REPORT ON PROPOSAL TO FORM
A CLINICAL TRIAL UNIT
OF THE COPENHAGEN HEALTH SERVICES

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'To be free of large random errors trials must be large; for trials to be large, busy clinicians must be willing to enter their patients into them; therefore, trials should be designed to minimise the amount of paper to be read and forms to be filled in, and to make the management of trial patients deviate as little as possible from normal clinical practice with all its intuitive judgements and fuzzy edges. Thus, trials should generate the least possible amount of extra work for hard-pressed clinicians'.

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SUMMARY
INTRODUCTION
BACKGROUND
DEFINITION OF CONCEPTS
CURRENT INTERNATIONAL AND NATIONAL MULTI-CENTRE TRIALS
ORGANIZATION, COSTS, AND PRODUCTIVITY OF THE CLINICAL TRIAL UNITS
THE PRESENT STATUS AND FUTURE POTENTIAL OF RANDOMIZED CLINICAL TRIALS
CONTRACT RESEARCH ORGANIZATIONS (CROS)
DRUG AND DEVICE INDUSTRIES
RECENT DEVELOPMENTS OF RANDOMIZED CLINICAL TRIALS
REGULATIONS AND GUIDELINES AFFECTING CLINICAL TRIALS
CURRENT ORGANIZATION OF RANDOMIZED MULTI-CENTRE CLINICAL TRIALS IN COPENHAGEN AND DENMARK
RATIONALE FOR ESTABLISHING A CLINICAL TRIAL UNIT OF THE COPENHAGEN HEALTH SERVICES
GENERAL ARGUMENTS
INTERNATIONAL ARGUMENTS
DANISH ARGUMENTS
COPENHAGEN ARGUMENTS
PROPOSAL FOR THE FORMATION OF A CLINICAL TRIAL UNIT OF THE COPENHAGEN HEALTH SERVICES
OBJECTIVES AND AIMS OF THE COPENHAGEN CLINICAL TRIAL UNIT
ORGANIZATION AND STAFF OF THE CLINICAL TRIAL UNIT
COSTS OF THE CLINICAL TRIAL UNIT
ORGANIZATION OF THE RANDOMIZED CLINICAL TRIALS
PROJECTED PRODUCTIVITY OF THE CLINICAL TRIAL UNIT
COLLABORATION AND PUBLICATION POLICY
START OF THE CLINICAL TRIAL UNIT
RESEARCH TOPICS FOR THE CLINICAL TRIAL UNIT
PROPOSED DANISH NAMES FOR THE CLINICAL TRIAL UNIT
WEAKNESSES AND DISADVANTAGES
WEAKNESSES
POTENTIAL DISADVANTAGES
APPARENT DISADVANTAGES
CONCLUSIONS
ACKNOWLEDGEMENTS
APPENDICES
Appendix 1
DEFINITION OF ASSIGNMENT
Appendix 2
CLINICAL TRIALS
Appendix 3
LIST OF INTERVIEWED EXPERTS AND INSTITUTIONS, INTERNATIONAL AND NATIONAL

Appendix 4.1
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.2
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.3
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.4
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.5
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.6
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.7
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 4.8
Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.
Appendix 5
Appendix 6 METHODOLOGIC ADVANCEMENTS IN RANDOMIZED CLINICAL TRIALS
Appendix 7 HEALTH ECONOMICS
Appendix 8
QUALITY-OF-LIFE
Appendix 9
Drug Information Association-Forum on EUROPEAN BIOSTATISTICS GUIDELINES
Appendix 10
CURRENT RANDOMIZED CLINICAL TRIALS ACTIVITY WITHIN THE COPENHAGEN HEALTH SERVICES
Appendix 11

SUMMARY

The present report intends to answer four questions. How are international randomized clinical trials currently organized? Second, is there a rationale for the Copenhagen Health Services in establishing a Clinical Trial Unit? Third, which objectives and aims should such a Unit have and what would be an appropriate organization of a Unit? Finally, what are the potential weaknesses and disadvantages of a Clinical Trial Unit?

Randomized clinical trials are the cornerstone in evaluating the efficacy and potential adverse effects of new interventions. They are used for the approval of new drugs, and will in the future be used much more for the evaluation of surgical procedures, preventive interventions, etc. The increasing number and quality of randomized clinical trials will improve the quality of clinical practice.

How are International Randomized Clinical Trials Currently Organized?

During the last 30 years, a number of organizations have successfully specialized in facilitating and performing clinical trials. These organizations have proven their efficiency in performing large randomized clinical trials and improving the way that these trials are conducted. During the summer of 1993, a total of 43 European and North American institutions with a large experience of conducting randomized clinical trials were visited. Based on the experience and recommendations from a number of international and national clinical research organizations, it seems that randomized clinical trials can be organized in more effective ways. The methods used for raising the effectiveness of randomized clinical trials encompass increased information to the public and patients, formation of networks of researchers critically evaluating the ideas for trials, phone randomization procedures, methods for increasing patient recruitment, advanced data management systems, and speeding up publication and dissemination. International Clinical Trial Units coordinate a phase III randomized clinical trial at a cost of about DKK 1-5 millions and the coordinating team (medical trialists, statisticians, programmers, administrators, secretaries, data managers, data monitors) can coordinate about one trial per person every five years. By optimalizing the way randomized clinical trials are conducted, the results of the trials can be obtained at a faster speed and with more reliable results for the benefit of both actual and future patients. Hence, randomized clinical trials become more ethically acceptable.

Is there a Rationale for the Copenhagen Health Services in Establishing a Clinical Trial Unit?

The Copenhagen Health Services are engaged in a number of randomized clinical trials. However, the activity varies both within the primary and secondary health care sectors. At present, the Copenhagen Health Services do not have an non-specialty oriented organization facilitating, coordinating, and performing clinical trials. With the introduction of the EU guidelines for Good Clinical Practice in 1991 and the expected EU guidelines for 'Good Statistical Practice', 'Good Data Management', quality-of-life assessments and health economics, the requirements for conducting clinical trials have increased substantially during the recent years. It is therefore proposed that the Copenhagen Health Services should organize a non-profit, non-specialty oriented Clinical Trial Unit. Establishing a Clinical Trial Unit can be assumed directly to influence the quality of care of the Copenhagen Health Services, and is consequently of direct benefit to the citizens of Copenhagen.

Which Objectives and Aims should such a Unit have and what would be an Appropriate Organization of a Unit?

The proposed Clinical Trial Unit of the Copenhagen Health Services should facilitate, coordinate, and perform preventive as well as therapeutic randomized trials in both the primary and the secondary health care sector, facilitate and perform systematic reviews, participate in the further development of trial methodology, and teach clinical trial methodology at the graduate and postgraduate level. A Unit need not take initiatives in areas within the Copenhagen Health Services where randomized clinical trials are well functioning, but should rather develop new areas of research and facilitate trials in areas where a collaboration is considered advantageous.

With the proposed core staff of 5-6 people (two medical trialists, one programmer, one administrative personnel, one secretary) plus - depending on the activity - additional personnel and consultants (statistician, data monitor, lawyer,

health economist) it should be realized that a Unit will only be able to make a modest increase in the current research activities or to engage itself in a small part of the current research activities of the Copenhagen Health Services. However, a Clinical Trial Unit will create a number of advantages and opportunities for an estimated annual funding of about DKK 3 million.

