expiry.

The regulatory authority together with the ethics committees form a crucial element in any trial, because these bodies are responsible for reviewing the scientific and ethical validity of a planned clinical drug trial before its commencement. Furthermore, the quality of a clinical trial depends on whether it is being done according to the quality standards of clinical
drug research, i.e. Good Clinical Practice (GCP). A clinical trial is successful when every process is performed as planned, GCP and other regulatory requirements are followed, and the motivation of the different parties involved in planning and implementing the trial is high. Despite the consistent emphasis on the importance of high quality, there is still a need to improve the quality of the trial processes (Bohaychuk 1998a,b, Gwede et al. 2000, Szpindor 2000, Gamache 2001). Furthermore, a number of problems related to investigators, sponsors, and study subjects exist despite well-planned trial protocols, detailed instructions, and professional parties involved. Problems can be manifold, i.e. from the collective issues of regulatory affairs to individual personal factors. These can cause significant delays in single trials, the drug development process, and in introducing new medicines onto the market. These problems, together with poor planning and performance of trials, and quality deficiencies at any stage, not only ruin the trials, waste time and money, but they can make the trials unethical: a clear violation of all regulations and standards of clinical drug research (Tassignon 2000). On the contrary, transparency and various factors favouring trials/motivating factors of investigators, sponsors, and subjects facilitate trial performance and enhance success rate in trial completion.

Conducting clinical drug trials in Finland is important from a scientific, healthcare, and financial point of view. Valuable knowledge about possible subtle effects of cultural, environmental, nutritional or other extrinsic factors can be obtained. Also, patients can gain access to new drug treatments early and their physicians will be more experienced in the use of the new drugs when they have participated in its development process. Better treatments with more effective drugs improve healthcare and Finnish medical know-how can be spread to the international research communities via clinical trials. The high standards of the medical sciences, educated health care personnel, country-wide disease registers, compliant subjects, and authorities’ positive attitude towards clinical trials create favourable conditions to carry out trials in Finland (Bengtström 2002). However, the ability to be competitive in time, costs, and quality of the trials are challenges to be met to retain the attractiveness and to guarantee that clinical trials will be performed in Finland also in the future.

It was felt that the barriers to and the factors favouring trials, and attitudes of physicians and the pharmaceutical industry representatives towards conducting clinical drug trials are important issues to study, and factors which have not been previously examined in Finland. Furthermore, little is known about the work of ethics committees' and regulatory authorities' reviews of
clinical drug trial applications/notifications, which are integral parts in maintaining a high ethical and methodological standard of clinical drug trials. Even less is known about clinical drug trials conducted in special populations, such as in children or healthy volunteers. Information and knowledge about these aspects of conducting clinical drug trials in Finland can provide valuable insights into ways to maintain a high research activity and how to improve the undertaking of future trials in Finland.
2. REVIEW OF LITERATURE

2.1. Development of the quality principles in clinical drug research

2.1.1. Development of ethical principles

Every clinical trial requires a careful assessment, about whether it is ethically acceptable; to avoid unnecessary suffering, inconvenience and loss of freedom, for subjects to participate in the planned manner (Procock 1983). Particularly, it is essential to obtain informed consent from each subject. Since the Second World War, experimentation in human subjects with the increasing number of participants in those experiments has generated difficult problems. In general, if many subjects had been aware that they were participating in an experiment or truly had been alerted to their exploitation or the risks involved, they would have not participated (Beecher 1976).

Protection of human subjects was initiated with the Nuremberg Code in 1947, developed for the Nuremberg Military Tribunal as the standards by which to judge the medical experiments on human subjects which were conducted by the Nazis (Penslar and Porter 1993, Allen 1996). Close to this time, around the 1950s in the United States there were serious abuses of the rights of vulnerable groups, such as prisoners and mentally handicapped subjects. Some of the cases which came to light were very serious, such as the notorious Tuskegee Syphilis Study carried out in impoverished poorly educated blacks (Allen 1996, Freimuth et al. 2001). Flaws or negligence of pharmaceutical industry and researchers occurring during the drug development processes, such as the consequences of thalidomide tragedy, unethical trials conducted in developing countries, suppressing, delaying or not publishing unfavourable trials results or conflict of interest issues, have aroused public concern and have tightened the surveillance by drug regulatory authorities and standards of drug development (Angell 1997, Lurie and Wolfe 1997, Stern and Simes 1997, Skolnick 1998, Stelfox et al. 1998, Lewis 2001).

The Nuremberg Code formed the basis for the creation of the significant document, Declaration of Helsinki, which was adopted by the World Medical Assembly in Helsinki, Finland, 1964 (World Medical Association 2000). Since that time, the Declaration of Helsinki has been amended five times, with the latest modification in Edinburgh in 2000, followed by
a clarification in Washington 2002. The principles of informed consent were already stated in
the Nuremberg Code and thereafter were further developed in the Declaration of Helsinki. In
the United States, the Belmont Report was submitted in 1979 which set forth the basic ethical
principles, i.e. respect for persons, beneficence, and justice, as well as guidelines for the
protection of human subjects in research (National Commission for the Protection of Human
Subjects of Biomedical and Behavioral Research 1979).

2.1.2. Development of Good Clinical Practice

GCP is an international ethical and scientific quality standard for designing, conducting,
recording, and reporting trials in human subjects. It outlines the responsibilities of ethics
committees, investigators, and trial sponsors. The emphasis is placed on the rights, safety, and
well-being of trial subjects as well as on the credibility of trial data. The GCP guideline is
followed when clinical trials are carried out and which are intended to be included in the
marketing authorisation application of the drug submitted to the regulatory authorities (ICH
GCP 1997).

GCP is the youngest member of a family of the Good Practice Guidelines, including also
Good Manufacturing Practice, GMP, and Good Laboratory Practice, GLP, which developed
in the 1960s and 1970s. GCP evolved in the United States at the end of 1970s in response to
some serious frauds and abuses of rights of vulnerable groups, e.g. prisoners, mentally
handicapped subjects, and elderly (Allen 1996). The Food and Drug Administration (FDA)
first proposed regulations on the responsibilities of investigators and sponsors in 1977 which
developed the system referred to as GCP (Allen 1996). Around the turn of 1990s, there were
local movements in Europe when several country-specific GCP guidelines were produced,
e.g. in the United Kingdom, France, and Germany (Allen 1996). In Scandinavia, Finland
together with the other Nordic countries prepared the Good Clinical Trial Practice guideline
(GCTP) issued by the Nordic Council on Medicines in 1989 (Nordic Council on Medicines
1989, Westman Næsset 1993). This guideline was later used as a basis for the Australian GCP
guideline and partly in the preparation of the World Health Organisation (WHO) GCP
guideline (Strandberg 1993, Korteweg 1994).

The legal basis for the GCP guideline was provided by the rules governing medical
European GCP guideline was published and implemented voluntarily across the member states of the European Union (EU). In 1992, the WHO issued its first draft GCP guideline which was finalised in 1995 (Idänpää-Heikkilä 1999). The WHO GCP guideline has been used by several countries if there is no local guideline or has been used as a template in developing and modifying their own GCP guidelines, for example in East Asia (Tsutani 1997). Each country has its own regulations and long-standing traditions in medical ethics, and there is extensive diversity in the notification and submission procedures for national regulatory authorities. Thus, both industry and regulatory authorities have endeavoured to standardise certain processes and to initiate reporting on a worldwide scale (Brunier and Nahler 1999a). Thus, in 1990, the drug regulatory authorities and the pharmaceutical industry representatives from Europe, the United States, and Japan initiated a tripartite harmonisation project, International Conference on Harmonisation (ICH) aiming to harmonise research guidelines on quality, safety, and efficacy research and marketing authorisation requirements in these three regions. The WHO, the European Free Trade Association, and Canada act as observers and as a link with non-ICH countries and regions. As a result of this intense activity, numerous guidelines have recently been issued, e.g. the ICH GCP guideline (ICH GCP 1997). In 1997, this was adopted in the EU, the United States, and Japan and it is becoming the standard throughout the EU with the implementation of the European Directive on GCP (the European Parliament and the Council of the European Union 2001). Thus, the submission process will be harmonised in the member countries of the EU. The WHO GCP guideline and the EU GCP guideline are followed in the non-ICH or non-EU countries, though there is a movement to adopt the ICH GCP guideline also in these areas, e.g. in Eastern European countries (Paál 1997, Neal 2001).

2.1.3. Progress in Finland

The Finnish Medical Association adopted its first ethical guidelines in 1956 which were based on the Declarations of Geneva and London of the World Medical Association. Ethical review of clinical trials started in 1972 when the first ethics committee was established in a university hospital. This establishment was encouraged by the decision from the National Institutes of Health in the United States that each research project sponsored by that facility had to be submitted to ethics committee review. In 1977, every medical faculty in Finland had
an ethics committee (Finnish Medical Association 1996). Before 1999, there were no detailed regulations issued to ethics committees and a wide network of institutional and regional ethics committees existed, i.e. there was no national guideline on the review of applications submitted or factors related to decisions on the trials planned to be carried out in their region. The decisions by the local ethics committees were final. In 1999, detailed regulations to ethics committees were issued (Parliament of Finland 1999a,b). Thus, only 29 ethics committees remained in the five university hospitals and district central hospitals. Since that time, only the ethics committees of hospital districts remained to be responsible for reviewing single centre trials in their region and national multicentre trials when the person responsible for the trial comes from that region or the majority of the trial will be conducted in their region (Parliament of Finland 1999b). Additionally, a centralised ethics committee procedure was started in 1999 with the establishment of the national ethics committee (Parliament of Finland 1998 and 2000). This board has a Sub-Committee on Medical Research Ethics, which now issues national opinions on international multicentre trials.

Initial regulatory guidance for clinical trials started earlier than guidance for ethical review. The regulatory guidance started in 1965 when an administrative circular was issued. Thus, based on this guidance, notification of clinical trials started from that date. Subsequently, a note for guidance was issued in 1978 followed by an administrative circular in 1985, and then another administrative circular was issued in 1987. Since that time, 1987, clinical trials were based on the authorisation defined in the medical research act. The 1990s was a fruitful decade for the growth of GCP. The GCTP guideline of the Nordic Council on Medicines was recommended to be followed in clinical drug trials in accordance with the note for guidance in 1990. Soon thereafter, the EU GCP guideline (1991) and the WHO GCP guideline (1995) were provided. In 1997, the ICH GCP guideline was adopted in the national regulations of the National Agency for Medicines (NAM) and this is currently the guideline to be followed (National Agency for Medicines 2000). The regulation, clinical trials on medicinal products in human subjects, was issued in 1993 and it was valid until 2001 (National Agency for Medicines 1994). Thereafter, a revised regulation, clinical trials on medicinal products in human subjects, was issued which is currently being followed, at least until the end of 2003 (National Agency for Medicines 2000).
2.2. Regulations and guidance in clinical drug research

2.2.1. International regulatory requirements and guidance

The current international regulatory requirements and guidance in the EU, the United States, and Japan are based on the ICH guidelines. In Europe, the implementation of the GCP directive will start from May 2004 at the latest. This provide the legal framework for the member states of the EU (the European Parliament and the Council of the European Union 2001). The directive contains items such as definitions, protection of trial subjects, ethics committees, trial conduct, data change, investigational products, and reporting serious adverse reactions. As the regulatory requirements dealing with approval procedures of clinical trials between countries vary substantially, the GCP directive streamlines the processes and time limits with respect to applications for opinions from ethics committees and notifications for regulatory authorities. For example, ethical and regulatory reviews of trial applications/notifications have to be completed within 60 days, except in the case of drugs for gene therapy, somatic cell therapy, including xenogenic cell therapy or drugs containing genetically modified organisms.

Thus, these existing numerous national regulations and guidelines in the member states of the EU had to be incorporated into the contents of the directive by May 2003 and have to be applied from May 2004 at the latest. In other ICH countries, i.e. in the United States, the ICH GCP has been incorporated into their legislation, the Federal Register, by the FDA; and in Japan, it has been published in their Pharmaceutical Affairs Law by the Ministry of Health and Welfare. Though a common basis for the conduct of clinical trials should be achieved by the GCP directive, its implementation will be challenging as each country’s own cultural and social differences in medical ethics will continue to have an effect on the trial performance (Bohaychuk et al. 1998d, Brunier and Nahler 1999a, Griffiths 2000).
2.2.2. Regulatory requirements and guidance in Finland

2.2.2.1. Ethics committees and their review process

The intention to start a clinical drug trial has to be submitted for an ethical review before the trial begins. In parallel to this process, the application can be submitted to the regulatory authority, the NAM. A clinical trial application is submitted to a regional ethics committee if the trial is a single centre trial or if the trial is a national multicentre trial. The regional ethics committee used is determined according to where the majority of the trial will be conducted or according to the location of the person responsible for the trial. Every hospital district has at least one ethics committee. The central ethics committee, the Sub-Committee on Medical Research Ethics, issues national opinions on international multicentre trials but it may delegate assignments to one of the regional ethics committees (Parliament of Finland 1999a). A copy of the ethics committee’s opinion is delivered to the regulatory authorities when it becomes available. Ethics committees of the university hospitals used to review approximately 1 500 applications annually before 1999. By October 2002, the Sub-Committee on Medical Research Ethics had received 655 applications, reviewed 131 of the applications itself and delegated the rest to the regional ethics committees. In 2001, the average time for the ethical review was 48 days (National Advisory Board on Health Care Ethics 2002).

2.2.2.2. Regulatory authority review process

The intention to start a clinical drug trial has to be reported to the NAM before the trial begins. In practice, the notification procedure is equivalent to tacit authorisation, which the NAM has full powers to revoke before it takes effect. Thus, if no objections have been raised within 60 days after the submission, the trial can be started, except in the case of drugs for gene therapy, somatic cell therapy, including xenogenic cell therapy, or drugs containing genetically modified organisms where written permission from the NAM is required (National Agency for Medicines 2000). During recent years, the review has taken approximately 40 days (National Agency for Medicines 2002). If the submitted documents are not sufficient, the NAM can ask for additional information, request amendment(s) to the
trial protocol, or refuse permission to undertake the trial. The notification requirement applies
to medicinal products that do not have marketing authorisation, and in special cases also to
marketed products, e.g. when investigating in special subject population, a new indication, or
in the case of controlled or multicentre trials. If a trial is suspended, prematurely terminated
or completed, or if any relevant changes occur during the trial, the NAM should be informed.
Serious adverse reactions and protocol amendments also have to be reported. Within 90 days
of the completion of the trial, the NAM has to be notified, and a report on the results of the
trial has to be submitted within one year (National Agency for Medicines 2000).

2.3. Clinical drug trials - practical implementation

2.3.1. The parties: ethics committee, investigator, sponsor, regulatory authority, subjects

*Ethics committee:* The ICH GCP guideline outlines the operations and ethical principles
of an independent ethics committee, i.e. responsibilities, composition, functions, operations,
procedures, and records. The prime responsibility of the ethics committee is to safeguard the
well-being, rights, and safety of trial subjects (ICH GCP 1997). Ethics committees should be
kept aware of the changes of trials, such as if a trial is prematurely terminated or completed,
or if any relevant changes are made to the trial protocol or other documents related to the trial.
Ethics committees vary widely from country to country in Europe, not only their names, but
their regulatory procedures are different which is one cause for significant delay in the
initiation of trials at all trial centres and complicates trial coordination. In the United States,
institutional review boards (IRBs) as ethics committees are controlled by the government.
The level of control is the major difference to European ethics committees. The composition
and constitution of IRBs are regulated by law and are subject to formal inspections (Jenkins
1997).

*Investigators:* The ICH GCP guideline outlines the requirements dealing with
investigators' qualifications and agreements, resources, medical care of trial subjects,
communication with ethics committees, various trial procedures, as compliance with protocol,
informed consent of subjects, records, and reports. Physicians, as clinical trial investigators, are
responsible for the recruitment of the trial subjects within the constraints of the accepted trial
protocol and schedule and must have sufficient time and qualified staff to conduct the trial.
properly (ICH GCP 1997). Investigators and their assisting personnel at a trial site are the only party in a clinical trial with direct contact to the subjects. Thus, their responsibility for obtaining informed consent, sufficient subject recruitment, and subject retention are challenging responsibilities which have a critical effect on the success of a trial, the quality, and completion time of a trial. According to the ICH GCP guideline, the investigator/institution should prepare a written trial application to the ethics committee to obtain approval to start a trial and otherwise communicates with the ethics committee throughout the duration of the trial.