What are the Potential Weaknesses and Disadvantages of a Clinical Trial Unit?

It should be possible to overcome the weaknesses, potential disadvantages, and apparant disadvantages of forming such a Unit, which should be seen as a service opportunity. It is not the intention to create new barriers or introduce new control mechanisms of current or future research activities, neither within or outside the Copenhagen Health Services. No real disadvantages have been identified.

INTRODUCTION

BACKGROUND

In spite of the significant progress in understanding the causes of diseases, which has occurred mainly in this century, our ability to prevent and treat these diseases leaves a lot to be desired. Moreover, there is consensus that the ability to prevent and treat the multitude of diseases will not generally be improved by single discoveries (e.g. like insulin for the treatment of diabetes mellitus) but rather through collaborative systematic research that improves the efficiency of prevention and treatment, stepwise but steadily.

Preventive and therapeutic research has increased considerably during the last four decades, nationally as well as internationally. Such research is conducted through the performance of controlled clinical trials, preferably randomized clinical trials (RCTs) (vide infra for definition) (Pocock, 1990). In order to gain more effective preventive and therapeutic possibilities, however, this research activity has to be intensified. The current research activity varies widely among different departments and sectors of the health services, and so does the quality of research (SOFIE Report, 1992; Organisationsudvikling i Krbenhavns Sundhedsdirektorat, 1993).

According to Pocock (1990) the main requirements for improvement of RCTs are better trial designs, more effective organization of trials, larger patient groups to be studied through multicentre collaboration, and more relevant questions to be answered. Internationally, a number of organizations have been developed during the last 30 years which facilitate and perform RCTs. This development has especially gained momentum during the 1980s. At present, no independent non-specialty oriented RCT organization exists in the Copenhagen Health Services or in Denmark, which can facilitate the performance of clinical trials in the primary and secondary health care sector.

Since the 1970s, many scientists in Copenhagen have shown an interest in forming an organization which could facilitate the performance of RCTs. In August 1991, the Copenhagen Health Research Council (Krbenhavns Sundhedsfaglige ForskningsrDd) concluded that it was necessary to examine the function and organization of leading international organizations in order to form an operational basis for deciding whether to form an organization in Denmark or not. This led to the actual assignment for the Planning Group of preparing an operational basis for this decision to be taken by the Copenhagen Authorities (Appendix 1).

The present report is a product of the discussions in the Planning Group, and an investigation of the research activities in Denmark and abroad. On the basis of information gathered in clinical research organizations, and in the drug and device industry, the present report will describe how international institutions successfully perform RCTs, the current activity of RCTs within the Copenhagen Health Services, and the possible structure of an organization, that could fit into the Danish environment, and could be built up in Copenhagen. The report intends to be a condensed version of the gathered information, and more detailed information may be obtained in the references and in a number of interviews with leading, internationally respected researchers in different areas and in the appendices of these interviews.

DEFINITION OF CONCEPTS

Clinical trials

The term 'clinical trial' may be applied to any form of planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients with a given medical condition. For a more detailed description of the phases of clinical trials see Appendix 2.

Randomized Clinical Trials

A randomized clinical trial (RCT) is a trial where a treatment (or intervention) is compared to another active reference treatment, placebo treatment, or no treatment. The fact that patients should be randomly assigned is not intuitively appealing either to the layman or to the medical profession. Randomized clinical trials encompass a number of ethical and practical problems. However, from non-randomized studies it is very difficult to obtain valid and reliable assessments of treatment efficacy and adverse effects (Pocock, 1990). Therefore, the randomized clinical trial is today the accepted method for evaluating therapies and interventions. RCTs form the basis for approval of medicine according to the law in Denmark, EU, and in other parts of the world.

Systematic Reviews and Meta-analyses

It is not reasonable to expect clinicians, policy makers, or patients who want reliable information about the effects of health care to unearth the relevant evidence from original research. Most people must rely on reviews, and during the 1980s a number of systematic reviews have appeared (Cochrane Collaboration, 1992). Meta-analyses are a relatively new method for reviewing and combining results from multiple controlled trials (Spilker, 1991). The present experience demonstrates that meta-analyses are a very strong instrument, which in the future may reduce the need of the very large trials if and when the data (preferably data from individual patients) from smaller trials are presented in a uniform manner (Antman et al., JAMA 1992; 286:240-248).

Clinical Research Organizations

A Clinical Research Organization is an organization, which facilitates, coordinates, and performs clinical trials, mostly RCTs. A CRO may be build up as an in-house organization in the drug and device industry or may exist as an organization outside the industry. In the latter case, these organizations may be divided into profit organizations or Contract Research Organizations (CROs) and non-profit organizations. These non-profit organizations - facilitating, coordinating, and performing clinical trials - are mostly called Clinical Trial Units (CTUs) in UK, and Clinical Research Centers (CRCs) or Clinical Research Organizations in the USA. In the following, CTU will be used for these organizations.

CURRENT INTERNATIONAL AND NATIONAL MULTI-CENTRE TRIALS

CURRENT COORDINATION OF MULTI-CENTRE TRIALS

The method and the scientific rationale of clinical trials have been touched upon in Chapter 1 and in Appendix 2 and a thorough description is given by Pocock (1990) and Spilker (1992). Randomized clinical multi-centre trials are performed mainly in three different ways:

1. Smaller trials (a few departments involved) may be coordinated from a single department with some external assistance, e.g. from statisticians.

2. An independent organization (a CTU) coordinates the trial.

3. The drug and device industry builds up an in-house organization or hires a CRO to coordinate the trial.

The increasing need for larger multi-centre trials has accelerated the formation of CTUs, in-house trial organizations in the industry, and CROs during the last 30 years, with a substantial increase during the last 10-15 years.

Although the process of conducting late phase II trials and phase III trials (Appendix 2, i.e. RCTs comparing a new intervention with no intervention, placebo, or an intervention which has been proven effective) is well described, a number of aspects of such trials are under constant development and refinement. This chapter will describe the current organization of leading international CTUs, the organization of CROs, recent developments of randomized phase II and III clinical trials in leading international research organizations, recent development of European guidelines having an impact on clinical trials, the preliminary attitude of the drug and device industry to the possibility of forming a CTU in Copenhagen and, finally, mention the current activity and organization of clinical trials in Copenhagen and Denmark.

SELECTION AND CHARACTERISTICS OF LEADING CLINICAL TRIAL ORGANIZATIONS

As some trial organizations have developed certain aspects of RCTs more than others, it was decided to visit several institutions in order to get an up-dated impression of the current organization of clinical trials. In the following, a summary of the major highlights will be given, referring to the general organization of CTUs internationally, and their evaluation of the present status of RCTs, and the potential of RCTs.

Based on the knowledge of the Planning Group and experts of the Copenhagen Health Services a number of institutions which had gained a reputation of performing relevant applied science in the context of multi-centre trials were identified. They were requested to advise about how they performed RCTs and how to evaluate the present and future potential of RCTs. On these experts' advice further institutions were identified, and meetings were arranged.

Appendix 3 gives the names of the specialists consulted and the names and addresses of the organizations conducting clinical trials in Europe and North America. In Appendix 4 (Appendices 1-8), the dates these institutions were visited, the names of the institutions, their special field of interest, the experts that were interviewed, and highlights resulting from the interviews are shown. As demonstrated, a total of 43 institutions were visited during the period from April to October 1993, and more than 60 experts in this field willingly made their experience available to the Copenhagen Health Services.

Structured Interview Questionnaire

A structured questionnaire was developed (Appendix 5 showing, as an example, the responses of Honorary Director Adrian Grant, The Perinatal Trials Service, National Perinatal Epidemiology Unit, Oxford, UK (Interview 7)), touching on the organizational aspects of the CTUs and how RCTs are performed. Each of these interviews (without Appendices) may be obtained in English by contacting the Institute of Preventive Medicine. Appendices to each individual interview must, however, be obtained from the respective Institutions (see Appendix 3) in order to ensure that the CTUs know who gets this often semi-confidential information.

Characteristics of the Clinical Trial Organizations

The geographical distribution of the 43 institutions encompassed 21 European Institutions (8 in UK, 5 in Denmark, 3 in Italy, 2 in Spain, and 1 in Scotland, Belgium, and France each) and 22 North American Institutions (14 in USA and 8 in Canada).

The 43 Institutions encompassed 31 non-profit CTUs, two profit CROs, two organizations specializing in systematic reviews and meta-analyses, six representatives of the drug and device industry, the US Food and Drug Administration (FDA), and the National Institutes of Health (NIH).

Of the 31 CTUs, five were involved in RCTs in a number of different specialties (Interview (I): 17, 21, 25, 26, 30), seven in mainly cardiovascular RCTs (I: 2, 6, 9, 28, 29, 31, 39), three in mainly cancer trials (I: 5, 6, 38), three in mainly hepatology RCTs (I: 1, 8, 13), two each were involved in RCTs mainly within AIDS (I: 3, 23), infectious diseases (I: 10, 12), gynaecology and obstetrics (I: 4, 24), psychiatry (I: 16, 32), and one each in RCTs within perinatology (I: 7), ophthalmology (I: 34), osteoporosis (I: 37), quality-of-life (I: 36), and primary health care sector (I: 27). Further, four of the CTUs involved in RCT activity within secondary health care sectors were also engaged in RCT activities within primary health care sectors (I: 1, 9, 17, 39).

ORGANIZATION, COSTS, AND PRODUCTIVITY OF THE CLINICAL TRIAL UNITS

Foundation

The oldest CTU visited was the European Organization for Research and Treatment of Cancer (EORTC) founded in 1962 (I: 38). Some of the CTUs were founded during the 1960s and 1970s (I: 16, 17, 26, 30, 39), but the majority of the CTUs were established during the 1980s or later.

Ownership

The ownership of the CTUs varied, reflecting the different cultures and the different organization of the health care systems. Most often the CTUs were co-owned by the hospital administration and the local university, or by the university or the hospital administration alone. In some instances, the owner was the local research council and/or national specialty organizations.

Funding

Funding for the CTUs originated from various sources, i.e. public funds (local health authorities, universities, national boards), private funds, and the drug and device industry. Some CTUs would only accept free delivery of drugs from the industry (I: 6) in order to remain independent, while the funding of other CTUs from the industry amounted to 100% of the costs (I: 31). The majority, however, obtained 20-40% of the total costs from the industry.

Board of Directors

In about a third of the CTUs there was a formal Board of Directors (5-11 members) which followed the CTUs and advised on actions to take. These boards met at 6-12 months intervals. In the remainder of the CTUs no formal board was formed, but some CTUs were in the process of doing so. The CTUs without formal boards were, however, supervised by their universities, their national founders, or the grant holders, and reported every 1-5 years.

Objectives and Aims

The objectives and aims varied according to the specialty orientation of the individual CTUs and the way each organization was built up. However, the general objectives and aims were:

* to identify questions relevant for the public to be researched;

* to help designing the trials and writing of trial protocols;

* to further develop trial methodology;

* to coordinate the trials;

* to analyse the data from the trials;

* to help writing up the results of the trials;

* to assist disseminating the results of the trials.

Although the majority of the CTUs were mainly involved in a special field some were diversifying into other therapeutic areas (I: 2, 7, 24), a number were working successfully in a variety of therapeutic areas within both the primary and secondary health care sector (I: 1, 9, 17, 21, 25, 26, 27, 30, 39), and the vast majority agreed that a CTU should not confine itself to a specific therapeutic area. However, it was necessary for the CTUs always to involve specialists (national and international) in the design of all trials. Two therapeutic areas, cancer and AIDS, however, seemed to pose a number of special problems and these therapeutic areas were most often handled by specialty oriented CTUs (I: 3, 5, 6, 23, 38).

Staff

The staff of the CTUs varied greatly with regard to educational background and number of employees, reflecting the cultural differences, the educational background of the leaders, the special tasks of the individual CTU, and the age of the CTU.

The main staff groups encompass medical trialists, statisticians, programmers, administrative personnel, secretaries, data clerks, and data monitors.

The smaller CTUs had a staff of 10-15 people (I: 2, 7, 8, 9, 13, 24, 37), while others had grown to much bigger institutions with 40-60 employees (I: 6, 17, 31, 38, 39) and some, involved in more general planning of research or combining basic and applied research, had grown to more than 100 employees (I: 21, 26).

Cost of Coordinating Randomized Clinical Trials

It is difficult to get a precise estimate of the cost of coordinating trials due to differences in defining what coordination costs actually are, differences in salaries in different countries, the size of individual RCTs, and the different ways in which trials were performed. Furthermore, the relation between variable and fixed costs also varied substantially, partly due to the differences in age of the CTUs.

A CTU in the US with extensive experience in RCTs (I: 16) estimated the total coordinating cost of phase II trials to range between DKK 1,050,000 and 1,400,000, and phase III trials to range between DKK 1,500,000 and 5,000,000 (1,000 DKK corresponds to about 130 ECU or USD 147). The coordinating cost of a mega-trial in the US, however, amounted to DKK 175,000,000 or 4,300 per patient (I: 31). In Europe, trial coordination costs were generally lower than in North America (I: 7). Accordingly, the French CTU (I: 39) estimated the coordination costs to be about DKK 1,400-1,800 per patient.

Cost of Randomized Clinical Trials

The total cost of running phase II and phase III trials also varied substantially, again reflecting the different cultures and the different ways in which trials are performed, different costs of the interventions, and variations in how the costs were calculated.

The median lowest cost of phase II trials amounted to DKK 14,000 per patient (range DKK 2,800-35,000 per patient) and the median highest costs amounted to DKK 42,000 per patient (range DKK 30,000-84,000 per patient).

The median lowest cost of phase III trials amounted to DKK 30,000 per patient (range DKK 7,000-35,000 per patient) and the median highest cost amounted to DKK 63,000 (range DKK 7,700-210,000 per patient). The highest cost originates from a surgical trial in the US involving 300 patients (I: 34).