Sponsors: The ICH GCP guideline outlines sponsors' quality assurance and quality control requirements, use of a contract research organisation (CRO), medical expertise, various trial procedures, such as design, management and data handling, investigator selection, compensations and financing, communication with regulatory authorities, confirmation of review by the ethics committee, investigational product affairs, record access, safety information, and adverse drug reaction reporting, monitoring, auditing, and trial reporting (ICH GCP 1997). The trial sponsor (or the sponsor and the investigator) submits a notification/application to regulatory authorities for obtaining an approval to start a trial and otherwise communicates with the regulatory authorities throughout the duration of the trial. Confirmation of review by ethics committee is done by obtaining the appropriate documents from the trial investigator/institution. The responsibility for implementation and maintenance of quality assurance and quality control systems is emphasised to ensure that a trial is conducted and the data are generated, documented, and reported in compliance with the trial protocol, GCP, and the applicable regulatory requirements (ICH GCP 1997).

Regulatory authority: The regulatory authority is the party having final and full powers to accept or revoke the start of a trial or terminate it prematurely. The ICH GCP guideline does not outline the regulatory authority's responsibilities, instead it refers that to the other parties, i.e. ethics committees, investigators, and sponsors, to comply with the applicable regulatory requirements of a country where a trial is undertaken. The regulatory authority should be kept aware if a trial is suspended, prematurely terminated or completed, or if any relevant changes occur during the trial. Furthermore, serious, unexpected adverse drug reactions have to be reported (ICH GCP 1997). When planning a clinical trial with a new pharmaceutical substance, the regulatory authority may be consulted in the FIU to obtain scientific advice or assistance in protocol preparation. The impact of these meetings and procedures has been
shown to be successful in expediting drug development and the regulatory review process. Guidance in scientific issues often occurs in the United States when an investigational new drug application for a new drug is submitted (DiMasi and Manocchia 1997, EMEA 2003a,b). Nowadays it is more common also in Europe when applications to the European Agency for the Evaluation of Medicinal Products (EMEA) are submitted (EMEA 2003a).

Subjects: An essential part of any clinical trial is trial subjects. The ICH GCP guideline does not outline the subjects' responsibilities but it places the responsibility of protecting trial subjects on the shoulders of the ethics committees, especially in trials which include vulnerable subjects. The guideline outlines detailed instructions for investigators on how to obtain informed consent and the items to be included in the written information given to subjects. Additionally, investigators are instructed to promptly report to the ethics committee any changes that increase the risk to the trial subjects, such as serious, unexpected adverse drug reactions, changes to the trial protocol, or any new information that may have an adverse effect on the subjects' safety. With respect to the sponsors, the ICH GCP guideline outlines trial monitoring activities, as a quality control function, to verify that rights and well-being of trial subjects are protected, as well as audits, as a part of quality assurance, to evaluate compliance with protocol, standard operating procedures (SOPs) and GCP, and the applicable regulatory requirements (ICH GCP 1997).

2.3.2. International profile of clinical trials

Over 50% of drug candidates drop out during the non-clinical stage of the development before entering clinical trials and thereafter approximately one quarter are stopped at phase II of clinical trials. Only 1 out of 5 000 to 1 in 10 000 screened drug candidates is finally approved as a new drug. In 2001, there were an average of 6 000 drugs in the pipeline but this resulted in 36 (0.6%) new active substances (EFPIA 2002). Less than half of the drugs in pipeline enter in clinical development. The majority of trials investigate drugs for cancer, anti-inflammation, central nervous system or cardiovascular system diseases. R&D investments in the United States and in Europe are approximately 30 000–40 000 million Euros annually (Clemento 1999, EFPIA 2002, PhRMA 2003). Investments have doubled every five years since 1970, one of the reasons is the increased requirements imposed on these trials. In 2000, the pharmaceutical industry in Europe invested about 17 500 million
euros in R&D (ETPIA 2002) while the pharmaceutical industry in Finland invested 167.7 million euros in 2000 (Aaltosen 2002). Increasing consumer demand, i.e. from patients and their families as well as pressure from the industry's own business management and company shareholders, can influence the actions of regulatory authorities, physicians, and opinion leaders in academic medicine, to get new, safe, and effective drugs on market more rapidly (Niblack 1997). Thus, cost-effectiveness and speed in drug development is now firmly in the spotlight.

There is a paucity of published information about the country-specific characteristics of clinical trials. Regulatory authorities rarely publish detailed descriptions of their work concerning clinical trials. Only short descriptions in their annual reports or the reports of the national associations of pharmaceutical industries may be available. For example, in Denmark, the annual number of trial applications submitted to the Danish regulatory authority have amounted to approximately 300 during 1999 to 2002. Approximately 1 to 2% of the applications have been rejected (Danish Medicines Agency 2003). In Sweden, the annual number of ongoing clinical drug trials has been around 580 during 1998 to 2000, with approximately 60,000 to 80,000 trial subjects and approximately 4200 Swedish trial centres participating each year (Swedish Association of Pharmaceutical Industry 2002). The published reports in the literature are normally concerned with the number of new chemical substances in clinical testing, the number of subjects, the number of initial evaluations of applications for marketing authorisations, approval times needed by national regulatory authorities in marketing authorisation processes or the success rate of applications for product authorisations (Mattison et al. 1984, Rawlins and Jefferys 1993, Rawson et al. 1998, Thomas et al. 1998, Rawson 2000, EMEA 2003a).

The number and quality of clinical trial reports submitted to the marketing authorisation applications and summarised reviews on the quality of clinical trials made on 1950s to 1970s in Finland and other Scandinavian countries have been previously investigated, identifying the need for improvements in trials and their designs (Hemminski and Falkum 1980, Hemminski 1981 and 1982). However, few studies provide information about country-specific characteristics of clinical trials, when the applications submitted to the ethics committees had been examined: Venturini et al. (2001) studied 449 trial protocols submitted to ethics committees in Italy. They concluded that most trials were multicentre studies, with antineoplastic drugs, and only a few of the protocols related to innovative research. Ihole et al.
(2001) have investigated the influence of the pharmaceutical industry on clinical research in Norway: 965 pharmacology/pharmacotherapy projects were submitted to the five regional ethics committees during 1988 to 1990 and 1997. Two thirds of these trials were sponsored by the pharmaceutical industry. Ninety-two of 112 projects examined by one of the ethics committees were conducted in university clinics or other university institutions (Høle et al. 2001).

Most clinical trials are undertaken in adult subjects. However, the need for clinical trials in special populations, like children, elderly, and ethnic minorities have come into a focus of active discussion during the last decade (Iovato et al. 1997). Though populations at risk for a certain disease or receiving treatment should be represented in appropriate clinical trials (El-Sadr and Capps 1992, Huring 2000), the issue is complicated due to a variety of reasons. For example, an increasing number of trials are being carried out in developing countries due to better recruitment opportunities, but this raises special ethical concerns (Angell 1997, Gill and Kurz 2002, Shah 2003), as these countries do not have a tradition of scientific research or the necessary infrastructure needed, and the new treatments developed may well be too expensive, and thus never accessible to the population in that country (Idänpää-Hokkilä 2001, Shapiro and Meslin 2001). In the United States, it is rather uncommon for populations, such as racial and ethnic groups, to participate in clinical trials, e.g. even among the cancer patients it tends to be affected by structural, cultural, and linguistic factors (Millou-Underwood et al. 1993, Roberson 1994, Giuliano et al. 2000). Nevertheless, trials which previously tended to focus primarily on middle-class white male subjects are nowadays moving towards trials involving both sexes and persons from all ethnic and racial groups (Swanson and Ward 1995). Thus, wider coverage of different populations and trial results which are more generalisable are obtained.

With respect to trials in children, the pharmaceutical industry has not been eager to carry out clinical trials in children due to economic and practical reasons (Choonara 2000, Gennery 2000, Kmiotowicz 2000, Jong et al. 2002, Shaddy et al. 2002) though children (0 to 14 years) account for 30% of the total population globally and 20% of the total in the EU (Statistics Finland 2001, European Commission 2002a). In addition, there are both legal and ethical issues (Smyth and Weindling 1999, Barrett 2002, European Commission 2002a). Over 50% of the new drugs coming to the market and administered to children have been estimated not to have undergone sufficient clinically testing or to have inadequate instructions for paediatric
patients (Nordenberg 1999, Jong et al. 2002). Thus, the need to carry out clinical trials in children has been increasingly emphasised (Barrett 2002, Jong et al. 2002). In the United States, the FDA has encouraged the undertaking of paediatric trials by changing its legislation (FDA 1997, 1998, 2002) and similar plans exist in the EU for trials in children (CPMP 1997, European Commission 2002a,b).

Women of child-bearing age are nowadays encouraged to be included in all four phases of trials though previously they were often excluded (FDA 1997, LaRosa et al. 1998). Initiatives have also arisen with respect to the elderly (O'Donnell 2003), and trials in older people have also been encouraged by international guidelines (ICH 1993). It has been reported that older people are less likely to be referred to trials (Benson et al. 1991, Siminoff et al. 2000, Hutchins et al. 2003, Lewis et al. 2003), the reasons being their age, underlying comorbidities, worries about increased toxicity, preferences of the patients and/or family, or practical factors, e.g. inconvenience or time constraints (Kornblith et al. 2002, Yee et al. 2003). Naturally, the elderly suffer from more diseases and health problems and use more health care resources than younger people. Their medical treatment requires special attention due to the physiological changes caused by ageing and the several concurrent diseases, which can increase the risk for drug interactions (Schmucker and Vesell 1999, Crome 2001). Thus, not only the demand for health care but also the problems associated with treatment increase when people grow older.

Biotechnological products are rapidly becoming major items in clinical testing of drugs. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), 371 biotechnology drugs are in clinical development phase, the majority of them for cancer therapy or related conditions (Holmer 2002). The majority of clinical trials in gene therapy are also conducted in cancer therapy. Out of 425 trial protocols, 310 trials (73 %) were underway in the United States and 97 trials (23 %) in Europe (Gene Therapy Clinical Trials 2000). It has been predicted that genomic sciences and bioinformatics as new technologies will have the greatest impact on the process of drug development (Dykes 1996, Roses 2000a, Brännback et al. 2001). Pharmacogenomics is an important technology being introduced into clinical trials to make them more focused (Norton 2001). New drug targets, the ability to eliminate compounds at earlier stages in the process, and improvements in the selection of clinical trial subjects have been predicted to impact on the time and costs of the drug development and to change the pharmaceutical industry fundamentally (Roses 2000b,
Ginsburg and McCarthy 2001, Norton 2001). In the future, it is envisaged that advances in human genome research will lead to personalised drug therapy - the possibility to provide right treatment for the right patient at the right time - which will change drug discovery and patient care and replace the traditional practice of medicine (Roses 2000a,b, Ginsburg and McCarthy 2001). Apart from new technologies, new techniques have been recently used in clinical trials, such as computer simulation, telemetry techniques, and electronic data capture (Kubick 1998, Bonate 2000, Brännback et al. 2001). However, the actual impact of new technologies and techniques, whether they revolutionise traditional drug development or not, will only be seen in the future.

2.3.3. Clinical trials in Finland

Research into new active substances started at least about 40 years ago (Hemminki and Falkum 1980). Detailed quality guidelines did not exist at that time but during the 1990s major advances were made in this respect. Finland has a long tradition in undertaking clinical trials. Extensive clinical trials have been conducted in Finland for decades, both national and international, for example, trials reported by Mänttäri et al. (1987), Pedersen et al. (1996), Miettinen et al. (1999), and Dahlöf et al. (2002). Recently, Finland has been involved in approximately 9% of the total number of new chemical drug entities being evaluated in ongoing clinical drug trials (phases I to III) worldwide (Pharmaceutical Information Centre 1999). Annually, 260 to 300 new clinical drug trials are initiated (National Agency for Medicines 2003). The number of trials is tenfold higher than might be expected on the basis of the Finnish population and pharmaceutical market. However, the number of new trials started has not increased in recent years. In 2001, there were 523 on-going clinical trials, with the trials being conducted for 314 drugs; 262 (83%) of them new chemical substances (Bengtström 2002). The number of subjects participating in the trials has varied between 32 000 to 61 000 in 1995 to 2002. Out of 60 pharmaceutical companies operating in Finland, approximately 40 carry out clinical trials in the country. There were 370 pharmaceutical industry employees involved in carrying out clinical trials in 2002 (Pharmaceutical Information Centre 2003). R&D expenditure of the pharmaceutical industry in Finland amounted to 167.7 million euros in 2000, which was an increase of 16.9% compared to 1999.
(Aaltoinen 2002). In 2002, the figure had risen to 252 million euros (Pharmaceutical Information Centre 2003).

The situation of special populations has also been considered and the regulatory authorities and legislation support clinical trials in children. The medical research act (1999) emphasises the special position of children in clinical trials and a discussion document on the ethical aspects of trials in children has been issued to try to create common rules and to provide recommendations for conducting paediatric trials (Löjtönen et al. 2002). There is a long tradition of undertaking paediatric clinical trials in Finland, e.g. large vaccine trials have been done in Finland for decades, for example the trials reported by Peltoła et al. (1977), Karma et al. (1985), Takala et al. (1998), Eskola et al. (2001), and Pang et al. (2001).

2.3.4. Barriers to and factors favouring trials

2.3.4.1. Barriers to and factors favouring trials from the viewpoint of investigators

The implementation of a trial often encounters various practical problems, failures, and barriers despite well-prepared trial protocols and other plans. In the literature, several published papers dealing with studies of investigators' factors favouring trials and barriers to their participation or to subject accrual exist, a clear majority of them in cancer therapy. Questionnaires or interviews as data collection methods have been used in those publications. The papers are based on the study data providing either general information about the issues or specific results obtained in a certain subject population or treatment area, or the papers provide general information or experiences not based on the original study data, in the form of special communications and review articles or commentaries. Some representative studies with their objectives, methods, settings, and number of respondents are presented in Table 1.

There are many barriers to physicians' participation, either affecting their decision to participate or willingness to recruit subjects into clinical trials (Table 2). In the literature, time constraints and administrative burden have been highlighted. The increasing management and administrative duties associated with clinical trials falling on the physician-investigators apart from their other work activities, data recording and completing forms, lack of training or previous experience in carrying out clinical trials as well as lack of assisting personnel have been identified as factors influencing participation and/or subject recruitment in trials. If
Table 1. Some representative studies of physicians’ views of participating and recruiting subjects in clinical trials

<table>
<thead>
<tr>
<th>Author(s) and reference</th>
<th>Objective</th>
<th>Method</th>
<th>Setting and country*</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al. 1984 and Taylor 1985</td>
<td>subject accrual/physician (non)participation</td>
<td>questionnaire</td>
<td>breast cancer specialists CAN, US</td>
<td>91</td>
</tr>
<tr>
<td>Taylor and Kelner 1987</td>
<td>physician (non)participation/subject accrual</td>
<td>questionnaire &amp; interview</td>
<td>breast cancer specialists SEVERAL</td>
<td>484</td>
</tr>
<tr>
<td>Taylor et al. 1987</td>
<td>physician (non)participation/response to informed consent regulations</td>
<td>questionnaire &amp; interview</td>
<td>breast cancer specialists SEVERAL</td>
<td>170</td>
</tr>
<tr>
<td>Penn and Steer 1990</td>
<td>physician (non)participation</td>
<td>questionnaire</td>
<td>obstetricians, consultants in 36 hospitals, UK (not applicable)</td>
<td></td>
</tr>
<tr>
<td>Benson et al. 1991</td>
<td>subject accrual</td>
<td>questionnaire</td>
<td>cancer oncologists, US</td>
<td>244</td>
</tr>
<tr>
<td>Fisher et al. 1991</td>
<td>subject accrual</td>
<td>questionnaire</td>
<td>cancer oncologists, US</td>
<td>75</td>
</tr>
<tr>
<td>Foley and Moertel 1991</td>
<td>subject accrual</td>
<td>questionnaire</td>
<td>cancer various specialists, US</td>
<td>209</td>
</tr>
<tr>
<td>Tognoni et al. 1991</td>
<td>subject accrual (report)</td>
<td>general practitioners cardiovascular, ITA (not applicable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor 1992a,b</td>
<td>physician (non)participation</td>
<td>questionnaire &amp; interview</td>
<td>ocular cancer various specialists CAN, US</td>
<td>96</td>
</tr>
<tr>
<td>Smyth et al. 1994</td>
<td>physician (non)participation</td>
<td>questionnaire</td>
<td>cancer, UK</td>
<td>287</td>
</tr>
<tr>
<td>Taylor et al. 1994</td>
<td>physician (non)participation</td>
<td>questionnaire &amp; interview</td>
<td>cancer various specialists, US</td>
<td>1485</td>
</tr>
<tr>
<td>Williams and Zwitter 1994</td>
<td>response to IC process</td>
<td>questionnaire</td>
<td>cancer, various specialists SEVERAL</td>
<td>60</td>
</tr>
<tr>
<td>Hjorth et al. 1996</td>
<td>physician (non)participation/subject accrual</td>
<td>questionnaire</td>
<td>cancer, various specialists NORDIC</td>
<td>93</td>
</tr>
<tr>
<td>Lynèe et al. 1996</td>
<td>attitudes to inform subjects</td>
<td>questionnaire</td>
<td>cancer various specialists, SWED</td>
<td>304</td>
</tr>
</tbody>
</table>
physicians have to do the trial administration without assistance or support of their own organisation, it may be too burdensome and incompatible with their clinical workload, as emphasised by Langley et al. (2000).

Difficulties in obtaining informed consent, informing subjects about the trial, or its interference with physician-patient relationship have been reported to be a substantial barrier, causing uncertainty or problems in several trials (Table 2). Additionally, ethical concerns with respect to informed consent or the randomisation procedure have been noted as being problematic (Schafer 1982, Taylor et al. 1994, Langley et al. 2000), thus causing problems in subject recruitment. Hjort et al. (1996) stated that ethical issues are dependent on the scientific objectives of a trial; it is easier for participating investigators to cope with the ethical concerns if the scientific question underpinning a trial is sound and generally accepted.

When recruiting trial subjects, concerns on the impact on the physician-patient relationship have been raised (Table 2). According to some physicians, the relationship can be damaged if their patients participate in trials. Additionally, physicians worry about the
<table>
<thead>
<tr>
<th>Factor</th>
<th>Author(s), reference and country**</th>
</tr>
</thead>
</table>
| Time constraints (lack of time, time demands etc.)                   | Taylor et al. 1984 & Taylor 1985, CAN/US  
Benson et al. 1991, US  
Fisher et al. 1991, US  
Foley and Moertel 1991, US  
Taylor 1992b, CAN/US  
Mansour 1994*  
Smyth et al. 1994, UK  
Aaronson et al. 1996*  
Fallowfield et al. 1997, UK  
McCaskill-Stevens et al. 1999, US  
Ellis 2000*  
Sminoff et al. 2000, US  
Pallot et al. 2002, US  
Cohen 2003* |
| Administrative constraints (completing forms, data recording, lack of assisting personnel etc.) | Taylor and Kelner 1987, SEVERAL  
Fleming 1990*  
Penn and Steer 1990, UK  
Benson et al. 1991, US  
Fisher et al. 1991, US  
Foley and Moertel 1991, US  
Tognoni et al. 1991, ITA  
Taylor 1992b, CAN/US  
Mansour 1994*  
Smyth et al. 1994, UK  
Taylor et al. 1994, US  
Inoue 1998*  
McCaskill-Stevens et al. 1999, US  
Ellis 2000*  
Sminoff et al. 2000, US  
Christian et al. 2002*  
Cohen 2003* |
| Problems in informed consent process (obtaining consent, informing process etc.) | Taylor et al. 1984 & Taylor 1985, CAN/US  
Taylor and Kelner 1987, SEVERAL  
Taylor et al. 1987, SEVERAL  
Benson et al. 1991, US  
Fisher et al. 1991, US  
Smyth et al. 1994, UK  
Taylor et al. 1994, US  
Williams and Zwitter 1994, SEVERAL  
Aaronson et al. 1996*  
Fallowfield et al. 1997, UK  
Inoue 1998*  
Ellis 2000*  
von Raak et al. 2002* |
| Concern for the effect on physician-patient relationship, loss of autonomy | Taylor et al. 1984 & Taylor 1985, CAN/US  
Taylor and Kelner 1987, SEVERAL  
Taylor et al. 1987, SEVERAL  
Fleming 1990*  
Penn and Steer 1990, UK  
Benson et al. 1991, US  
Tognoni et al. 1991, ITA  
Taylor 1992a,b CAN/US  
Mansour 1994*  
Taylor et al. 1994, US  
Lynöe et al. 1996, SWE  
Fallowfield et al. 1997, UK  
Inoue 1998*  
Ellis 2000* |
| Trial-related issues (inflexibility, lack of scientific sound, uninteresting etc.) | Taylor et al. 1984 & Taylor 1985, CAN/US  
Fleming 1990*  
Penn and Steer 1990, UK  
Benson et al. 1991, US  
Foley and Moertel 1991, US  
Tognoni et al. 1991, ITA  
Taylor 1992b, CAN/US  
Mansour 1994*  
Taylor et al. 1994, US  
Hjorth et al. 1996, NORDIC  
Lynöe et al. 1996, SWE  
McCaskill-Stevens et al. 1999, US  
Ellis 2000*  
Sminoff et al. 2000, US  
Lars et al. 2001, US  
Paller et al. 2002, US |
Table 2. (continues).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Author(s), reference and country**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject-related issues</td>
<td>Fleming 1990*</td>
</tr>
<tr>
<td>(cost to subjects, other</td>
<td>Benson et al. 1991, US</td>
</tr>
<tr>
<td>concerns, treatment benefits</td>
<td>Fisher et al. 1991, US</td>
</tr>
<tr>
<td>etc.)</td>
<td>Foley and Moertel 1991, US</td>
</tr>
<tr>
<td></td>
<td>Mansour 1994*</td>
</tr>
<tr>
<td>Reimbursement/financial</td>
<td>Taylor and Kelner 1987, SEVERAL</td>
</tr>
<tr>
<td>issues</td>
<td>Benson et al. 1991, US</td>
</tr>
<tr>
<td>(financial compensation</td>
<td>Tognoni et al. 1991, ITA</td>
</tr>
<tr>
<td>recognition, prestige etc.)</td>
<td>Taylor 1992a, CAN/US</td>
</tr>
<tr>
<td></td>
<td>Taylor 1992b, CAN/US</td>
</tr>
<tr>
<td></td>
<td>Fleming 1994*</td>
</tr>
<tr>
<td></td>
<td>Mansour 1994*</td>
</tr>
<tr>
<td></td>
<td>Smyth et al. 1994, UK</td>
</tr>
<tr>
<td></td>
<td>Taylor et al. 1994, US</td>
</tr>
<tr>
<td></td>
<td>Hjorth et al. 1996, NORDIC</td>
</tr>
<tr>
<td></td>
<td>Fallowfield et al. 1997, UK</td>
</tr>
<tr>
<td></td>
<td>Glass and Kane 2000, SEVERAL</td>
</tr>
<tr>
<td></td>
<td>Lara et al. 2001, US</td>
</tr>
<tr>
<td></td>
<td>Joffe and Weeks 2002, US</td>
</tr>
<tr>
<td></td>
<td>Paller et al. 2002, US</td>
</tr>
<tr>
<td></td>
<td>van Raak et al. 2002*</td>
</tr>
<tr>
<td></td>
<td>Cohen 2003*</td>
</tr>
</tbody>
</table>

*) Papers based on reviews, general information, experiences etc. but not on study data.
**) Country: CAN = Canada, ITA = Italy, NORDIC = Nordic countries, SEVERAL = several countries, SWE = Sweden, UK = United Kingdom, US = United States

complex role of being both a researcher and a healer (Taylor et al. 1984, Taylor et al. 1987, Penn and Steer 1990, Taylor 1992a,b, Langley et al. 2000). Since the study protocol has to be strictly followed in any clinical trial, it restricts the decisions of physicians on how best to treat their patients. This has been reported to affect the decisions of the physicians in subject recruitment. Also, uncertainty about the best treatment for a subject has been a major cause for concern for the physicians (Taylor et al. 1984, Taylor and Kelner 1987, Benson et al. 1991, Taylor 1992a,b, Taylor et al. 1994, Siminoff et al. 2000).

Trial-related factors, such as lack of a scientifically valid question, an uninteresting trial or inflexibility issues have also been identified as influencing factors for participation (Table 2). Scientific aspects of a trial, e.g. study question, design, or uninteresting trial, may be reasons why a physician may refuse to participate or recruit/refer subjects to a trial (Benson et al. 1991, Foley and Moertel 1991, Tognoni et al. 1991, Lynøe et al. 1996, Paller et al. 2002), or the complexity of the trial or complicated eligibility criteria can be inhibitory factors.
Correspondingly, contribution to the progress of science, medical care benefits and innovative compounds may be major reasons supporting participation (Hjorth et al. 1996, Glass and Kane 2000, van Raak et al. 2002). It has been emphasised that the trial protocol should be pragmatic, clear, simple, and address a question that is of clinical importance (Foley and Moertel 1991, Ross et al. 1999, van der Windt et al. 2000). In fact, inadequate planning at all levels of a trial results in problems in subject recruitment (Lovato et al. 1997), and poorly planned and executed trials are clinically unethical (Pocock 1983). Subject-related factors, such as concerns for extra costs or burden for subjects, caused by the trial participation have been raised by several authors (Table 2).

Reimbursement factors, rewards contributing to the investigator's career prospects or the institution's reputation, payments or other personal inducements have been reported as an incentive or their non-existence as barriers to participate (Table 2). Educational benefits, e.g. learning more about current treatment methods, have been reported to be a promoting factor for investigator participation in clinical trials (Hjorth et al. 1996). Hjorth et al. (1996) and Fallowfield et al. (1997) found out in their studies that financial aspects had only minor importance both for the physicians' participation in trials and subject recruitment. However, participants requesting reimbursement for the numbers of subjects that they recruited had higher inclusion rate compared to those that did not request payment (Hjorth et al. 1996). Langley et al. (2000) stated that physicians' participation in trials was an additional burden and did require incentives and additional motivation. Thus, according to published papers it seems that reimbursement can influence the trial, either as an incentive or a barrier to physicians' participation (Benson et al. 1991, Fleming 1994, Mansour 1994, Taylor et al. 1994, Lara et al. 2001, Cohen 2003). According to Glass and Kane (2000), financial factors for European investigators will become more important, since, similar to the situation in the United States, trials in Europe are carried out by younger investigators who are more price-driven than their older colleagues. When trial subjects were asked, they stated that they believe that physicians' major motive why physicians participate in clinical trials is for economic gain, i.e. support from the pharmaceutical industry (Madsen et al. 1999).

Regarding subject recruitment, a number of papers have been published concerning those factors which influence the accrual, especially in oncology (Table 1). According to the findings by Comis et al. (2000), even though physicians are aware that more cancer patients should be included in trials they do not uniformly encourage participation as most of them think that their
patients would be reluctant to take part. Gottay (1991) reviewed seven trials which aimed to find out the reasons for failure to accrue eligible subjects into cancer trials. Physician-related variables, such as medical considerations, were the major reason for failure while subject-related variables were less common (Gottay 1991). Since it is a critical step in any clinical trial, subject recruitment can be a major obstacle in the implementation of trials and can cause major delays in drug development (Humminghake et al. 1987, Lovato et al. 1997, Yee 2003). If there is an excessively low rate, i.e. lower than planned, it prolongs the duration of the trial, delays the analysis and time when the results are obtained, or even can jeopardise the entire trial (Taylor et al. 1994, Siminoff et al. 2000, Iam et al. 2001). Thus, the co-operation of physicians is essential in the success of any trial as they act as gatekeepers by encouraging or discouraging subjects to participate (Taylor et al. 1984, Taylor and Kelner 1987, Swanson and Ward 1995, Lovato et al. 1997). This role has been identified as contributing to an ethical problem, as most subjects trust their physician's opinion and may view any recommendation to participate as representing their optimal medical care (Cassileth et al. 1982, Bevan et al. 1993, Lymoë et al. 1996, Inoue 1998, Cox 2002, Getz 2002).

The subjects' individual characteristics may be impeding or facilitating factors when physicians approach potential subjects and tell them about potential trials. For example, a subject's low intelligence or educational level, poor disease status or prognosis, age, lack of trust in medicine, and poor emotional stability with a pessimistic or anxious attitude have all been reported to be impeding factors. Conversely, high intelligence or educational level, trust in medicine, and good emotional stability with optimistic and motivated attitude have been reported as promoting factors (Taylor et al. 1994, Fallowfield et al. 1997, Siminoff et al. 2000). Taylor (1992b) has found out that extremities in these subject characteristics may obstruct physicians in their desire to approach potential subjects.

It is evident that physicians' personal attitudes towards clinical trials have a substantial impact on their decisions to participate or recruit subjects into trials. Taylor (1992b) has stated that those factors which affect a physician's decision to participate in one trial may differ from those factors which affect his/her decision to participate in a particular trial. With the help of a questionnaire, Physician Orientation Profile, published by Taylor and Kelner (1987), physicians could be differentiated either to be researchers/experimenters or clinicians/therapists according to their attitudes toward subjects and clinical trials. Taylor and Kelner (1987), Taylor (1992b) and Fallowfield et al. (1997) have reported that most
investigators tend to be more oriented towards the clinician-type (therapist) than to the research-type (experimenter). Therapist-oriented physicians are more willing to consider their role as being responsible for primary decision making, are more reluctant to try new treatments, and are more sceptical towards the efficacy of unproved therapies. Their relationships with their current patients are individual and direct. Experimenter-oriented physicians consider that their task is to obtain scientific data and medical uncertainty is a prerequisite for future research - thus they feel they have a responsibility for future patients (Taylor and Kelner 1987). Joffe and Weeks (2002) also came to similar conclusions in their study. Additionally, variation between different professional groups of physicians has been identified (Benson et al. 1991, Fallowfield et al. 1997, Joffe and Weeks 2002). As Pocock (1983) has stated, individual ethics and collective ethics may mutually compete when a physician makes decisions and each trial requires a balance between these polarities.

According to the findings by Fallowfield et al. (1997), reluctance of physicians to participate in a trial is a larger barrier to its successful completion than the reluctance of subjects. They noted that 269 (76%) out of 353 investigators had included less than 50% of their eligible patients. Langley et al. (2000) identified four stages which could be viewed as barriers to clinicians: awareness of ongoing trials, acceptability of trials to recruiting investigators, acceptability of trials to subjects, and whether the clinical situation is conducive to actual recruitment. Lata et al. (2001) summarised the barriers into four groups, 1) physician, 2) protocol or eligibility, 3) subject, and 4) funding barriers.

2.3.4.2. Barriers to and factors favouring trials from the viewpoint of subjects

Several papers dealing with subject barriers to and factors favouring trials have been reported. The factors influencing subjects' participation in clinical trials as stated in some representative studies are presented in Table 3. The subjects' reasons for unwillingness to participate are manifold. Trial-related and attitudinal factors, such as fear of receiving placebo, unknown adverse events, being used as a “guinea pig”, desire for another treatment, concern about getting an inferior treatment, and informed consent issues have been commonly identified (Table 3). Randomisation is a complex issue. Dislike of the possibility of randomisation may be a significant obstacle or may confuse subjects (Llewellyn-Thomas et al. 1991, Hokkanen et al. 1997, Fallowfield et al. 1998, Featherstone and Donovan 1998) or it
may have no influence on the subjects' attitudes towards clinical trials (Madsen et al. 1999 and 2000). Practical issues, such as lack of time or other time considerations, distance from the trial centre, transportation or parking problems have also been identified as obstacles (Table 3).

Lack of information about on-going trials can be a reason for non-participation. Generally, individuals other than those actually working in the healthcare field consider clinical trials as something of a mystery and do not know much about them, how they are actually organised, their objectives, and significance to medical science. As stated by Kjaergaard et al. (1998), this raises the question of whether an increase in general knowledge about the basics of clinical research might positively affect the subjects' attitude towards clinical trials. They determined that better knowledge was associated with a more positive attitude towards participation (Kjaergaard et al. 1998).

Apart from lack of general information about trials, unawareness of a clinical trial and its procedures may cause concern. For example, understanding what a clinical trial really is, its basic premises, or what randomisation means, are aspects not easily perceived (Roberson 1994, Featherstone and Donovan 1998, Kjaergaard et al. 1998, Snowdon et al. 1998, Cohen 2003). On the contrary, there are subjects who would like to participate in trials but cannot be included due to entry criteria defined in the trial (Taylor et al. 1994, Lara et al. 2001, Comis et al. 2003, Neuer 2003). Additionally, the impact of the media reporting on public trust may cause hesitation and create obstacles to participation in a clinical trial (Kelch 2002, Yee 2003). There are also the well-known past abuses of subjects in clinical research, such as the Tuskegee Syphilis Study which can still cause suspicion and mistrust (Freimuth et al. 2001).