The median annual costs of phase III trials per patient included were DKK 13,000 (range DKK 1,000-90,000). The lowest price originates from a simple mega-trial (i.e. trials involving several thousands or ten thousands of patients).

The above prices do not include expenses for drugs and monitoring, as the former vary substantially and the latter may increase the costs of a trial by 40%. According to the Good Clinical Practice guidelines trials must be monitored.

Productivity of the Clinical Trial Units

It is difficult to evaluate the productivity of the CTUs as the complexity of the trials they are involved in varies considerably, as does the CTUs degree of involvement in writing the protocols, data monitoring, quality control, etc.

The number of RCTs open for patient entry in 9 CTUs (most of which had been functioning for a number of years) varied between 0.13 and 2.27 per employee (median value 0.5 studies per employee) (I: 3, 4, 5, 6, 11, 29, 31, 38, 39).

The number of RCTs at different stages of maturity per 5 year period varied between 0.4-1.1 per employee (median value 0.7 RCT per employee per 5 years) in 5 CTUs (I: 3, 7, 9, 12, 29).

It is estimated that a statistician is able to handle the statistical aspects of about 5-6 RCTs per year (I: 5).

THE PRESENT STATUS AND FUTURE POTENTIAL OF RANDOMIZED CLINICAL TRIALS

The development of RCTs until now has generally been considered positive, although the financial resources are considered too small. Therefore, only a small part of the total number of questions relevant for further research could be dealt with in a sufficient manner.

Generally, the CTUs considered the future possibilities of doing RCTs as positive because:

* RCTs represent the way for further development;

* There is an increasing public understanding of the necessity of doing RCTs;

- In the US, AIDS activist groups have now changed their aggressive attitude against RCTs towards demanding to be entered into RCTs. This attitude has spread to other groups, e.g. breast cancer patients. The public understanding of the necessity of RCTs in the US is spreading to Europe as well.

- This understanding has, among other factors, been supported by the development of small books informing the public and patients about the basic ideas of RCTs. Through such booklets patients are informed about the general principles of doing RCTs before physicians inform them about their diagnosis and invite them to participate in a specific study.

- Physicians become better educated in the methodology of RCTs, and educational programs have been developed, including videos describing the methodology of RCTs.

- In certain countries there is an increasing governmental understanding of the necessity of performing RCTs and increased financial support for applied research has recently been given in e.g. France (I: 39) and Germany (Gesundheitsforschung 2000, Programm der Bundesregierung, 1993).

- Preventive research has increasingly come into focus and an expansion of preventive research is expected in the USA ('The American Health Security Act of 1993' from the Clinton Administration).

- Registration and licensing of medicines are carried out on the basis of RCTs.

CONTRACT RESEARCH ORGANIZATIONS (CROS)

Worldwide there are about 600 CROs, of which about 300 are situated in the USA and 180 in the UK (I: 4). These CROs work for industry and are involved in RCT activity in different kinds of specialties within the primary and secondary health care sectors. The market is estimated to grow by 300% between 1990 and 2000 and until now this projection has proved to be correct (I: 4, 33, Director C. Difiche, Pharmaco::LSR, USA, personal communication). The increase in the market is partly explained by the number of new drugs and devices to be tested and partly by a present trend in the drug industry trying to reduce the growth of their in-house trial organizations (I: 33).

One CRO in the UK and one in the USA were visited. The major selling points of the CROs are strong quality control of participating physicians, data and quality assurance systems, Standard Operational Procedures (SOPs) developed for every aspect of a clinical trial, and a high degree of professionalism in running trials including data management and security (I: 4, 33).

It is not possible to obtain information on the exact number of studies performed, their price, and contents of SOPs of the CROs, as this information is confidential.

DRUG AND DEVICE INDUSTRIES

The Danish Drug and Device Industry

The Danish drug and device industry has an annual turnover of DKK 15.3 billion, of which DKK 11.4 billion is exported (Medico/Sundhed, Ressource omrDdeanalyse, Erhvervsfremmestyrelsen, 1993). The drug and device industry is organized in two associations:

* **MEFA** (Foreningen af danske Medicinfabrikker/The Association of Danish Pharmaceutical Industry), representing 10 Danish pharmaceutical industries with a total sale of DKK 8.6 billions in 1991 (of which about 92% is exported), invests about DKK 195 million in clinical research. It is estimated that about 50% of this amount is used for clinical research in Denmark and the rest is used abroad (Medicine and Health Care, Facts 1992, Denmark, MEFA).

* **MEDIF** (Medicin Industriforeningen/The Medicine Importers' Association) representing 46 international pharmaceutical industries with a total sale in Denmark of about DKK 4 billion, invests about DKK 250 million on clinical research in Denmark. This amount of money is obtained from the mother firms in competition with subsidiaries in other countries. Of the DKK 250 million invested in research, about DKK 125 million go to out-house research activities, which generates in-house expenses of another DKK 125 million.

Preliminary Evaluation of a Clinical Trial Unit of the Copenhagen Health Services

Researchers employed in four Danish (I: 40, 41, 42, 43 - the four biggest members of MEFA) and two US (I: 14, 15) drug and device industries were visited and a meeting was held with members of the Clinical Research Committee of MEDIF.

The preliminary evaluation of setting up a Clinical Trial Unit in Copenhagen was generally positive. The Danish industry was, however, not interested in competition from a CTU and did not want new barriers created. However, a Copenhagen CTU could possibly be an interesting option if it could:

* coordinate and facilitate RCTs - especially within the primary health care sector;

* function as a broker between industry and clinical departments by having a detailed knowledge of the activities of the departments;

* develop know-how on quality-of-life assessment and pharmacoeconomics;

* improve the general educational level of the health services on how to perform trials;

* live up to the highest FDA and GCP requirements and secure a sufficient number of patients enrolled in a given trial at a given time.

A Copenhagen CTU should market itself towards the industry by developing brochures, advertise through the Drug Information Association (DIA), and set up meetings with the drug and device industry.

The industry carefully consider their partners (CRO or CTU) before engaging them in a trial (the expertise of the investigators, number of patients that could be enrolled per unit of time, data quality, ability to adhere to the GCP guidelines, university affiliation, size of the market, price of the trial), and normally several possibilities were examined before a trial was mounted in out-house facilities.

RECENT DEVELOPMENTS OF RANDOMIZED CLINICAL TRIALS

Based on the interviews with national and international experts in the various clinical trial organizations, the following summarizes the way these organizations performed RCTs focusing on the highlights listed in Appendix 4 (Appendices 1 to 8).

Definition of the Purpose of the Trial

Definition of the purpose of a single trial either comes from scientists within the CTU or from specialists outside the CTU. In the latter case, the idea could originate from a clinical specialist or a sponsor - either the drug and device industry or a governmental institution.

One of the first tasks to fulfil when a new idea for a trial is put forward, is to perform a systematic review of the literature and, if possible, perform a meta-analysis (vide infra and in Appendix 2) of the trials performed within the area in order to secure that the question has not been answered already before a trial is launched (Antman et al., JAMA 1992; 268:240-248).

It characterized the more successful CTUs that the idea for a trial is offered for open discussion among leading international experts in the field, either by asking them to comment on the general idea (I: 21) or by asking them to form part of an Advisory Group following and criticizing the protocol as it is developed. Very often, these experts later join the Data Monitoring and Safety Committee of the trial, but are not otherwise involved in the RCT.

Trial Registration

Trial registers are public registers listing each new trial by name, purpose, and contact person. Such registers have been operative for some years regarding cancer trials in the US (Physicians Data Query), but it is a fairly new development in other specialties such as cardiology and thrombosis, HIV and AIDS, perinatology, and neurosurgery (Dickersin & Garcia-Lopez, Controlled Clinical Trials 1992; 13:507-512). Although such registers pose some problems for the drug and device industry, which has natural interests to protect (and interests which should be protected in some form), they also create an openness that is considered ethically correct. First, everyone can follow what is going on in a given specialty and decide whether to collaborate in trials or not. Second, such registers may harmonize trials so that later combination of data from individual patients becomes easier. Third, such registers may one day prevent too many trials on the same problem being run more or less simultaneously forcing too many patients into the same design. This would neither be ethically correct, nor cost-effective. With the introduction of electronic mail, the prompt screening of a trial register is feasible within minutes at a low cost. Therefore, in future one may see development towards registration of trials from the day of the basic idea, open to the comments of everybody, a second registration at the moment the local ethical committee and other controlling institutions have accepted the trial, and a third registration on the day the trial is launched.

Public Participation in Trial Design

Some CTUs now include the public in the design phase of an RCT. By involving the public (e.g. activists of the community or representatives of patient organizations) in the very early phase of protocol development, a better understanding for the RCT is developed, critical points can be discussed and the protocol adjusted accordingly, and later on these persons may recommend the RCT for the relevant patient groups.

Patient Recruitment

It is essential that a trial does not run too long (Zelen, J Chronic Dis 1974; 27:365-375) and that a sufficient number of patients are included. It is often difficult to sustain the interest in a trial among the investigators and others if it runs for more than a couple of years, and accrual phases longer than 18-24 months should be regarded as unacceptable for studies that target reductions in mortality as a major end point (Wittes & Friedman, J Nat Cancer Institute 1988; 80:884-885).

There are a number of ways to increase the recruitment of patients into RCTs, among others:

* Involvement of nurses in parallel trials (e.g. on quality-of-life) involving the same patients. This will increase the collaboration in the department and the interest of both nurses and physicians in recruiting patients for a given RCT (I: 2).

* Develop books or booklets for patients and relatives about trial methodology and the necessity of performing RCTs (I: 3).

* Improve the information given in and the quality of Newsletters for physicians and nurses, and publishing them at regular intervals. Some CTUs even mail weekly posters to the clinical sites (I: 31).

* Publication of Patient Newsletters, where patients in a trial can obtain information on the experience of previously entered patients and follow the recruitment and other aspects of the trial (I: 31).

* Marketing, - by

- making the trial a multi-centre one either involving clinical sites in a whole region, a whole country, or by performing multinational trials. Such multinational, multi-centre trials now include up to 1200 different Hospital Departments (I: 6, 31) and recruit 40,000-56,000 patients (I: 2, 6, 31);

- making the departments involved in the trial recruit more patients by advertising the trial in newspapers, radio and television (I: 33), and informing the community and general practitioners (GPs) about the trial through specially trained and selected 'outreach coordinators' (I: 23);

- ensure that the clinical sites are able to provide for the patients before they are included in the trial;

- regular meetings of the clinical investigators, offering them interesting education, not necessarily related to the trial, in combination with information about the trial (I: 6, 28).

* By paying more to patients and investigators. This is the practice which has been especially used in North America and has certain advantages, but also raises a number of questions of ethical nature. Furthermore, the moment money is involved the risk of fraud and misconduct increases (Lock & Wells, 1993; National Academy of Sciences, 1993). In Denmark, it is not customary to pay patients for participation in trials, apart from reimbursing lost wages and transportation expenses.

Randomization

Central randomization is the uniform advice from almost all of the CTUs. It is at present often done by a 24 hours 7 days a week secretary operated telephone service, through which the randomization is carried out. This has the advantage that physicians preferring someone to talk to get that and the secretaries may also contribute to reducing the rate of patient withdrawal (vide infra). However, during the last couple of years, press button phone randomization has been successfully introduced (I: 11, 17, 24, 44) (Appendix 6). This method substantially reduces the costs of central randomization. In certain systems (e.g. DataFAX) fax randomization is also possible (I: 25, 28). Moreover, in the future EuroCODE, developed for EU money and used within cancer trials, may also become a system for randomization (I: 6, 38), and the French MINITEL is used as well (I: 39).

Data Management

During recent years a number of data management systems have been developed which improve data management considerably and facilitate the handling and analyses of large data banks. This development has greatly facilitated the performance of large RCTs. There are many different data management systems on the market, and they all seem to have virtues and draw backs. Some of these systems are described briefly in Appendix 6.

Patient Withdrawal

It is essential that a patient stays in a trial and is not prematurely withdrawn. By providing a 24 hours 7 days a week telephone service where a secretary puts a number of prepared questions to the physician wishing to withdraw a patient, it has been possible to reduce the withdrawal rate to about half (I: 31).

Quality Assurance

Prospective controlled trials represent a valuable instrument for obtaining quality assurance of the work of clinical departments. By comparing the prognosis of patients having the same prognostic factors and receiving the same treatment important information on the quality of health care can be obtained (Baunes, Nord Med 1993; 108:246).

Health Economics

Clinical trials have largely ignored the cost implications of competing therapies and have measured 'end points' of limited use to purchasers. In the future, health economics are going to play an increasing role in relation to RCT activity (Appendix 7). Although the methodology is not finally developed (MEFA: qkonomiske evalueringer af lFgemidler, April 1993; Conference on Pharmacoeconomics and Competition, April 1993) health economics should be considered in the planning and design of future clinical trials.

Quality-of-Life

Quality-of-life (Appendix 8) is another aspect that has been recognized too little in most trials in the past. In Canada, however, quality-of-life assessments are already a requirement for the registration of a new drug. The assessment of

quality-of-life is difficult, but has to be implemented in more trials in the future. However, the whole field is at present under study and it is not possible to give guidelines on how to measure quality-of-life in the best and easiest way, but instruments for detecting important effects in clinical trials are available (Guyatt et al., Ann Intern Med 1993; 118:622-629). Patient computer systems have been developed (PadLife, Appendix 6) which enable the patient on a continuing basis to report the quality-of-life to a portable computer.

Legal Aspects

The patients/healthy volunteers taking part in a clinical trial should be satisfactorily insured against every injury caused by the trial. The liability of the involved parties (sponsor/manufacturer/coordinating centre/hospitals/departments/investigators) should be clearly outlined before the start of a trial and lawyers are taking an increasing part in the formation of clinical trials (I: 16, 24).

Publication

A recent development has been the possibility of sending an RCT manuscript to a traditional journal and at the same time to submit it to The Online Journal of Current Clinical Trials (available via Internet). When accepted, the article is available to subscribers after 48 hours. In the future, it is likely that manuscripts on clinical trials will include a disc with information on the variables of the individual patients. In this way, data from individual patients of different RCTs on the same questions can more easily be combined in meta-analyses.