A large telephone survey by Comis et al. (2000 and 2003) identified the existence of a pool of potential participants. The public, cancer patients, physicians, and journalists were interviewed about their attitudes towards cancer clinical trials; it did seem that awareness of clinical trials among patients as a treatment option was very low. The general public respondents had a positive attitude towards clinical trials and eight out of ten would consider participating in a trial if they suffered cancer (Comis et al. 2000 and 2003). This positive attitude by the general public and out-patients was also reported by Madsen et al. (1999).

A subject's willingness to participate in further trials may be influenced by prior experiences and satisfaction with previous trial participation (Hudmon et al. 1996, Suomen 4S-tutkimusryhmä 1996, van Stuijvenberg et al. 1998, Madsen et al. 2000 and 2002, Niles 2003).
Table 3. Factors influencing subjects' participation in clinical trials.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Author(s), reference and country</th>
</tr>
</thead>
</table>
Table 3. (continues).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Author(s), reference and country*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altruism (benefiting future patients, contribution to science)</td>
<td>Carew et al. 1987, US</td>
</tr>
<tr>
<td></td>
<td>Bevan et al. 1993, UK</td>
</tr>
<tr>
<td></td>
<td>Hokkanen et al. 1997, FIN</td>
</tr>
<tr>
<td></td>
<td>van Stuijvenberg et al. 1998, NL</td>
</tr>
</tbody>
</table>


*) Country: AUS = Australia, DK = Denmark, FIN = Finland, NL = Netherlands, SWE = Sweden, UK = United Kingdom, US = United States

However, former participation may also have an adverse impact. Madsen et al. (1999) reported that former participation had changed several subjects' attitude negatively, mainly due to the lack of feedback of trial results. Trial subjects are rarely informed about their treatment allocation at the end of trials (Di Blasi et al. 2002). Thus, after-care of trial subjects should not be forgotten.

Subjects' motivations/reasons to participate have been identified also, such as receiving better care and attention or benefit for one's condition, receiving new(er) or better treatment, or to comply with the physician's request or recommendation (Table 3). The subject's trust in his/her physician can be a critical factor when he/she makes a decision on whether or not to participate (Lynøe et al. 1996). Expectations to be treated as a special subject in a trial may have a positive impact on participation (Madsen et al. 2000). Furthermore, the presence of an ethics committee which guarantee the conduct of the trials according to accepted ethical principles has been found out to have a significant positive effect on the subjects' attitudes towards clinical trials (Madsen et al. 1999 and 2000). Altruism, such as benefiting future patients or contribution to science, has been a common reason to participate as identified by
several authors (Table 3). However, the review paper by Edwards et al. (1998) points out that subjects’ self-interest rather than altruism seemed to be a more frequent motive for participating in clinical trials. As Beecher (1976) has stated, it is evident to every investigator that ordinary patients will not knowingly risk their own health or their own life for the sake of science. Financial issues, such as compensation or incentives, have been pointed out to be a positive factor to participate in a trial. On the contrary, the participation may have a negative impact on subject’s insurance (reimbursements) and thus be a negative factor (Table 3).

2.3.4.3. Barriers to and factors favouring trials from the viewpoint of the pharmaceutical industry/sponsor

There is little published information comprehensively examining the barriers to and the factors favouring trials from the viewpoint of the pharmaceutical industry. In general, most published papers provide anecdotal experiences or comments from pharmaceutical executives when they struggle to undertake clinical trials for their new drugs more rapidly, cost-effectively, and with high quality. Apart from the burdens in cost attributable to drug development in general, the barriers or problems seem to be linked with regulatory affairs of trials, trial start-up activities, the relationships with investigators and investigators/trial sites, delays in subject accrual, and the public image of industry-driven clinical research.

Several barriers and problems in regulatory affairs have been identified. The increasing bureaucracy generated by the EU and its less pragmatic approval process have been criticised. Additionally, harmonisation has been seen as being too difficult due to variations in interpretation and implementation of the EU directives in the many member countries (Donald 2001, Sullivan et al. 2003). Especially, slowness or problems in obtaining ethics committee approval have been criticised by several authors as causing significant delays in obtaining trial results from the drug development cycle (Ahmed and Nicholson 1996, Redshaw et al. 1996, Dal-Ré et al. 1999, Lux et al. 2000, McNay et al. 2002, van Raak et al. 2002). A burdensome or complex application procedure or national/local ethics committees’ diversity in practice have been special causes of concern (Ahmed and Nicholson 1996, Redshaw et al. 1996, Dal-Ré et al. 1999, Tully et al. 2000, McNay et al. 2002), which presumably are obstacles to the pharmaceutical industry but also to the investigators. Lack of administrative and financial support have been noted, especially local ethics committees have
been reported to lack resources and training, and hence, being overwhelmed by the extensive documentation they have to review and its related administrative burden (Burman et al. 2001, Raymond 2001, Maloy et al. 2002). Tully et al. (2000) reported that local ethics committees asked for many non-local changes to the application of their large multicentre trial which they submitted to one multicentre ethics committee and 125 local ethics committees in the United Kingdom. Additionally, the need for standardisation of practices is evident, e.g. with the help of standardised forms and instructions, as has been emphasised by several authors (Smyth et al. 1994, Middle et al. 1995, Redshaw et al. 1996). International multicentre trials can be a special problem due to the diversity of ethics committees and their practices in different countries which causes extra burden in wasted time and financial resources to trial sponsors (Bruner and Nahler 1999b, Binns and Driscoll 2000, McNay et al. 2002). Thus, problems exist both at the national and international levels.

Start-up is a challenging phase in any trial. According to Bonner (2002), about 20% of the sites conducting clinical trials have reported increasing complexity of the contractual and budgeting process over the past few years. Bureaucracy of both sponsors and universities frustrate both parties (Paller et al. 2002). Zapol (2001) has pointed out that the difference between academia's and the pharmaceutical industry's structures is a major cause for the slow and problematic negotiation process. Inflexibility or inefficiency of academic institutions, with their awkward bureaucracy, and sluggishness to respond to the increasing pressure for rapid decisions have been noted (Ferguson et al. 1999, Schuster and McGill 2001). In general, contracting, budgeting, and payments have been considered to be the most inefficient parts in trial start and obtaining all the required approvals can be overwhelming, or at least the most cumbersome part of a trial (Bruner and Nahler 1999a, Maloy et al. 2002, Shah 2003). Greed and tardy responses from the trial sites due to their inexperience or bureaucracy have been causes of complaint and the need for a more business-like approach and professionalism in administrative affairs have been requested by the sponsors. However, trials sites seem to blame sponsors for the same reasons (Maloy et al. 2002). Established networks of investigators and other site management services have been realised to facilitate the tedious start-up processes and to be a way to introduce more professionalism into administrative affairs (Ferguson et al. 1999, Vincent-Gattis et al. 2000, Allen 2001, Zisson 2001).

Lewis (1997) reported that activities done in clinical trials have been underrated in academic medicine for decades. Thus, the change which has occurred in these attitudes is welcomed. The need for a better quality of the sponsor-trial site relationship has been recognised. Allen (2002) described in a European survey that two thirds of the trial sites assessed the relationship with sponsor and trial sites as average or poor. Additionally, most (57%) delays in the development of new drugs are due to problems occurring at the trial sites (Glass and Kane 2000, Brittain-Dissont 2001). Delays in subject recruitment and problems in selecting investigators cause major expenses and workload of trials (Hunninghake et al. 1987, Swanson and Ward 1995, Bonner 2007).

Problems in subject recruitment causes the largest delays in the drug development process (CenterWatch 2003). About 25% of delays in the drug development phase are caused by recruitment failures (Getz and Kenna 1998). It has been estimated that about 80% of trials fail to reach their target number of subjects recruitment within the agreed schedule (Getz and de Bruin 2000, Maloy et al. 2002). According to Bonner (2002), almost 60% of trial centres have reported that they must prolong subject recruitment beyond the project schedule. Thus, it is evident that the pharmaceutical industry places increasing demands on the investigators and trial sites to speed up the process to get their products to market. To enhance this crucial aspect of subject accrual, sponsors have taken a larger role in supporting the process and increased the financial support invested for the promotion of recruitment (CenterWatch 2003). Subject recruitment and retention activities, as well as administrative affairs, need time and effort. Hence, having a coordinator has been considered as helpful, even essential, by both sponsors and trial sites (Engelking 1991, Petrovitch et al. 1991, Mansour 1994, Bonner 2002, Paller et al. 2002).

The relationship with the mass media is also complex. Throughout the world, television, radio, and newspaper seem to be the leading channels where people learn about trials. These channels have been successfully used in clinical trials in subject recruitment, for example in the trials reported by Lewis et al. (1998), Löfdahl et al. (1998), and Kusek et al. (2002). On the contrary, the media can shape people’s opinions and arouse public concern about clinical trials which may cause subject hesitation and create obstacles (Grilli 1999, Alcasey and Dodson 2001, Kelch 2002, Yee 2003). According to Yee (2003), knowledge about clinical trials continues to be misunderstood by the media and the public, and media campaigns can even cause substantial harm (Passalacqua et al. 1999, Remuzzi and Schieppati 1999).
Generally, published articles in the media tend to be about failures or tragedies in clinical trials or the attitude/approach is negative (Madsen et al. 1999, Drennan 2001).

Conflicts of interest in clinical research are also counterproductive (Angell 2000, McCrady et al. 2000, Schulman et al. 2002, Baird 2003). For example, financial conflicts of interest, either direct or indirect, in the relationship between physicians and their patients have been considered to be especially problematic and the recommendation is that there should be complete transparency to avoid damaging the public’s confidence in clinical research (Keleher 2002). Since today physicians, hospitals, and other research centres are more active in business or they have many different roles: a physician may act sometimes as a physician or at times be a researcher (Lancet 2001), or an inventor, even a business executive etc., i.e. they may face major difficulties to reconcile all these roles and the physician-patient relationship may be challenged (Keleher 2002). In the worst scenario, failure in managing these roles can lead to fraudulent activity which in turn naturally arouses the media’s interest. This may dub the entire pharmaceutical industry with a negative image or reputation since they were sponsoring these scandalous trials. Additionally, it has been noted that the pharmaceutical industry has a major impact on the research topics which are selected. To avoid this problem, the relationship between researchers and the industry should be more independent (Bodenheimer 2000, Hole et al. 2001). However, there is another side to the coin: the profits generated from the projects sponsored by the pharmaceutical industry provides researchers with a degree of financial freedom to carry out other research of their own choosing (Hole et al. 2001).

2.3.4.4. Suggestions for improvements

Improvements in submission practices. To minimise delays or other problems in the submission processes associated with the struggle of the local ethics committees to cope with handling the masses of paperwork with their limited resources, Maloy et al. (2002) suggested that there should be a move towards the use of a central ethics committee. This would be more efficient and competent in its operations management and help in eliminating the problem of duplicate reviews by different ethics committees. However, it has to be stated that the reverse, i.e. decentralisation of the approval system from the central level to local ethics committees, has been implemented in Italy in an attempt to reduce approval times (Venturini
et al. 2001). Thus, the most efficient system seems to depend on the nature of the ethics committees and does seem to be a country-specific issue. The need for standardisation of the practices as well as registering and accreditation of IRBs have been discussed (Maloy et al. 2002, McDaniel et al. 2002). It has been suggested that registration of trials should be obligatory and decisions made by ethics committees should be public record (Savulescu et al. 1996, Blunt et al. 1998, Tonks 1999, Ashcroft and Pfeffer 2001, Ferris 2002, Mann 2002). This could help to prevent a company from starting duplicate trials of compounds shown already to be unsuccessful and avoid unnecessary effort and wasting resources. In Italy, decisions made by all local ethics committees have to be notified to the Italian Ministry of Health and these are included in its national database (Venturini et al. 2001).

Enhancing subject recruitment. According to Swanson and Ward (1995) and Ross et al. (1999), few researchers ever describe how they have overcome barriers to recruitment. Ross et al. (1999) highlighted four major ways to improve recruitment: 1) understanding the problems experienced and solutions used in current trials, 2) making sure that the optimum structure, personnel, and organisation for the trial exist, 3) identifying robust scientific trial designs which are attractive to investigators and trial subjects and which are compatible with routine medical care, and 4) understanding more clearly the reasons why investigators and trial subjects (non)participate in trials. Several papers have been published concerning the factors contributing to subject recruitment in cancer therapy (Table 1) as only 3% of adult cancer patients are estimated to participate in clinical trials in the United States (McCaskill-Stevens 1999). According to the findings of Comis et al. (2000), even though physicians are aware that more cancer patients should be included in trials, physicians do not uniformly encourage participation, as most of them believe that their patients would be reluctant to take part in a trial. The recruitment process should be planned carefully and preferably piloted to avoid poor recruitment. Additionally, demands of the trial protocol should be kept to a minimum, and dedicated trial personnel could assist in trial procedures, e.g. provide information, assist in subject recruitment, and monitor the recruitment process (Ross et al. 1999, Cohen 2003). King (2000) has suggested the creation of databases of subjects and investigators to enhance the recruitment of both. Online enrollment via the internet has been initiated and has increased rapidly, and there are positive signs that this may be an important channel in the future (Getz and Kenmon 1998). This has led to the establishment of commercial enterprises offering recruitment services (McDonald 2001, Waring 2002).
Swanson and Ward (1995) have suggested an extensive series of 20 steps which should be routinely included in the recruitment phase to improve recruitment of minorities, but could also be extended to other populations. The steps include: 1) a survey of the defined population, 2) using focus groups to identify barriers, 3) recruitment of community leaders, businesses, social organisations, and other groups to give advice in trial development and implementation, 4) developing and presenting outreach programs and services for collaboration with the communities, 5) providing adequate funding and training for community providers and facilities, 6) recruiting and training trial staff from target populations, and 7) developing support groups to facilitate trial participation (Swanson and Ward 1995). According to Brown et al. (2002), successful recruitment of women needs a linkage of practical strategies and social skills. As reported by Roberson (1994) it is important to appreciate and understand the cultural traditions of special groups to be better aware of their preferences and barriers to participating in trials.

_Treating subjects as customers._ As highlighted by Neuer (2003), subjects should be treated as customers. According to the results of an online interview of approximately 1000 subjects, poor customer service was a major problem: approximately 40% of pre-qualified subjects failed to be recruited due to inconvenience and lack of responsiveness from the trial centre (Neuer 2003). Creating special relationships with participants and giving them a medical check-up have been identified as important factors in recruitment, even a major incentive, to participate in a trial (Brown et al. 2002). El-Sadr and Capps (1992) have suggested that unawareness about the nature, aim, and procedures of clinical research among people is a significant obstacle in recruitment. Building understanding, trust, and educational programs for the general public about the requirements and aims of clinical trials are needed as well as describing how trials are actually conducted (Baum 1993, Millon-Underwood et al. 1993, Ellis et al. 2001, Kermani and Bonacossa 2003). Additionally, giving more detailed information about clinical trials may improve the subjects' attitude and hence likelihood of their participation (Kruse et al. 2000, Yee 2003). If subjects were more aware about the general principles and practice of clinical research already before they entered into a trial, it would benefit the investigators in their possible struggles with ethical and time burdens, such as in their conflicting role as a physician and a researcher, or in the time needed to inform subjects at the start of the trial. Additionally, as Di Blasi et al. (2002) emphasised, patients should be treated as participants rather than subjects to increase their commitment to the trial.
While subjects have to be well informed at the trial start they should also be informed at the end of the trial. This could help to avoid negative attitudes or persisting bad memories due to lack of information, misunderstandings or other outstanding issues (Di Blasi et al. 2002). Also, this could alleviate the feeling being used as a "guinea pig".

Increasing information, education, and training. Lack of information about clinical trials, as well as education and counselling have been highlighted (Foley and Moerel 1991, Kjaergaard et al. 1998, Schuster and McGill 2001), especially when special populations, such as particular racial or ethnic groups, are concerned (Roberson 1994). There appears to be a chasm between perception of non-participation and reality between physicians and subjects (Roberson 1994, Swanson and Ward 1995, Comis et al. 2000, Siminoff et al. 2000). The ability to communicate can be overcome by giving training in communication skills to the investigators. This is especially useful when they are approaching potential trial subjects, informing them, and obtaining consent (Fallowfield et al. 1997, Albrecht et al. 1999). Additionally, training of trial staff can eliminate delays in trial conduct (Bonner 2002). Not only should written information be provided to potential participants. Alternative information tools, like audio/videotapes or interactive computer programs, as well as other ways could be used to educate subjects. Also more suitable, less complicated, text might be one way to increase the participation rate (Aaronson et al. 1996, Weston et al. 1997, Brown et al. 2002, Cox 2002). Kruse et al. (2000) reported that detailed written information can significantly improve the subjects' attitudes and participation in clinical trials. The internet could be a novel way to inform potential subjects about starting and ongoing trials and to facilitate subject accrual, and it would also increase overall awareness of clinical trials (Getz and Kennon 1998, King 2000). Nowadays people can view new and ongoing trials via the internet through several web sites of trial listings (McDonald 2001). Additionally, people can register their e-mail address listing even several medical conditions from which they suffer, so that when the relevant clinical trials are started, they can be automatically notified.

Interaction with primary health care and other interest groups. Partnerships with primary care communities could enhance subject recruitment. McCaskill-Stevens et al. (1999) reported a promising initiative, i.e. they organised workshops between minority communities and research centres to increase minority accrual to cancer clinical trials, and developed communication material, such as newsletters, brochures, and pocket cards, to aid recruitment. However, these types of operations require additional resources to arrange and coordinate the
interaction with physicians and also need time and resources to explain the trials to the subjects, to handle the extra paperwork and other administrative tasks, as emphasised by McCaskill-Stevens et al. (1999). By creating functional, two-way communication channels with community physicians, useful networks are created providing opportunities for both patients and physicians (Cohen 2003). Furthermore, close communication between the trial organisation/sponsor and (referring) investigators has an important effect on subject accrual. This includes, for example, awareness of the trials to be started and participation in investigator meetings (Fleming 1990, Benson et al. 1991, Fisher et al. 1991, Mansour 1994, Hjorth et al. 1996, McCaskill-Stevens et al. 1999). Facilitating and encouraging these interactions has also been emphasised by several authors, e.g. Fleming (1990), Giuliano et al. (2000), Langley et al. (2000), and Schuster and McGill (2001). Experiences gained from the involvement of consumers, such as (potential) patients, carers, or organisations representing the interests of consumers, in the design and conduct of trials have been positive (Hanley et al. 2001). At the very least, the consumers’ contributions should bring a more pragmatic aspect into the planned trials. Additionally, extra time and resources (Giuliano et al. 2000) as well as adequate funding and better contribution from the government in recognition of the importance of clinical trials in cancer have been proposed (Smyth et al. 1994).

Collaboration with the mass media. Since it is the principal source of information about health issues, the mass media may positively affect the use of health services and act fruitfully at the interface between research and health services (Grilli 1999). The mass media is an increasingly important tool in shaping opinions and increasing public awareness of clinical trials (Foley and Moertel 1991, Grilli 1999, Alcasey and Dodson 2001). Additionally, the mass media can be a powerful tool in educating the general public of the benefits of clinical trials (Foley and Moertel 1991, Freimuth et al. 1991, Niles 2003). However, the use of public relation companies and direct marketing in subject recruitment is more limited in Europe than in the United States (Barzilay 2002). According to Grilli (1999), both journalists and health care professionals should follow common rules and have a common language to build a bridge between the parties, in order to avoid misunderstandings and negative publicity (Passalacqua et al. 1999, Remuzzi and Schieppati 1999). Drennan (2001) has emphasised the need for building public goodwill. Dedicated call centres or multimedia call centres, i.e. a mix of traditional telephone, public access points, e-mail, and interactive television, have been used and claimed to be beneficial (King 2000).
Improving site management affairs. The working environment in a hospital can encourage physicians to participate in trials (Fallowfield et al. 1997). In the United States, the establishment of clinical trial offices in academic health centres is quite a new phenomenon. It is estimated that since 1992, almost 90 out of the largest 125 academic health centres have set up centralised clinical trial offices (Borfitz 2002, Paller et al. 2002). Positive experiences from these centralised clinical trial offices have been reported by Schuster and McGill (2001) and Paller et al. (2002). These authors claim that the offices help investigators and enhance collaboration with trial sponsors. Paller et al. (2002) reported time savings at the start of a trial (reduction from 171 to 57 days) and in time needed to obtain ethics committee’s approval (reduction from 62 to 44 days) due to the more efficient clinical trial office activities. They highlighted the importance of budget negotiations, prompt and frequent communication with sponsors, and the fundamental benefits of creating sustainable relationships. To make the negotiation process more efficient, Zapol (2001) has pointed out that the negotiators should have easier access to the sponsor’s decision makers. Lewis and Lewis (1997) have suggested more professionalism, courtesy, and amenities by the academic institutions towards the trial sponsors to make themselves more attractive as trial sites. Furthermore, they highlighted the opportunities and benefits provided by clinical trials both in the view of academic missions and the finances that they generate (Lewis and Lewis 1997). The slowness of trial sites, their inexperience, and overwhelming bureaucracy have been causes of complaint as have their poor business-like manner. Thus, the site management organisation (SMO) has been born. SMOs have evolved quickly to fill this niche, since they can act in a more business-like manner cutting through bureaucratic red tape as well as increasing the efficiency of subject and investigator recruitment (Vineent-Gattis et al. 2000, Allen 2001, Brittain-Diasont 2001). Additionally, web-based clinical trial management systems have been reported to bring benefits in centralising trial information and co-ordinating the trial processes, thus enabling trial sites to focus more on medicine, clinical practice, and science rather than on trial administration (Santoro et al. 1999, Dorman et al. 2000, Marks et al. 2001).
2.4. Quality and regulatory compliance of clinical drug trials

2.4.1. Quality assurance and audits

The responsibility of the trial sponsor is to implement quality assurance activities in their clinical research. Quality assurance covers all the planned and systematic actions which are in place to ensure that the trial is performed and the data are generated, documented, and reported in compliance with GCP and the relevant regulatory requirements (ICH GCP 1997). Audit, as a part of quality assurance, is a systematic and independent examination of a trial related activities and documents to assess whether the trial was conducted and the data were recorded, analysed, and accurately reported according to the trial protocol, the sponsor's SOPs, GCP, and the relevant regulatory requirements (ICH GCP 1997). Audits are sample-like; not all trials are submitted to audits. The number of trials to be audited depends on the sponsor's SOPs and audit plans which are linked to the importance of the trial in relation to submission to regulatory authorities, trial type and complexity, the risk levels to the subjects, or any problem(s) identified in the trial (ICH GCP 1997). Apart from assurance of trial quality or deficiencies found which need to be corrected, audits can give valuable information for future trials to improve their quality or to better conduct in practice. In extreme cases, audit results may reveal serious GCP violations and misconduct in clinical trials (Chaturantabut 2000, Gottlieb 2000, Mudur 2001, Sidney 2001). To assess the quality of randomised controlled trials, several scales and checklists have been developed since 1981 as reviewed by Moher et al. (1995).

Jenkins (1994, 1995a,b, 1996), Brunier and Nahler (1998), and Bohaychuk et al. (1998a,b,c,d,e, 1999a,b) have performed wide international audits in several countries. These independent auditors have reported major deficiencies in GCP compliance. Based on their databases of 226 GCP audits of trial centres, reports, laboratories, databases, and SOPs in over 20 countries in Australia, Europe, and the United States, from 1989 to 1995, the auditors Bohaychuk et al. (1998a) declared only an average of 67% level of GCP compliance. They also found out that GCP compliance was not dependent on any particular country, therapeutic area, CRO used, or the phase of a trial (Bohaychuk et al. 1998a). According to the findings of Brunier and Nahler (1998), slightly more weaknesses were revealed in eastern than in western European countries but this was not confirmed by Neal (2001). On the contrary, according to
Bohaychuk et al. (1998a), GCP compliance was dependent on the pharmaceutical company sponsoring the trial, with non-compliance ranging from 21% to 57% between 31 companies. In contrast, Brunier and Nahler (1998) did not find any clear dependence on the sponsor between 12 companies and their 23 clinical trials undertaken in 80 trial centres. An average of 2 to 3 serious and 9 to 10 less serious events of non-compliance per trial site were found out in 88% of the trial sites that Bohaychuk et al. (1998b) audited. The most serious events that they identified were significant discrepancies between source data and case record forms (CRFs), inadequate evidence that subjects had fulfilled the inclusion criteria, safety issues in storing investigational products at the trial site, and discrepancies in the drug accountability. Thus, the quality of the SOPs from the sponsors could be improved (Bohaychuk et al. 1998b,c).

Frequent deficiencies in quality, timing, and documentation of consent have been disclosed with respect to audits of informed consents in 306 trial centres (Bohaychuk et al. 1998d). Similar findings were reported by Jenkins (1995b). Brunier and Nahler (1998) detected more GCP violations in informed consent process, e.g. missing consent forms, in eastern European countries. Audits of 114 trial protocols dealing with their contents and management have shown non-compliance with many common requirements and guidelines and resulted in only a 60% level of GCP compliance (Bohaychuk et al. 1999b). With respect to dealings with ethics committees, few serious non-compliance events were identified, but less serious events have been frequent, such as deficiencies in approval documents received from ethics committees, or serious adverse events not reported to ethics committees (Bohaychuk et al. 1998a,b). There were also many significant deficiencies found in the audits of documents concerning ethics committees' review of trials at 321 trial centres in over 20 countries: Bohaychuk et al. (1998e) found an overall compliance level of 55%; i.e. 60 of 109 query items of their audit. Thus, there have been serious doubts about the timing, i.e. which documents exactly were reviewed by ethics committee, by whom, and according to which procedures (Jenkins 1995a, Bohaychuk et al. 1998e). Since Bohaychuk et al. had applied the same standards to all of their audits, they conceded that differing requirements in different countries, such as ethics committees' procedures, might have influenced their results. Thus, this should be taken into account when interpreting their results.

Based on the reports of audit results published in the literature, there is much to be improved in overall GCP compliance globally. There was little change in overall compliance
from 1991 to 1995, i.e. Bohaychuk et al. (1998a) were clearly disappointed to note that very little progress had been achieved despite the introduction of new regulations and guidelines during the first half of the 1990s. Additionally, the authors did not expect much improvement due to forthcoming ICH guidelines unless better control is obtained via GCP inspections (Bohaychuk et al. 1998a).

2.4.2. Inspections

As a distinction to audits performed by trial sponsors, inspections represent the activities by regulatory authorities to perform an official review of trial documents, facilities, and records. Any other resources located at the trial centre, sponsor, CRO, or at other establishments considered by the authority(ies) to be related to the trial can be the targets for inspections (ICH GCP 1997). Inspections are sample-like and, hence, are similar to audits. If a new drug application is submitted to the EMEA to go through the centralized procedure, the EMEA coordinates the GCP inspection. The inspection is sample-like and retrospective, reviewing information backwards from the summary of product characteristics up till the submission of the separate clinical trial reports. The inspections concern mainly pivotal trials and can be carried out at any time during the review process of the application. During the active phase of the trials, inspections can also be carried out by the authorities of the countries in question (Sweeney 2001). Inspections have revealed GCP deficiencies, for example, the Committee for Proprietary Medicinal Products (CPMP) recommended intensive post-marketing surveillance for all new patients using a particular drug and new clinical trials to be undertaken after deficiencies were revealed in two of the three pivotal trials, on which marketing authorisation of the drug had been based (EMEA 2001).

The GCP directive states that the EU countries have an obligation to appoint inspectors to monitor trial facilities, especially the sites where trials are performed, manufacturing facilities of investigational drugs, laboratories where clinical analyses are made, and/or sponsor’s facilities. Inspections are carried out under the authority of the member state in question and on behalf of the whole community. Then, other member countries mutually recognise the findings of the inspections (the European Parliament and the Council of the European Union 2001). Member states of the EU share a common database of clinical trials, EudraCT, which contains also data concerning inspections made and their outcomes (European Commission
2003). Despite the low figure of GCP inspections carried out for centralised procedures in 2000, their number has increased markedly and will increase in the future (EMEA 2003a,b, Sweeney 2003). Currently, a total of 56 site inspections have been conducted (Sweeney 2003). With respect to national GCP inspections, about 120 per year have been conducted in the EU and the European Economic Area. Identified deficiencies, such as protocol compliance, validation of laboratory assays, adequacy of monitoring and follow-up, and investigational product accountability, indicate failures to comply with the basic principles of GCP (Sweeney 2003).

In the United States, the FDA has conducted inspections of clinical investigators since 1962 (Lisook 1994). GCP inspections are heavily targeted to investigators, and GCP violations may lead to sanctions, i.e. being placed on a "black list" of investigators; disqualification or restrictions in his/her professional activities. Since 1995, there have been 300 to 400 annual investigator inspections carried out in the United States. Most of the deficiencies have dealt with protocol deviations and inaccurate records (Lepay 1999, CenterWatch 2003). The FDA reports that, both in 1999 and 2000, there was a tenfold increase in the number of complaints reported against trial centres and this trend has still been increasing in 2002 (Gamache 2001, CenterWatch 2003). In Japan, since 1997 there have been 331 trial centre (hospitals) inspections covering 775 trials. Most of the deficiencies between 1997 to 2000 have dealt with documentation in CRFs, inappropriate work of IRBs or protocol deviations (Ono et al. 2002) though informed consent deficiencies have also been found (Lepay 1999, Ono et al. 2002). In Finland, the regulatory authorities have conducted 2 to 5 trial site inspections per year during recent years (National Agency for Medicines 2003).

Apart from inspections of investigators and trial centres, also ethics committees have been inspected in the United States since 1980. Annually, there have been 250 to 300 IRB inspections, and 4 to 5% of them result in official action; typically a notification to the FDA of steps to be taken to come into compliance. Most of the deficiencies have dealt with quorum, minutes, and written procedures (Woollen 2000). Similar deficiencies have been reported by Ono et al. (2002) in Japanese IRBs. According to the report by Russo (2000), inadequacy of IRBs have been revealed by the Office of Inspector General in the United States leading to a call for better and more comprehensive training of investigators, better resources for IRBs, and a faster response from IRBs. Systems of IRBs have been criticised and accreditation of IRBs has been recommended (Morcno et al. 1998, Russo 2000, Donato
and Gibson 2001): these are now voluntarily underway similar to IRB registration (Maloy et al. 2002).

2.4.3. Quality and regulatory compliance of trials

There is little published data on the regulatory authorities' review of clinical trial submissions. However, safety concerns or protocol deficiencies/methodological issues have been reported by some authors after reviews by the authorities of new drug applications (EFPIA/FMEA 1998, FMEA 2000, FMEA 2003a) and after examining the reasons for withdrawals of new active substances from the market (Jefferys et al. 1998). Generally, poor study protocols have been reported to be the major reason for ineffectiveness being demonstrated during a clinical development. Nonadherence to the protocol has been the leading deviation reported by the FDA during their routine inspections (Lepay 1999), and protocol contents and management have been shown to be noncompliant with many of the common requirements and guidelines in many countries (Bohaychuk et al. 1999b). The FDA has reported that 25-50% of clinical trials supporting each new drug approval submission fail to fulfil their aims (King 2000). Analysis of the outcomes by the EMEA has highlighted the methodological concerns, such as trial design or choice of endpoint. Major objections have been raised over methodological issues related to efficacy (EMEA 2000). According to GCP inspections, clinical trial reports have sometimes failed to provide accurate description of the trial or have failed to report the problems, e.g., protocol violations, encountered during the trial (Sweeney 2003). The control of clinical development programmes as a whole has been criticised as being inadequate in many European countries (Anonymous 2000a), and there is a clear need to respond to the increasing criticism against the overall ineffectiveness of the clinical development process (Lightfoot et al. 1998, Tassignon 2000, Takeuchi 2002).

Generally, deficiencies in the informed consent procedure represent one area where there is the poorest GCP compliance (Bohaychuk et al. 1998d, Anonymous 2000b). A wide range of informed consent queries have been raised by ethics committees, e.g., inadequate information, use of jargon, poor clarity, incomprehensible consent forms, or consent procedures (Neuberger 1992, Kent 1999, Boyce 2002). Items related to trial protocols, such as design, statistics, trial procedures, or lack of information of the contents, have also been the sources of frequent criticisms (Winther and Iole 1997, Dal-Ré et al. 1999, Tully et al. 2000,
Boyle 2002), as have the safety issues associated with the trial (Wise and Drury 1996, Kent 1999, Boyle 2002). Additionally, Wise and Drury (1996) have reported remuneration considerations as a cause for concern due to the effect of possible inducement for physicians to recruit or retain subjects in a trial. Smith et al. (1999) have reported deficiencies in the follow-up monitoring of a sample of 30 trials that their local ethics committee had approved. They monitored several items, e.g. whether the trial had been started at all, adherence to the protocol, subject recruitment, and availability/completeness of consent forms and case records. As a result, incorrect completion of informed consent forms, inadequate filing of case notes and consent forms, and non-reporting of the abandonment or non-starting of projects were revealed (Smith et al. 1999). Additionally, they recommended that some monitoring of the trials that ethics committees have approved should be done, as has also been proposed by Neuberger (1992) and Berry (1997).