Meta-analyses

Both when planning an RCT and when an RCT has been performed it is natural to do a meta-analysis on the available data in order to provide an overall conclusion of the present therapeutic area and in order to assist in the dissemination of the results. In this respect, international collaborations are being formed at present. The most well known is the Cochrane Collaboration founded in the UK in 1992 (I: 36, Grtzsche, Bibl LFg 1993;185:17-29); a Nordic Cochrane Centre at Rigshospitalet, Copenhagen was opened in 1993. The Cochrane Collaboration intends to assemble and evaluate all RCTs and to perform systematic reviews (meta-analyses) within all specialties and thereafter update the analyses every half year. There was in the USA also a major interest in performing meta-analysis and several centres have been created (I: 20, 22), even profit centres (I: 20).

Other centres (e.g. in Lyon and Copenhagen) have succeeded in assembling the data from all individual patients of all trials published within a special field in one data-base (I: 39). The activities of the Cochrane Collaboration and the assembly of individual patient data shall be seen as complementary as it will probably be impossible to assemble individual patient data more than 5-10 years back.

REGULATIONS AND GUIDELINES AFFECTING CLINICAL TRIALS

INTERNATIONAL

The Helsinki II Declaration

The World Medical Association has formulated a set of recommendations, the Helsinki II Declaration, guiding any physician performing clinical research. These recommendations aim at protecting the individual person or patient participating in clinical research so that the interest of science or society will never prevail over the well-being of the individual. All clinical research must adhere to these recommendations (GCP, 1991).

Food and Drug Administration

The US FDA acts as a public health protector by ensuring that all new medical products are safe and effective (I: 18). Any trial wishing to obtain FDA approval (either as an IND (Investigational New Drug Application) or as an NDA (New Drug Application)) must meet a number of strong quality control requirements. Only 20% of INDs will be approved for marketing (NDA).

Committee for Proprietary Medicinal Products

The EU Committee for Proprietary Medicinal Products (CPMP) has three main objectives:

1) to consider appropriate scientific and administrative requirements for the submission of applications for marketing authorization for new medicinal products;

2) to give an opinion as to whether a particular medicinal product complies with the requirements set out in EU Directive 65/65/EEC and to give an opinion on applications for marketing authorization relating to medicinal products for human use (Quality, Safety, and Efficacy) (EU Directive 87/22/EEC);

3) to monitor and review scientific innovations and developments internationally.

The work of the CPMP does not end with the decision to grant or refuse a marketing authorization of a medicinal product. CPMP maintains a watchful eye on all medicinal products on the market and is constantly active in monitoring the safety and efficacy of these. The Deputy Chairman of the CPMP is Chairman of the Registration Committee, M.Sci.Pharm. Henning Hovgaard, The National Board of Health, Copenhagen, Denmark.

International Conference on Harmonization

International Conference on Harmonization (ICH) is in the process of harmonizing the international technical requirements (Quality, Safety, Efficacy) for registration of pharmaceuticals for human use. The first meeting took place in Brussels in 1991, the second was held in the USA in 1993, and a third is scheduled to 1995 in Japan. It is hoped that the international requirements will be harmonized after this meeting. The ICH is jointly supported by the EU CPMP, the US FDA, and the Japanese Ministry of Health and Welfare together with the international and regional associations of the drug and device industry.

Good Clinical Practice

The introduction of the EU-GCP guidelines in 1991 (GCP, 1992) has substantially increased the requirements for doing trials in Europe. The GCP guidelines represent requirements for clinical trials involving new drug indications, but are also a general guidance on how to do trials. Accordingly, the Copenhagen Health Services have to adhere to these and other guidelines.

Just as industry has developed SOPs for every detail of a trial, it is considered worthwhile that departments develop SOPs for the clinical part of trials, and in order to live up to GCP guidelines and FDA regulations it is necessary that every aspect of a trial is described in detail (GCP, 1992).

Good Statistical Practice

The Committee for Proprietary Medicinal Products (CPMP) has recently developed European Biostatistics Guidelines on 'Good Statistical Practice' (GSP), which will increase the requirements of protocol writing and statistical analyses of data of clinical trials. According to the quidelines, the type of tests and number of tests to be employed in the statistical analysis of a given trial should be clearly outlined in the trial protocol and signed by the responsible statisticians. A preliminary draft of the guidelines was discussed during a Drug Information Association meeting in October 1993 in London (Appendix 9), and the GSP guidelines are expected to come into operation during 1994.

Good Data Management

The guidelines for the Conduct of Research within the US Public Health Service (1992) states that it is expected that the results of research will be carefully recorded in a form that will allow continuous and future access for analysis and review. Attention should be given to annotating and indexing notebooks and documenting computerized information to facilitate detailed review of data.

In Europe, it has also been decided to deal with Data Quality Assurance and develop EU guidelines on the subject (Danish Standards Association, September 1993). It is therefore to be expected that the requirements for data management and storage will increase considerably in the future.

NATIONAL

Apart from being able to live up to international requirements and guidelines, RCTs also have to adapt to a number of national requirements. All RCTs involving humans must be approved by one of the regional ethical committees, and before collecting and storing data, the data security should be approved by the Danish Data Protection Authority. When testing drugs, the Drug Department of The National Board of Health should approve the clinical trial. Research performed in the primary health care sector should be approved by the Multi-Practice Research Committee (Multi-praksis Undersrgelsesudvalget).

CURRENT ORGANIZATION OF RANDOMIZED MULTI-CENTRE CLINICAL TRIALS IN COPENHAGEN AND DENMARK

The current organization of RCTs performed in the Copenhagen Health Services is either built up by the Principal Investigators (PIs) or run by in-house organizations in the drug and device industry or by CROs paid by the industry.

Organizations built up by PIs have certain advantages (flexibility, independency to choose scientifically relevant research) but also certain disadvantages (generally longer time to mount, launch, and conduct an RCT, longer data analyses due to unsophisticated data management systems, the organization often collapses after an RCT is finished).

Organizations built up by industry have certain advantages (no expenses for the Health Service, faster performance of an RCT facilitated by the international network of clinical departments of the industry, an economic incentive for the departments of the PIs). However, there are also certain disadvantages, including:

1. Industry determines the field of research, which often focuses on less important areas (e.g. 'me too drugs', repetition of antibiotic trials, etc.), will seldomly focus on areas where it is not possible to obtain a patent, and will in most cases not focus on non-pharmacological trials.

2. Industry controls the data in most cases - and in case the results are negative or demonstrates no effect, the message is not disseminated.

3. It is difficult to control the exact expenses for the Health Service that this research may incur.

4. The market of research may disappear the moment the industry can get their RCTs performed better and more cheap in other locations. In this respect, the industry has made it clear that the quality of clinical applied research in Denmark is not optimal and expressed a wish for more training of health personnel in the primary and secondary health care sectors (I: 40, 41, 43).

Appendix 10 briefly describes the City of Copenhagen and the organization of the Primary and Secondary Health Care Sector of the Copenhagen Health Services. Two large multi-centre RCTs were identified within the primary health care sector. Appendix 10 also shows the current RCT activity within the Secondary Health Care Sector of the Copenhagen Health Services. It is demonstrated that a total of 83 single centre and 40 multi-centre RCTs were finalized during the two year period 1991-1993, more than half of this activity taking place at Hvidovre Hospital. As of July 1993, 82 single centre and 65 multi-centre RCTs were active or soon going to be launched within the secondary health care sector. Again, about half of the activity is taking place at Hvidovre Hospital. Generally, the highest activity was found in the departments of abdominal surgery or general surgery. These figures may suggest an increasing RCT activity, but could also mean that a number of RCTs started are never finished.

During the last 30 years Denmark has, like other western industrialized nations, seen the development of a number of multi-centre trial groups within different disciplines of medicine. They have traditionally been organized by one or a few dedicated researchers, and have grown over the years as their science developed. They have in most cases been funded by various sources, most often from the Danish Medical Research Council and private funds. Most are working as national groups, but centres such as the those dealing with solid cancers and AIDS also receive substantial support from non-Danish funds such as the EU. The solid cancer group of Rigshospitalet, working closely together with other hospitals in Denmark, is taking part of the European Organization for Research and Treatment of Cancer (EORTC). A number of fields within medicine, however, are not covered by such trial organizations.

The recent Report of the International Panel Evaluating Danish Health Research (SOFIE, 1992) -the Panel evaluated one clinical discipline (cardiology) - concluded:

- The organization of Danish research in cardiovascular diseases is performed in university research institutes, university hospital departments, and in county hospitals. Most research programs are restricted to one department or research centre. However, the concept of brickless centres, i.e. groups, which are not limited to one defined centre, is beginning to develop and is to be encouraged.

- The Panel identified areas of research that are already strong in Denmark (about 35% of the research was graded research at a high international level), but which could be made even more effective if liaisons are created between a number of establishments.

This conclusion seems to apply well to the present situation within most clinical specialties in Denmark. Further, it has recently been concluded that Danish clinical research leaves a lot to be desired (Gjrrup & Walter, Ugeskr LFger 1993; 155:912).

In conclusion, the present organization of RCTs in Copenhagen raises some problems, there is no independent cross specialty CTU in Denmark, and although the present RCT activity in certain departments of the secondary health care sector is high, it is low in other departments and in the primary health care sector, and finally the number of preventive trials is low in the secondary health care sector and virtually missing in the primary health care sector.

RATIONALE FOR ESTABLISHING A CLINICAL TRIAL UNIT OF THE COPENHAGEN HEALTH SERVICES

The following arguments all point in favor of establishing a Clinical Trial Unit in Copenhagen.

GENERAL ARGUMENTS

1) There is a massive global need for more applied research on preventive and therapeutic interventions. Further amendments and activities are needed in order to reach the goals of future health, e.g. the WHO 'Health for all year 2000'. It is therefore necessary to further build up a critical mass of individuals who are involved in research programs that produce new, useful knowledge.

2) Studies have demonstrated that non-randomized clinical trials using historical controls found therapies better than control regimens in 79%, whereas the same therapies were better than control regimens in only 20% in RCTs (Sacks et al., Am J Med 1982; 72:233-240). Such data suggest that bias in patient selection may irretrievably weight the outcome of historical controls in clinical trials in favour of new therapies. Therefore, the randomized clinical trial is today the accepted gold standard for evaluating preventive and therapeutic interventions.

3) Most patients entered into RCTs, regardless of whether they were randomized to receive experimental therapy, standard therapy, or placebo, have often a more favourable survival to patients not entered into RCTs, suggesting an inherent advantage of being enrolled into RCTs (Davis et al., Cancer 1985; 56:1710-1718; Stiller, BMJ 1989; 1058-1059). The precise nature of this trial associated 'effect' is not known, but may counterbalance certain of the potential disadvantages for patients in such trials. Additionally, other studies suggest that patients treated outside trial centres may receive more treatment than recommended (Pritchard et al., BMJ 1989; 299:835-836)

4) Research should not only be done by the few and selected, but should be performed in the main body of the health system, where the routine work is performed. However, as the working conditions often leave restricted amounts of time for the planning of research and as the mounting of an RCT is a complex process, a CTU may increase the general quality of RCTs.

5) The process of randomization and data management have both been considerably improved during recent years, facilitating the performance of larger RCTs which are able to search for smaller, but still relevant effects.

6) The increasing need for systematic reviews and meta-analyses makes it advisable that more groups are established to carry out this work in order to summarize and disseminate the present knowledge and identify new areas for research.

INTERNATIONAL ARGUMENTS

7) Several CTUs have been established abroad during the last 30 years and have proved their essential role in the prevention and treatment of diseases.

8) The complexity of mounting RCTs has increased substantially during recent years by the introduction of GCP and these guidelines are soon to be followed by guidelines for Good Statistical Practice and Data Management. This creates a need for a strong, local know-how centre.

9) There is a need for increased international collaboration facilitating the performance of large multi-national RCTs and the comparability among smaller RCTs.

10) The idea of forming a CTU in Copenhagen has gained wide support from international experts.

11) Internationally, the market for RCTs is expected to increase by about 300% during the 1990-2000 period.

12) International experience has demonstrated that the establishment of CTUs lead to increased funding from colateral sources, including industry, which will generate more employment.

DANISH ARGUMENTS

13) An independent, non-specialty oriented, non-profit organization able to facilitate, coordinate, and perform RCTs of scientific value in the interest of the public does not exist in Denmark.

14) The preliminary attitude of the drug and device industry was generally positive as a CTU could:

* attract more money for clinical research from abroad to Denmark from the mother firms abroad of the members of MEDIF;

* reduce the export of money for clinical research from the members of MEFA;

* function as a liaison between industry and the departments of the secondary health care sector;

* coordinate RCTs in the primary and secondary health care sectors.

15) The formation of a CTU in Copenhagen would fulfil the suggestions outlined in the report on Medico/Health - a business economic analysis (Medico/Sundhed, Ressource omrDdeanalyse, Erhvervsfremmestyrelsen 1993) requesting:

* a better structure for evaluating new interventions (devices and drugs);

* better public research, basic as well as applied;

* the creation of 'Centres of Excellence', in which research can be organized at a high international level;

* the creation of structures which can make it attractive to be a researcher, co-working with industry;

* increased international collaboration, Nordic as well as European;

* the creation of a 'Meditech Belt' in Copenhagen-Malmr-Lund, taking advantage of the good reputation of Nordic applied research and developing an environment for health economic analyses;

* increased collaboration between the health care sector and industry in developing new technology.

16) A CTU would facilitate the implementation of 'Continuous Quality Development: a Proposed National Policy' (World Health Organization, Regional Office for Europe, Copenhagen 1993).

COPENHAGEN ARGUMENTS

17) There is a need for increased research activity in the Copenhagen area encompassing preventive and therapeutic RCTs (Healthy City Plan 1994-1997, the Copenhagen Health Services, Central Office, 1993).

18) The citizens of Copenhagen have the advantage of the results of trials performed in other health services. On the other hand the Copenhagen Health Services have an obligation to facilitate the performance of further research of good quality, as expressed in 'Research Policy of the Copenhagen Health Services' (1992).