Bias in reporting results of clinical trials to the Finnish regulatory authorities, i.e. substantive evidence of selective reporting, have been revealed which may have resulted in inappropriate regulatory decisions. Bardy (1998) investigated 274 clinical trials submitted to the NAM in 1987 and their final reports received until 1993. Altogether 188 trials were classified as being positive, inconclusive, or negative outcome. The final reports of the trials with positive outcomes were significantly more often reported to the NAM than the trials with inconclusive or negative outcomes (Bardy 1998). The NAM has taken actions to handle the trial reports more expeditiously, i.e. by shortening the reporting timeline from two years to one year in their current regulation (National Agency for Medicines 2000), by renewing their data system to enable follow-up of the trials more closely, and by sending reminders to the trial sponsors. Melander et al. (2003) investigated 42 clinical trials submitted to the Swedish regulatory authorities between 1983 to 1999 and compared the results in the complete reports of the trials to the published reports. There were cases of multiple and selective publication. Selective reporting is the tendency to publish positive findings; in fact many publications reported the more favourable per protocol results rather than the intention-to-treat results (Melander et al. 2003). Thus, in clinical decision-makings reliance only on publicly available data from clinical trials may be based on biased evidence (Hemminki 1980, Keränen and Ylitalo 1999, Melander et al. 2003).
3. AIMS OF THE STUDY

Little is known about how clinical drug trials are conducted in Finland or the work of ethics committees' and regulatory authorities' reviews of trial applications/notifications, which are integral parts in maintaining a high ethical and methodological standard of clinical drug research. Furthermore, the barriers to as well as the factors favouring trials, and attitudes of physicians and the pharmaceutical industry towards conducting clinical drug trials have not been investigated in Finland. Information and knowledge about these aspects of conducting clinical drug trials in Finland could provide valuable insights into the optimal way to maintain a high research activity and how to improve the undertaking of future trials in Finland.

The specific aims were:

1. to examine the profile of clinical drug trials planned to be carried out in all study populations and separately in special populations such as children and adult healthy volunteers

2. to investigate the number and type of deficiencies in the applications/notifications submitted to the ethics committees and the regulatory authorities, concerning all study populations and separately children and adult healthy volunteers

3. to investigate the regulatory compliance of planned clinical drug trials

4. to assess the contribution of the GCP guidelines to the quality of trial applications/notifications during the 1990s

5. to assess the barriers to as well as the factors favouring trials, and attitudes of investigators and the pharmaceutical industry towards conducting of clinical drug trials
4. DATA AND METHODS

4.1. Data and study progress

4.1.1. Stages of the study

The study was performed in four stages covering different aspects as viewed by the interested parties, concentrating on two major factors: 1) quality and characteristics of clinical trials (stages 1 and 2), and 2) assessment for improvements in conducting the trials (stages 1 to 4).

The stages were:

<table>
<thead>
<tr>
<th>Stage 1.</th>
<th>To study the trials presented to ethics committees:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Profile of clinical drug trials submitted to ethics committees: characteristics of trials (number, type, design, phase, therapeutic area, duration, type of subjects, and centres)</td>
<td></td>
</tr>
<tr>
<td>- Number and type of deficiencies in the applications submitted</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2.</th>
<th>To study the trials presented to the regulatory authority:</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) - Profile of clinical drug trials submitted to the regulatory authority: characteristics of trials (number, type, design, phase, therapeutic area, duration, type of subjects and centres)</td>
<td></td>
</tr>
<tr>
<td>- Number and type of deficiencies in the notifications submitted</td>
<td></td>
</tr>
<tr>
<td>- Assessment of the effect of the GCP guidelines on the quality of trial notifications</td>
<td></td>
</tr>
<tr>
<td>- Assessment of the regulatory compliance</td>
<td></td>
</tr>
<tr>
<td>b) - Profile of clinical drug trials in special populations submitted to the regulatory authority: characteristics of trials (number, type, design, phase, therapeutic area, duration, type of subjects, and centres)</td>
<td></td>
</tr>
<tr>
<td>- Number and type of deficiencies in the submitted notifications of trials in special populations</td>
<td></td>
</tr>
<tr>
<td>- Assessment of the effect of the GCP guidelines on the quality of trial notifications</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3.</th>
<th>To assess investigators:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Assessment of the barriers to as well as the factors favouring trials, and attitudes of investigators towards conducting clinical drug trials</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4.</th>
<th>To examine the pharmaceutical industry:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Assessment of the barriers to as well as the factors favouring trials, and attitudes of the pharmaceutical industry towards conducting clinical drug trials</td>
<td></td>
</tr>
</tbody>
</table>
4.1.2. Data to study profile, regulatory compliance, and quality of clinical drug trials

The material to study the profile, regulatory compliance, and quality of trials and the impact of the GCP guidelines on them during the 1990s (I-III) consisted of the clinical trial applications submitted to two university hospital ethics committees (I) and notifications submitted to the NAM (II). The decisions of the ethics committees and the NAM on the applications/notifications during the years: 1992, 1994, 1996, and 1998 (I, II, III) and 2000 (III) were investigated. As the majority (63%) (II) of the clinical trials in Finland are carried out in the five university hospitals, two university hospitals' ethics committees were selected to represent these trial applications: Kuopio University & University Hospital Ethics Committee and Tampere University Hospital Ethics Committee (I). Between 57 to 112 applications for clinical drug trials were annually submitted to these ethics committees in these years. Amendments to the trial protocols approved in other years and notified during the years under our investigation were not included. Altogether 1174 notifications were submitted to the NAM during the four study years (II) and 1,437 notifications during the five study years (III), 362 of these trials involved special populations such as paediatric patients, the elderly, and adult healthy volunteers (III). The sample size enabled us to identify any trends in the quality of the notifications and also trends occurring in the characteristics of the trials. To cross-check notification compliance, the clinical trial applications submitted to the two university hospital ethics committees were reviewed to obtain the data for the examination and the data were compared to the notifications submitted to the NAM. The trials carried out in the university hospitals were cross-checked (II).

4.1.3. Data to assess barriers to and factors favouring trials from the viewpoint of investigators and the pharmaceutical industry

The material used to assess the barriers to as well as the factors favouring trials, and attitudes of investigators and the pharmaceutical industry towards conducting clinical drug trials consisted of the interviews of 20 physicians (IV) and 18 pharmaceutical industry representatives (V). Three subgroups of physicians and the pharmaceutical industry respondents were identified on the basis of their experience: long, limited, and negligible experience/reluctance to conduct clinical trials. The respondents in the subgroups were selected on the basis of information obtained from the chief or other physician(s) of the
clinics (IV) or on the basis of information from the pharmaceutical companies themselves (V), and according to the authors' personal knowledge of the respondents' involvement in clinical trials (IV, V). Sampling was discontinued when no new substantial information was obtained (IV, V).

4.2. Data collection

4.2.1. Profile, regulatory compliance, and quality of clinical drug trials

Retrospective investigation and data collection were carried out during July 1998 to May 2000 (I), January 1999 to September 2000 (II), and January 2002 to March 2002 (III). The applications, their amendments, the minutes of the ethics committees' meetings, and all other documents related to the trial applications available were analysed (I). The final study material consisted of 666 trial applications: the Ethics Committee of Kuopio University and University Hospital had reviewed 791 trials during the four study years, of which 285 were studies on medicinal products, and the Ethics Committee of Tampere University Hospital had reviewed 381 studies on medicinal products out of a total of 878 studies (I). Data were collected manually on special data collection forms by two data collectors, one in each university hospital. In case data interpretation was needed, the data collectors had agreed beforehand to use similar procedures. In case of ambiguous data obtained from the data collectors, they were contacted to clarify the situation. Also, missing items were enquired from the data collectors, i.e. they were asked to complete the items if possible by locating the missing information from the trial documents (I-III). Most of the data had been computerised by the NAM at the time of submission (II, III). The data which had not been computerised, the notifications, and related documents were examined and the data were collected manually (II, III). The manual data collection concerned altogether the notifications of 744 trials carried out in the five university hospitals (II), which is approximately two thirds of all notifications in Finland, and, 136 trials in special populations from 1992 to 2000 (III), i.e. two fifth of the notifications in those populations carried out in the five university hospitals.
4.2.2. Barriers to and factors favouring trials from the viewpoint of investigators and the pharmaceutical industry

In-depth personal interviews using a semi-structured questionnaire with eight (IV) and seven (V) pre-defined themes were used for data collection. In a semi-structured interview some aspects of the interview are fixed while the others not (Hirsjärvi and Hurme 2001). An introductory letter was sent to each of the selected participants, following a telephone or e-mail contact about arranging a personal interview. Personal information concerning the respondent and his/her experience of clinical trials was inquired at the beginning of the interview. The interviews were audiotaped and transcribed verbatim. Each interview took 1 to 2 hours. The themes/questions were pilot-tested with two clinicians (IV) and two pharmaceutical industry representatives (V) to check the appropriateness and the salience of any new key themes. The pilot interviews were not included in the analysis, except in study V.

4.3. Analysis of data

4.3.1. Profile, regulatory compliance, and quality of clinical drug trials

Descriptive statistics and cross-tabulations were used to present the profile of the clinical trials as well as their scientific and ethical validity by assessing the number and type of deficiencies in the applications (I) submitted to the ethics committees and in the notifications (II–III) submitted to the regulatory authority. Manually collected data were entered into the SPSS database (SPSS for Windows program version 8.0 (I, II), version 11.0.1 (III), SPSS Inc., Illinois, United States). An Excel format database (II, III) was received from the NAM and converted to the SPSS format. After the database had been edited, it was analysed with the computer program (I–III). Data regarding the reviews of Ethics Committees of Kuopio University and University Hospital and Tampere University Hospital were analysed separately (I). Data regarding the regulatory authorities’ review during 1992 to 1998 (II) and during 1992 to 2000 (III) were analysed initially year-to-year and the years were descriptively compared to assess the contribution of the GCP guidelines to the quality of trial notifications during the 1990s. Since almost all subjects of the special populations were adult healthy
volunteers or paediatric patients, these groups were analysed in detail and the results compared (III).

4.3.2. Barriers to and factors favouring trials from the viewpoint of investigators and the pharmaceutical industry

The interviews (IV, V) were analysed qualitatively by using content analysis. Qualitative methods are useful when trying to find out and to understand what lies behind phenomena about which little is known (Strauss and Corbin 1998, Hirsiärvi and Hurme 2001). Furthermore, the study area could be classified as being a more qualitative type of research as the intention was to find out the individuals’ beliefs, opinions, and attitudes. Data from the first interviews influenced and gave direction for subsequent data collection, and the pre-defined themes were supplemented or modified if new information emerged. Apart from the predefined themes/questions guiding the interviews, the analysis was started by the examination of the available data and determining what other items could be inferred that might be interesting. In practice, many content analysts start from this end though ideally a content analyst should first delineate the target for inferences (Krippendorff 1986). Similar or almost similar expressions of the respondents were combined and reduced to categories. Data coding was done based on the respondents’ answers, the study data, which is one valid approach with which to handle the coding (Hirsiärvi and Hurme 2001). The data were corroborated by multiple readings of the transcripts and considered adequate as soon as the findings seemed to iterate. Multiple coding was performed on five random transcripts, i.e. shared with a second author independently and the remaining fifteen (IV) and thirteen (V) transcripts were checked by the second author after the interpretations of the first author. Disagreements were discussed and resolved mutually. A word processor (Microsoft Word 2000, the United States) was used to facilitate the processing and management, e.g. searching and sorting of the data.

4.4. Ethical and confidentiality aspects

The study protocols were submitted to the Ethics Committees of Kuopio University and University Hospital (I, III) and Tampere University Hospital (I), and to the NAM (II, III).
After approval, they granted access to their archives by independent and designated persons (data collectors) who collected the data to maintain confidentiality (I-III). Approval to collect more detailed data of the trials was also obtained from all five university hospitals: University Hospitals of Helsinki, Kuopio, Oulu, Tampere, and Turku (II, III). All data received from ethics committees and the NAM were in an unidentifiable form; neither the medicinal product under investigation, the investigator, nor the sponsor could be identified (I-III). On behalf of all University Hospitals, the study protocol (IV) was approved by the Ethics Committee of Kuopio University and University Hospital. Minutes of the meetings of the Ethics Committee of Kuopio University and University Hospital, with the statement of the approval (IV) or the receipt of the application (V), were obtained before the interviews were started. All data obtained from the interviews were processed in an unidentifiable form, thus ensuring respondent anonymity (IV, V).
5. RESULTS

5.1. Profile of clinical drug trials in Finland (II, III)

5.1.1. Number of clinical trials

During the years 1992, 1994, 1996, and 1998, the Ethics Committee of Kuopio University and University Hospital reviewed a total of 285 and the Ethics Committee of Tampere University Hospital 381 clinical trial applications on medicinal products. The total number of trials had not changed during the course of the decade. A transient decrease in the number of phase IV trials was noted in the years 1994 and 1996 in Kuopio region, and an increase in the number of phase III trials in 1996 and 1998 in Tampere region (I: Table 1). During the years 1992, 1994, 1996, and 1998 the NAM had reviewed 1,174 clinical trial notifications on medicinal products (II). The annual numbers of notifications had ranged from 278 to 309. In 2000, the NAM had reviewed 263 notifications (III).

During 1992, 1994, 1996, 1998, and 2000, the NAM had reviewed 352 clinical trial notifications concerning paediatric patients and adult healthy volunteers with the minimum number being 46 and the maximum 99 per year (III). The annual number of notifications of paediatric trials ranged from 12 to 25 while the number of trials in adult healthy volunteers ranged from 19 to 75. The numbers of trials in all populations as well as in special populations have decreased since 1996 (II: Table 1), except for trials in paediatric patients which have increased (III: Table 1).

5.1.2. Characteristics of clinical trials

5.1.2.1. Trial phases, design, and object

Half of the clinical trials conducted in Kuopio and Tampere as well as in the whole country have been international studies (I, II). The majority (52%) of the clinical trials carried out in Finland have been international multicentre studies (II). Most studies undertaken in the 1990s have been phase III studies (I, II). The phase distribution of the trials have not changed markedly from 1992 to 1998 (II) (Figure 2).
When we examined the special populations, we noted that the majority (53%) of paediatric trials were phase III studies whereas phase I studies involved adult healthy volunteers (70%) (III). Placebo-controlled studies with or without active control drugs have been the most common trial design: in the trials undertaken in Kuopio (34%) and Tampere (37%) regions (I), in all populations (35%) (II), in paediatric trials (34%) (III), and in adult healthy volunteers with a cross-over design (42%) (III).

![Number of trials](image)

Figure 2. The clinical trial phases in the notifications reviewed by the National Agency for Medicines (NAM) from 1992 to 1998.

In a majority of the trials, regardless of whether they involved all study populations, special populations, or whether they were carried out in Kuopio and Tampere regions, a new chemical entity was investigated (Figure 3) (I: Figure 2) (II, III). Frequently, the trials conducted in Kuopio and Tampere involved investigations of some new indication or treatment combination (I: Figure 2). Moreover, new indication or postmarketing supportive items were frequently investigated in the trials involving all populations (Figure 3). In special populations, drug interaction trials (19% adult healthy volunteers) or trials in a new subject group (20% paediatric patients) were also frequently undertaken (III). Most of the trials in all populations (62%) and in special populations (55% adult healthy volunteers; 63% paediatric patients) were carried out on products which did not have marketing authorisation in Finland (II, III). Correspondingly, in both Kuopio and Tampere, half of the trials were carried out on products which did not have marketing authorisation (I). Most of the studies carried out in
Kuopio and Tampere pertained to nervous system or antinocplastic and immunomodulating agents (I). Nationwide, trials were mostly carried out with products for nervous and cardiovascular system diseases (Table 4). In special populations, the trials were mostly carried out with products for nervous system diseases (adult healthy volunteers) or anti-inflammation (paediatric patients) (III).

![Number of trials](chart)

**Figure 3.** The types of the trials in the clinical trial notifications reviewed by the National Agency for Medicines (NAM) from 1992 to 1998. Other = various trial types, e.g. new strength/dose/dosage regimen/drug combination, diagnostic trial or unspecified.

### 5.1.2.2. Trial participants, centres, and sponsors

Most trials (75%) were carried out in adult subjects (Figure 4). An average of one in every four trials included special populations, mainly adult healthy volunteers (71%) and paediatric patients (26%), but rarely the elderly (3%) (II, III). In the majority of the trials in Kuopio and Tampere, the number of subjects was between 101 and 500 (I: Figure 1). Nationwide, the number of subjects treated in Finland has ranged from 1 to 15 000, the
Table 4. Clinical trial notifications at the major therapeutic areas reviewed by the National Agency for Medicines (NAM) from 1992 to 1998

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Number of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>55</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>43</td>
</tr>
<tr>
<td>Anti-infectives for systemic use</td>
<td>24</td>
</tr>
<tr>
<td>Antineoplastic and immunomodulating agents</td>
<td>18</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>25</td>
</tr>
<tr>
<td>Genito-urinary system/sex hormones</td>
<td>22</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>27</td>
</tr>
<tr>
<td>Others</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>278</td>
</tr>
</tbody>
</table>

median number being 32 per trial (II). The international trials conducted in the university hospitals involved 16 to 15 000 subjects, with the median number of Finnish subjects in the whole trial being 330 (II). The number of child subjects enrolled and treated in Finland varied from 5 up to 30 000 and adult healthy volunteers from 5 to 450, with the medians being 44 and 13 per trial, respectively (III). In the international trials in paediatric patients conducted in the university hospitals, the figure ranged from 30 to 15 000, with the median being 300 (III). Most of the trial centres specified in the applications submitted to the Ethics Committees of Kuopio University and University Hospital and Tampere University Hospital were the respective university hospital clinics (74 %-78 %) (I).

Nationwide, university hospital clinics were the trial centre in 63 % of the trials. In multicentre trials, the proportion of university hospital clinics as trial centres was 40 % out of 1859 cases (Figure 5) (II). With respect to the special populations, the majority of the trials in paediatric patients were conducted in university hospitals (72 %) and private clinics (19 %). In adult healthy volunteers, most of the trials were carried out in university departments (29 %) and university hospitals (74 %). Most studies in special populations were single centre
trials (III). Most of the trials were sponsored by pharmaceutical companies; both trials involving all populations (81%), paediatric patients (78%), and adult healthy volunteers (66%), the rest being investigator-initiated trials (II, III).

Figure 4. Proportion of trial participants in the notifications reviewed by the National Agency for Medicines (NAM) from 1992 to 1998.

Figure 5. Diversity of trial centres in the notifications reviewed by the National Agency for Medicines (NAM) from 1992 to 1998.
5.2. Quality and regulatory compliance of clinical drug trials in Finland (I, II, III)

5.2.1. Acceptability by ethics committees

The Ethics Committees of Kuopio University and University Hospital and Tampere University Hospital raised questions or had comments on almost half (45%) of the submitted trial applications (I: Table 3). The percentage of approval by both ethics committees without any comments or questions decreased from 1992 to 1998, in Kuopio from 78% to 25% and in Tampere from 67% to 48% (I). Most of the questions pertained to subject information and the study protocol (I: Table 4).

5.2.2. Acceptability by regulatory authority

In accordance with the ethics committees' review, the regulatory authority raised questions or comments on almost half (45%) of the submitted trial notifications (II: Table 2). Most of the questions pertained to documentation of subject information but administrative issues and subject safety were also raised in several questions (II: Table 4). Some fluctuation in the number of questions regarding subject information, safety, and trial protocol occurred during the 1990s. Queries on subject information have increased but administrative questions have decreased since 1992. In 1996, there was a peak in the questions about safety issues, the highest during that decade (II: Figure 1).

Compliance with regulatory requirements was deficient in one third of the cases; reporting the trial commencements to the NAM was compliant in 76% of the trials approved by the Ethics Committee of Kuopio University and University Hospital and in 67% of the trials approved by the Ethics Committee of Tampere University Hospital. Out of 215 trials approved by the Ethics Committee of Kuopio University and University Hospital to be carried out in the university hospital, 157 (76%) of the trials had been notified to the NAM (8 trials from these 215 it ultimately appeared that such notification was not needed). Correspondingly, out of 324 trials approved by the Ethics Committee of Tampere University Hospital, 185 (67%) had been notified (49 trials from these 324 were considered not to need such notification) (II).
In the trials with special populations, one fourth (26% in adult healthy volunteer trials) to half (53% in paediatric trials) of the trial notifications were queried by the regulatory authority (III: Table 2). Most of the questions pertained to documentation of subject information in paediatric trials and subject safety issues in the trials with adult healthy volunteers (III: Table 4). Queries on subject information issues in paediatric trials have increased substantially since 1996 (III: Figure 1b) while queries on safety issues of trials in adult healthy volunteers were at their highest in 1996 (III: Figure 1a).

5.3. Barriers to and factors favouring clinical drug trials in Finland (IV, V)

5.3.1. Investigators' perspective

The major barriers seemed to occur at the beginning of the trial and mostly consisted of bureaucratic obstacles, lack of time, and laboriousness. Additionally, the inflexibility of the hospital routines and overtly strict in-house rules were said to be important factors which needed to be addressed in order to obtain greater flexibility, e.g. the setting up of a special research centre in hospitals or a SMO. An unsupportive attitude on behalf of the hospital or other collaborator(s), such as the municipal representatives, especially their inflexibility, decreased the investigators' motivation. On the other hand, vague rules or lack of information/operating procedures when starting a trial were a problem especially to inexperienced investigators. The least barriers were encountered in subject recruitment, clinical work, documentation, investigational product logistics, and communication with ethics committees (IV: Table 3a and b) (IV).

The reasons stated by investigators as dismotivating or motivating were often opposite to each other, e.g. financial issues or trial-related reasons. Apart from administrative affairs/bureaucracy, the greatest dismotivating factor reported was insufficient financial incentives. Sufficient financial incentives, the possibility to incorporate a personal sub-study or some other benefits for personal research/career were reported as the most motivating factors. Additionally, for most investigators, trial-related reasons, such as poor planning, poor design, and laboriousness, were common dismotivating factors, while the scientific and clinical interests of the trials were common motivating factors. In addition to scientific and clinical (pragmatic) interest in the trial, approximately half of all investigators reported their
motivation was increased by the availability of a study nurse, extra resources, or scientific merit. Having more time to do trials was often mentioned as a promoting factor (IV: Table 3a and b) (IV).

All subgroups of investigators expressed a positive attitude towards clinical drug trials. The possibility to conduct one's own sub-study and the scientific/clinical aspects that personally interested the investigator were experienced as being motivating factors. Investigators either with long or limited experience, but not those clinicians reluctant to participate in trials, were motivated by financial incentives. Experienced investigators tended to highlight bureaucracy/administrative constraints, a need for site management services, and criticised the attitudes and inflexibility of the hospitals. Those investigators with only limited experience reported a lack of information or inaccurate rules in the hospitals as being problematic and appreciated a study nurse's assistance and the educational aspects of clinical trials. The investigators who stated that they were reluctant to participate in trials were characterised by having scientific interests and a desire to gain merits (IV).

5.3.2. Pharmaceutical industry's perspective

The major barriers seemed to occur at the beginning of the trial and mostly consisted of bureaucratic obstacles. Current bureaucracy and the threat of its possible increase and, hence, a corresponding delay in the start of trials were worrying to the respondents. They hoped for a more positive attitude from the public sector, more flexibility in hospitals, and improved professionalism in practical implementation. Thus, if hospitals set up special research centres or site management services this was viewed as a welcome development and a clear way to obtain fluency and time savings. High costs were the greatest dismotivating factor and considered as a threat to carry out trials in the future. Moreover, if subject recruitment became problematic it would be a dismotivating factor to start trials in Finland. However, the respondents stated that currently subject recruitment was not a serious problem, nor were documentation, investigational product logistics, and communication with the regulatory authorities (V).

The quality, know-how, and reliability of the trial personnel, investigator register/pool, and increased, closer collaboration with the media in disseminating information about clinical trials to the general public were reported as highly attractive factors. This collaboration with the
media and efforts to promote clinical drug trials, e.g. with the help of campaigns, were appreciated not only because of the possibility to enhance subject accrual but also to disseminate general and impartial information about clinical trials to the public. Additionally, stricter timetable by all parties, e.g. by the NAM, ethics committees or investigators, in general were welcomed. According to the majority of the respondents, variations in the ways that local ethics committees carried out their activities was seen as problematic and it was felt that the ethics committees should adhere to common SOPs. Complete satisfaction was reported with the activity of the NAM, though one third of the respondents criticised the overlap of responsibilities between the ethics committees and the NAM, which could cause delays or other problems (V).

All subgroups of the pharmaceutical industry respondents expressed a common positive attitude towards carrying out trials in Finland, a need for training in GCP, bureaucratic constraints, a need for site management services, and co-operation with the media in disseminating information about clinical trials to the general public. The group with long experience emphasised the importance of successful subject accrual, considered financial issues as a threat, and criticised hospitals' attitude/inflexibility and in-house rules concerning the payment of the investigators' fees. The group with limited experience highlighted the contribution that could be made by other impartial interest groups to disseminate information about clinical trials to the general public. The group not carrying out trials in Finland complained that the small size of the national market influenced their attitude (V).

5.3.3. Similarities and differences in the responses of the investigators and the pharmaceutical industry

Bureaucracy was clearly the most frequently mentioned as a major barrier and dismotivating factor, either trial-related or related to the administration of sponsors or trial centres (hospitals). Since the bureaucracy/administrative affairs are concentrated at the trial start, it is evident that trial start-up activities were seen as a highly problematic aspect of a clinical trial by both the investigators and the pharmaceutical industry respondents. Additionally, a consensus was identified in their views on vague or unclear rules and operating procedures of hospitals: they both stated that there was a need for more professionalism in the site management activities. Since this deficiency also has its greatest
impact at the start of the trial it potentiates the obstacles raised by bureaucratic issues. Financial issues were stated as a dismotivating factor by both the investigators and the pharmaceutical industry respondents, though the focus of complaint was different. The pharmaceutical industry respondents criticised the general increase in the costs and the payment procedures of investigator's fees to hospitals while the investigators criticised the proportion of their fees deducted as administrative fees charged by the hospitals. The investigators' lack of time was commonly recognised by both the investigators and the pharmaceutical industry respondents (Table 5) (IV, V).

The investigators and the pharmaceutical industry respondents seemed to agree on what parts of the trial were most successful: subject recruitment, clinical phase of a trial, investigational product logistics, requirements for trial documentation, and investigator meetings (Table 5). GCP training was considered as beneficial by almost all investigators and the pharmaceutical industry respondents. The GCP training incorporated into the physicians' medical education programme was viewed as useful. Additionally, the award of a GCP certificate or some similar kind of authorisation to permit a physician to participate in a trial was also considered as a useful idea by most of the respondents. However, a voluntary system was preferred (IV, V).

Major differences were found in the factors favouring trials/motivating factors in carrying out clinical trials. For the investigators, personal motives, such as financial or other incentives and merits, were most important though scientific and clinical interests could be construed as representing more altruistic motives. In contrast, the motivating factors to the pharmaceutical industry were trial-related, i.e. how to get their trials performed more rapidly, conveniently, and with high quality. The company's responsibilities, objectives and motives naturally took precedence (IV, V).
Table 5  The barriers/problems and the factors favouring trials common to both the investigators and the pharmaceutical industry respondents in carrying out clinical drug trials.

| Current Problems: Barriers/problems in practical implementation of a trial | bureaucracy             |
|                                                                         | time constraints        |
|                                                                         | lack of hospitals' operating procedures / site management needs |

| Current Problems: Barriers/dismotivating factors in carrying out a trial as a whole | bureaucracy             |
|                                                                                     | financial issues        |
|                                                                                     | payment procedure of investigator fees |

| Current Problems: Most problematic activity in a trial | study start |
|                                                        | start-up negotiations / bureaucracy |

| Current Problems: Best arranged aspect in a trial | subject recruitment |
|                                                    | clinical phase       |
|                                                    | investigational products |
|                                                    | documentation        |
|                                                    | investigator meetings (important for both parties) |
6. DISCUSSION

6.1. Methodological considerations

The aim of this study was to investigate quality, the barriers to and the factors favouring practical implementation of clinical trials. The parties involved were ethics committees, the regulatory authority, investigators, and sponsors. Finland is a useful country in which to explore these issues because large numbers of subjects, i.e. from 32 000 to 61 000 during 1995-2007, participate in clinical trials annually (Pharmaceutical Information Centre 2003). In fact, the trial subjects are a fundamental part of any clinical trial, but they were not included in this study. Thus, it would be valuable to investigate their opinions in the future.

The aims of studies I to III were to characterise the profile of clinical trials undertaken in Finland. A qualitative approach, i.e. personal interviews in the studies IV and V, was utilised to obtain a better in depth insight during the face to face discussions. Furthermore, we could not include any pre-determined topics since these facets have not been investigated previously in Finland. The method made it possible for the respondents to declare which factors were important to them. However, a data collection method which relies only by interviews is limited in its ability to come to any robust conclusion of the topics being studied. Qualitative study reports typically do not give answers or do not justify generalised conclusions, but provide a description and an understanding of the situation. They generally augment and precede a quantitative study (Alasuutari 1999, Pope et al. 2000). Thus, the findings in studies IV and V mainly gave preliminary information and a verbal assessment of the current status, offering possible ideas for further studies.

In studies I to III, it was possible to describe the deficiencies in the trial applications/notifications but a deeper analysis, e.g. which kinds of deficiencies the subject information documents or trial protocols contained, could not be undertaken because detailed data were not available and examining of those files manually would not have been feasible. Additionally, the unavailability of trial protocols in the archives of the ethics committees created difficulties in obtaining accurate information for evaluating the regulatory compliance in reporting the trials to the NAM.

In interview studies, the sample size is usually small but the data obtained is extensive (Eskola and Suoranta 1998). Generally, the reliability of the data obtained by interviews is
subject to criticism, i.e. was the sample as well as the information obtained truly representative (Knappendorf 1986). Studies IV and V contained a small sample of interviewees and the respondents were encouraged to confide their opinions openly and sincerely. Sampling was continued until minimal or no new information was attained. The honesty of interviewees was assumed though an individual's tendency to give socially or generally acceptable answers (Hirsjärvi et al. 2000) cannot be totally ruled out. The interview guides were carefully prepared, and after pilot-testing we found no reasons to modify them either at all (V) or only marginally (IV).

The subgroups of the respondents (IV, V) with different lengths of experience in carrying out clinical trials meant that it was possible to have opinions from individuals with different experiences. In study IV, the investigators were selected from the speciality of cardiovascular research because it is a major therapeutic area, and a speciality involved in the investigation of many new drug entities in Finland. It also represents a widely-used therapeutic area compared to, for example, psychiatry which has specific distinct features. Thus, the selection of respondents might have interfered with the outcome of the results. The opinions of investigators working in cardiovascular medicine may not be strictly congruent with investigators in other specific therapeutic disciplines. In study V, no differences were anticipated between the responses from the approximately 20 companies participating (out of approximately 40 companies that perform clinical trials in Finland) compared to companies whose representatives were not selected to be interviewed, because the results of the interview findings seemed to be repeated over and over again. Additionally, the companies were selected from different therapeutic areas, though we did concentrate on those areas where most clinical trials in Finland are conducted. This guarantees that the findings are not specific to clinical trials of the therapeutic areas represented by one particular company. Additionally, both large and small pharmaceutical companies were selected.

The characteristics of the researcher can influence the reliability of a qualitative study (Eskola and Suoranta 1998). In these studies, the interviewer had worked for over 10 years in the field of clinical trials in a service provider company and was dependent neither on clinical investigators nor on the pharmaceutical industry. Her experience provided a solid foundation from which to conduct and interpret the findings. However, the objectivity of the interviewer had to be kept in mind during the interviews, especially the interpretation of the results as personal biases may easily influence how the interviews were interpreted. Hence, we
performed an independent multiple coding on five random transcripts by a second author. Additionally, the remaining transcripts were checked by the second author who confirmed the original interpretations. As the same person conducted all interviews, transcribed the first six tapes, confirmed all transcriptions of the remaining tapes, and coded all data, inter-individual variation was eliminated.

6.2. Clinical drug trials in Finland

Most of the clinical drug trials carried out in Finland during the 1990s were large international, phase III, placebo-controlled trials with/without active control(s) to investigate new chemical entities. The majority of the trials were carried out in the five university hospitals. Three fourths of the trials involved adult patients but one in every four examined adult healthy volunteers, paediatric patients or elderly persons. Out of this quarter, the proportion of paediatric trials was one in four while out of all the trials, paediatric patients were included in 6% of the trials. Most trials involving paediatric patients were phase III, placebo-controlled studies with/without active control(s), investigations on new chemical entities, and with products that did not have marketing authorisation. Only a few studies were carried out on elderly. Since children make up 18% of the total Finnish population (Statistics Finland 2001), they seem to be underrepresented in clinical trials, i.e. only 6% of trials were carried out in children (II, III). However, the number of new paediatric trials started in Finland is steadily increasing.

6.3. Quality and regulatory compliance of clinical drug trials

Based on the results in studies I to III, trial applications/notifications should be prepared more carefully when they are submitted to ethics committees and to the regulatory authority to obtain better compliance with the regulatory requirements and GCP, and in this way avoid unnecessary delays in the commencements of the trials. The number of deficiencies in the submitted documents increased most around 1994 and 1996, i.e. the time when GCP was increasingly adopted in clinical drug research. Additionally, based on the results obtained in study II, better compliance in the notification of trial commencements after receiving approval by the ethics committees is needed.
Ethics committees: Based on the review of documents submitted to two Finnish ethics committees, approximately half of the applications were incomplete. The ethics committees found most deficiencies in informed consent documents and trial protocols (I), as has been reported by others (Neuberger 1992, Dal-Ré et al. 1999, Kent 1999, Boyce 2002). The lack of detailed instructions issued to the applicants and the variations in practices of local ethics committees and their requirements may partly influence the number of questions raised. Similar problems attributable to the diversities in the practices of ethics committees have been pointed out also by other authors (Ahmed and Nicholson 1996, Redshaw et al. 1996, Tully et al. 2000). The findings in study I highlighted the urgent need to have written operating procedures for the ethics committees to improve and standardise their working practices and to help the applicants to prepare more complete documentation. The creation of well-defined, documented operating procedures by the ethics committees are imperative, not only for supporting the standardisation but also to ensure that the ethics committees comply with GCP guidelines. The need for standardisation of their activities has been emphasised by other authors (Idanpää-Helkkilä 1993, Scheinin 1997, McDaniel et al. 2002). Some progress in this matter has already occurred as the guidelines for submissions of clinical trials issued by the Sub-Committee on Medical Research Ethics have improved the quality of submitted trial documents (Halila 2001). However, about 40% of submitted applications still need re-evaluation and corrections. Subject information documents still seem to cause the greatest questions and problems (Halila 2001).

Regulatory authority: Approximately half of the submitted notifications to the NAM were not complete and the majority of the deficiencies dealt with subject information documents (II). In addition, more than half of the notifications on paediatric trials were not complete and most deficiencies occurred in subject information (III). Informed consent documents are generally found to be deficient in ethical review (Wise and Drury 1996, Kent 1999, Boyce 2002), in audits (Bohaychuk et al. 1998d, Brunier and Nahler 1998), and in regulatory inspections (Lepay 1999, Ono et al. 2002). Furthermore, the informed consent process can represent a (substantial) barrier to subjects and investigators against participating in trials. Indeed, informed consent is a complex process and the concept of clinical research is not easy for subjects to comprehend (Verheggen and van Wijmen 1996), two factors which makes the process challenging. There were some investigations and active debates about the amount and what kind of information should be given to trial subjects in the 1980s, during the advent of
randomised clinical trials (Schafer 1982, Simcs et al. 1986, Taylor et al. 1987, Williams and Zwiter 1994), and this has remained an active topic for investigations and discussions (Verheggen and van Wijmen 1996, van Stuijvenberg et al. 1998, Kruse et al. 2000). Given that informing children is more difficult than informing adults, ethics committees should provide clear instructions on how to prepare subject information to child patients. The ethics committees should have members experienced in working with children, as has also been highlighted by other authors (Jong et al. 2002, Pinkerton et al. 2002). Additionally, according to the GCP directive, trials in children have to be reviewed in an ethics committee which has expertise in paediatrics or has access to consulting experts in clinical, ethical, and psychosocial problems (the European Parliament and the Council of the European Union 2001).

Based on the results in studies I and II, the high frequency of queries regarding subject information and subjects' safety is somewhat surprising, given that ethics committees had reviewed and approved the trial documents before the submission to the NAM. This raises the question of whether the ethics committees have done their work with the utmost care. Additionally, the results in studies I and II indicated that the responsibilities held by the ethics committees and the NAM for issues concerning the trial subjects seem to overlap considerably, which leads to confusion as to which party has the right to final authorisation. This is time-consuming and delays the review process as both parties spend time reviewing the same documents. Thus, it is proposed that there should be a clear-cut allocation of responsibilities. With respect to the overlapping responsibilities to evaluate the scientific aspects of a trial, it may be difficult to clearly define which body should have final responsibility. As Pocock (1983) has stated, the ethics committees' responsibility should not be limited to what happens to an individual subject, as the scientific merit of any trial is strongly connected to ethics.

The role of the regulatory authority in the drug development process is much more extensive than reviewing the notifications/applications. All respondents from the pharmaceutical industry (V) were satisfied with the activity of the NAM when submitting their clinical trial notifications. There did not seem to be any need to have scientific consultation or more active communication with the regulatory authority, except for only one respondent who reported that this is generally desired by all drug developers (V). The more active role and openness from the NAM was also noted by the stakeholders in a survey conducted by the NAM (National Agency for Medicines 2002). Internationally, the
importance of the collaboration with the regulatory authorities in the drug development process has also been emphasised by other authors (DiMasi and Manoccha 1997, Takeuchi 2002). The EMEA reports that in 2002, about 42% of the approved medicinal products had previously benefited from scientific advice of the EMEA, compared to 90% of the withdrawn applications where scientific advice was not requested (EMEA 2003a).

6.4. Barriers to and factors favouring clinical drug trials

There were several factors identified which inhibited Finnish physicians from participating in clinical trials: time constraints, administrative burdens, trial-related factors, and financial issues. These are in accordance with the findings reported by other authors (Table 2). Additionally, trial start was found out to be the most problematic part of a clinical trial; investigators felt they were entangled with administrative issues/bureaucracy in hospitals. As Paller et al. (2002) have also reported, bureaucracy on the part of both sponsors and universities is frustrating to both parties. Though it is time-consuming, carefulness, meticulousness, and completeness during this phase of a trial by both sponsors and investigators/trial centres are crucial to avoid problems in the later phases. A lax attitude or inflexibility from the hospitals as well as their lack of professionalism in management, which were identified in this study, have been highlighted also by Lewis and Lewis (1997). In Finland, a more positive attitude to trials from municipal authorities has been noted (Vainikainen 2000). In fact, it is now appreciated that clinical trials in general in academic centres are under threat. If they are to continue, then attitudes and practice must be seriously addressed (Lewis and Lewis 1997, Larmas 2000, Schuster and McGill 2001, Zapol 2001, Paller et al. 2002). Frequent deficiencies in the start-up phase of trials have been identified in international audits (Bohaychuk and Ball 2000) which increases the pressure on the selection of trial centres (feasibility) and initiation processes of trials. Communication and transparency between investigators and sponsors are crucial. Potential sources of conflicts between investigators and sponsors are financial agreements and time limits (Wells 2001). The influence of financial issues on investigators' participation identified in this study has also been reported by others (Fleming 1994, Glass and Kane 2000, Langley et al. 2000).
6.5. Recommendations and future aspects conducting clinical drug trials in Finland

The Finnish health care system with its detailed patient records, medical know-how, technologically advanced infrastructure, and networking between the universities and the pharmaceutical industry provides an optimal environment and a solid basis for conducting clinical trials. However, based on the results of this study, several recommendations can be made to enhance their potential attractiveness:

*Improving submission practices.* Minimisation of delays and finding ways to achieve improvements in the whole application process, including the preparation of subject information documents and trial protocols, could be attained if the working practices of the investigators, applicants, and the ethics committees were standardised. More resources should be allocated to the implementation of the duties of the ethics committees. Regional ethics committees need standardisation of their submission practices, such as well-defined SOPs, common standardised forms, document tracking, and instructions for applicants (Smyth et al. 1994, Middle et al. 1995, Redshaw et al. 1996, McDaniel et al. 2002). Additionally, a clarification of the division of responsibilities between ethics committees and the NAM would save time and resources of the parties and, hence, minimise delays.

*Enhancing subject recruitment and management.* As highlighted by Benson et al. (1991) and Neucr (2003), subjects should be treated in a patient-friendly manner and viewed as customers, not subjects. The use of modern information technology in creating both subject and investigator databases could enhance their recruitment and help in managing the relationships more efficiently (King 2000). Indeed, well-managed, personalised relationships and satisfied subjects are the best advocates for future trials (Terenius 2000). Especially, the physicians’ role is crucial in informing subjects about available trials in which he/she can participate. Unawareness about the nature, aim, and procedures of clinical research among the general public is a significant obstacle to subject recruitment as has been reported by El-Sadr and Capps (1992). Thus, to improve understanding and trust, we should develop educational programs aimed at the general public about the needs and aims of clinical trials as well as the way that trials are conducted, as also stated by several authors (Foley and Moertel 1991, Baum 1993, Millon-Underwood et al. 1993, Ellis et al. 2001, Kermani and Bonacossa 2003). Furthermore, the potential contribution from patient groups and other interest groups should not be overlooked. Disseminating information about trials and encouraging a more active role
by physicians could markedly increase participation, as has been reported by Comis et al. (2000 and 2003) and Neuer (2003). To increase the number of children in clinical trials and the common acceptance of paediatric trials, both physicians and nurses as well as caregivers need training about the reasons and the ways how these trials are conducted, as stated by Kmietowicz (2000), Löjönen et al. (2002), and Shaddy et al. (2002).

**Interaction with primary health care system.** A better interaction with primary health care providers, i.e. health care centres, could enhance subject recruitment. As the majority of trial centres are organised in the university hospitals and concentrated in cities, collaboration with and access to the physicians and their patients in rural areas could be a potential source of new recruits. Communication with rural municipalities and their referring physicians could be fruitful and it would increase mutual collaboration and trust, and create useful networks allowing for both these patients and the physicians to participate in the trials, as documented by Mansour (1994), Giuliano et al. (2000), Vainikainen (2000), and Cohen (2003). The dissemination of informative material, e.g. newsletters or brochures, could not only facilitate recruitment, but would be productive in spreading awareness about the trials available and to encourage interaction (McCaskill-Stevens et al. 1999).

**Collaboration with the mass media.** Recruitment via the mass media, such as television, radio, and newspapers, has been shown to be effective (Levenskron and Farquhar 1982, Löfildal et al. 1998, Kusm et al. 2002). In Finland, as generally in Europe (Ganbrill 2002), recruitment using other channels than advertising in newspapers is rare. Thereby, valuable recruitment tools are not being utilised. Additionally, there should be enhanced use of the internet and e-mail when informing potential subjects about new and ongoing trials as well as disseminating general current information about clinical research. These technologies could greatly facilitate subject accrual and increase overall awareness of clinical trials (King 2000). The increased awareness may have a positive effect on the individual subjects’ potential to participate in a clinical trial (Kjaergaard et al. 1998). Educating the public about clinical trial participation, as highlighted by Foley and Moertel (1991) and Fallowfield et al. (1997), and a positive image of a trial among the target population are crucial (Levenskron and Farquhar 1982, Petrovich et al. 1991, Kermani and Bonacossa 2003).

**Investments in site management affairs and GCP training.** To overcome the delays and cumbersome onset of the trial due to administrative aspects and bureaucracy, as well as to manage the critical subject recruitment process, the establishment of special research centres
within hospitals or an extra-mural SMO could be a valuable resource. Thus, problems encountered due to the laconic attitude of the representatives of the public sector, inflexibility of the hospitals, inexperience in administrative affairs, and lack of specific operating procedures when starting a trial, could be counteracted. This may represent one way to curtail the spiralling costs and the red tape constraints due to bureaucracy. However, the hospital districts with university hospitals need financial support to build up an efficient, competitive, and attractive environment as places to conduct clinical trials and to create working relationships with municipalities (the local government area which pays for primary health care), primary health care providers, and other relevant interest groups. It is also recommended that greater resources be invested in GCP training of investigators, as pointed out previously by Keränen et al. (1998), this being preferably incorporated into the physicians' medical education programme or provided by SMOs. Likewise, GCP training is important also to other trial staff, e.g. to study nurses or coordinators. The training could be supplemented with a GCP certificate or equivalent program, at least for those physicians or individuals who intend to work in clinical research during their careers. Additionally, GCP training should be incorporated into the pharmacy education and provided to all members of ethics committees.
7. SUMMARY AND CONCLUSIONS

The majority of the clinical drug trials carried out in Finland are large international multicentre studies, placebo-controlled trials with or without active controls to study new chemical entities, mainly with products to treat nervous and cardiovascular system diseases. Most of the trial subjects are adult patients/subjects. One fourth of trials include special trial populations, mainly paediatric patients and adult healthy volunteers.

1. Both ethics committees and the regulatory authority raise questions or comments on almost half of the trial applications/notifications submitted to them. Most of the questions posed by the ethics committees pertain to subject information and the study protocol, whereas those presented by the NAM concern subject information, technical issues, and about the safety of subjects. Thus, submitted documents should be prepared more carefully to avoid unnecessary delays in the start-up of the trials and to achieve better GCP compliance.

2. Concerning the trials in special populations, one fourth to half of the notifications are queried by the regulatory authority. Most of the questions pertain to the documentation of subject information in paediatric trials and subjects' safety in the trials with adult healthy volunteers. Also these documents should be prepared more carefully than is currently the case.

3. Not all trials, nor the majority of trial completions, are reported to the regulatory authority though according to the regulations they should be reported. Thus, better compliance with regulatory requirements is needed.

4. Standardisation of the submission practices is needed to achieve better GCP compliance in the work of ethics committees. The variety of regional ethics committees is considered to be problematic, and the need for common SOPs is highlighted. The regulatory agency and ethics committees that review clinical trial documents should improve their present practices via a more distinct division of responsibilities.
5. Finnish investigators and the pharmaceutical industry have a positive attitude towards carrying out clinical trials in Finland. The least barriers for both the investigators and the pharmaceutical industry are encountered in subject recruitment, clinical work, documentation, investigational product logistics, and communication with ethics committees and the regulatory authority. Thus, many practical items of trials occur in a seamless manner which is viewed as an advantage when in the decision to undertake clinical trials in Finland.

6. The major barriers for both the investigators and the pharmaceutical industry occur at the beginning of the trial and mostly consist of bureaucratic obstacles. The most dismotivating factors for the investigators are insufficient financial incentives, trial-related reasons, and administrative affairs/bureaucracy. Correspondingly, the most dismotivating factors for the pharmaceutical industry are high costs and the constraints imposed by bureaucracy. Thus, financial issues and administrative management of trials entangled with bureaucracy need urgent actions to improve initiation of clinical trials in Finland.

7. Both clinical investigators and the representatives of the pharmaceutical companies sponsoring the trials would like to see a more positive attitude from the public sector, more specific in-house rules, flexibility and support from the hospitals, and professionalism in the practical implementation of clinical trials, e.g. the setting up of special research centres or site management services. Thus, investments are needed to improve on-site management activities and establishing this kind of services where they do not exist.

8. Training in GCP, mainly training incorporated into the physicians' medical education programme, or else a separate certificate or equivalent are generally considered as soon being necessary though a voluntary system is preferred. Thus, the medical faculties of the universities need to take urgent action to correct this deficit.

9. Collaboration with the mass media and other relevant parties to disseminate information about clinical research to the general public and promotion of GCP compliance are essential ways to approach the general public and to improve the public image of clinical
trials. Thus, there should be collaboration between the investigators/trial centres, the regulatory authority, the ethics committees, the pharmaceutical industry, and the Finnish mass media. This collaboration would be anticipated to ease some of the obstacles encountered in organising clinical trials.

The barriers to and the factors favouring trials found in this study should be considered in decision-making, to try to satisfy the various needs of all parties involved: trial subjects, investigators, trial centres, regulatory authority, ethics committees, and the pharmaceutical industry. This would ensure the creation of optimal conditions to guarantee that clinical trials are carried out in Finland also in the future.
8. REFERENCES


Borfitz D. Rethinking the role of AHC clinical trial offices. CenterWatch 9 (10): 1, 4-8, 2002.


Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Clinical Investigation of Medicinal Products in Children. CPMP/WP/467/97, March 1997


clinical/index2.html


LaRosa JC, Sneader GB, Boyle C. What kinds of studies should be required to probe efficacy and safety of drugs in special populations? Am J Cardiol 81 (8A): 84F-86F, 1998.


Smith T, Moore EJH, Tunstall-Pedoe H. Review by a local medical research ethics committee of the conduct of approved research projects, by examination of patients' case notes, consent forms, and research records and by interview. Br Med J 314: 1588, 1999.


Sweeney F. GCP inspection co-ordination. Presentation in: EMEA Workshop on Ethical Consideration in Clinical Trials London, November 7/01