19) Clinical practice is based on the results of RCTs. Increasing the number and quality of RCTs will increase the quality and up-to-dateness of clinical practice. Thus, establishing a CTU can be expected to influence the quality of care in the Copenhagen Health Services and would consequently be of direct benefit to the citizens of Copenhagen.

20) The formation of a CTU in Copenhagen would fulfill the objectives of the 'Research Policy of the Copenhagen Health Services' (1992), which are:

* strengthening research of relevance to the inhabitants of Copenhagen;

* supporting creative research environments;

* creating more stable conditions for research;

* increasing the quality of research;

* increasing research collaboration among the institutions of the Copenhagen Health Services, other health services, and industry;

* increasing the visibility of the research commitment of the Copenhagen Health Services.

21) A CTU in Copenhagen could attract more research investment from the drug and device industry.

Chapter 4

PROPOSAL FOR THE FORMATION OF A CLINICAL TRIAL UNIT OF THE COPENHAGEN HEALTH SERVICES

OBJECTIVES AND AIMS OF THE COPENHAGEN CLINICAL TRIAL UNIT

Based on the information summarized in the previous chapters and appendices, the formation of a non-profit Clinical Trial Unit of the Copenhagen Health Services, the largest health care provider in Denmark, is proposed.

A Clinical Trial Unit should facilitate, coordinate, and perform RCTs within the region, the country, and at a multi-national level. The principle of the RCT is an essential cornerstone in the evaluation of any health related intervention (diagnostic tools, drugs, devices, surgery, psychotherapy, nursing, health care, health education, etc.). Since high quality RCTs can only be conducted in populations presenting a pertinent health problem, all RCTs performed by the CTU will by definition meet the requirements of relevance for the citizens of Copenhagen. The activity of the CTU will always be considered an integrated part of the general evaluation of diagnoses and interventions. This general evaluation also encompasses basic clinical research on one hand as well as more qualitative and society oriented clinical research on the other.

The following objectives and aims of the CTU are proposed, and then an organizational structure is suggested.

The Clinical Trial Unit should

A. Facilitate, coordinate, and perform randomized preventive trials in the primary and secondary health care sectors within scientifically relevant areas. Such trials can be initiated by investigators in the scientific community, the drug and device industry, or the unit itself.

B. Facilitate, coordinate, and perform randomized therapeutic trials in the primary and secondary health care sectors within scientifically relevant areas. Such trials can be initiated by investigators in the scientific community, the drug and device industry, or the unit itself.

C. Facilitate, coordinate, and perform scientifically relevant systematic reviews of RCTs, including meta-analyses, thereby identifying relevant areas of research and contributing to the dissemination of the results of randomized clinical trials.

D. Participate in the further development of trial methodology and technology, in order to achieve status as a strong centre for randomized clinical trials in Denmark, being able to provide service and assistance for the primary and secondary health care sectors.

E. Teach at the graduate and post-graduate level about methodology of controlled clinical trials and meta-analyses and thereby facilitate the further development of applied research of the Copenhagen Health Services.

The CTU should not interfere with the relevant RCT activity already going on within the Copenhagen Health Services but develop new areas of research. During the start-up phase of the CTU, the tasks will therefore mainly be within:

1. Preventive trials within the primary health care sector (Aim A).

2. RCTs in collaboration with these parts of industry which have not developed in-house trial organizations or which have insufficient capacity (Aim A and B) and function as a liaison between the drug and device industries and the Health Services.

3. Development of systematic reviews and meta-analyses in close collaboration with the Nordic Cochrane Centre, which was established at Rigshospitalet in October 1993 (Aim C).

Through this development and after having proven that the CTU is able to run trials in an effective way, the CTU might in the future be able to offer assistance also to already well functioning clinical groups, and other parts of the industry if they so wish. This start-up phase is expected to take about 3-4 years.

ORGANIZATION AND STAFF OF THE CLINICAL TRIAL UNIT

Board of Directors

A CTU should have a Board of Directors consisting of 5-7 members with experience in conducting RCTs and including at least two foreign experts (2-3). The Board of Directors should meet at least annually with the Head of the CTU in order to evaluate the activity of the unit, possibly including international independent evaluation, and advise in the further development of the activities of the CTU.

Affiliations with the University of Copenhagen and other Departments of the Copenhagen Health Services

The CTU should be affiliated with the University of Copenhagen in order to contribute to and utilize the academic resources of the University and thereby attract young scientists and the national and international drug and device industry.

It would be appropriate to place the CTU in connection with or in a research oriented environment of the Copenhagen Health Services, where the related methodological and technical competence is developed. Therefore it is proposed to establish the CTU within the Institute of Preventive Medicine of the Copenhagen Health Services.

Limits of Dimension of the Clinical Trial Unit

Drawing on the experience of the international organization of CTUs and with the proposed objectives and aims of the Copenhagen CTU the lower limit of staffing will be described below, representing the smallest dimension in order to create a well functioning unit. The upper limit of a CTU is closely defined on the basis of the available resources and logistics of CTU activities at the local, national, and international level.

Core Staff

The CTU should be staffed with a core staff and additional staff, the numbers of which will depend on the number of studies performed.

The CTU should be staffed by two senior medical trialists, one of which should be the Head of the Unit, having a broad clinical experience, substantial experience in running trials and conducting meta-analyses, and knowledge of the Copenhagen Health Services as well as the international RCT community. The reason for having at least two senior medical trialists is the multitude of tasks that will be necessary, and this proposal is in accordance with the recommendation of the SOFIE Report (1992) suggesting that a new type of position should be created within the university system for several essential service functions.

One administrative person with a knowledge of finances is essential for taking care of administrative aspects, calculation of the costs of trials, running the office systems, etc.

A skilled data manager/programmer should be in charge of developing the systems for randomization and data management.

At least one secretary is needed in the start-up phase. However, at least one more will be needed when trials are running. It is essential that holidays and absence from work do not in any way obstruct the running of the trials.

Additional Staff

Depending on the number of trials run, the organization of each trial, and the size and complexity of each trial, a variable number of data managers, trial coordinators, statisticians, secretaries, monitors, health economics experts, and assistance from consultant lawyers may be needed. When the number of trials run by the CTU amounts to about 4-5 per year, a statistician should be added to the core staff.

In addition, clinicians wishing to take a sabbatical in order to conduct trials should have the possibility to work in the CTU during this period.

Younger scientists, wishing to develop the trial methodology further (e.g. within quality-of-life or health economics) should be able to work in the CTU while obtaining their Ph.D. degree.

The salary for these groups should be paid by the individual studies or from seeding money obtained when doing trials in collaboration with the drug and device industry or others.

COSTS OF THE CLINICAL TRIAL UNIT

Salaries

The total salary costs of the core staff amount to about DKK 1.6 million annually. It is envisaged that additional staff working at the CTU will be paid from the grants of the individual RCTs and other projects.

Investments and Running Costs

The CTU should have a work station or a large computer and a PC-network (with flexible expansion possibilities), electronic mailing system, filing system, printing facilities, software systems, and general office equipment.

The cost of these systems will amount to DKK 1-2 million during the first 1-2 year and the running expenses of these systems amount to an estimated DKK 300,000-400,000 annually depending on the number of trials.

Further, the running costs for consultative assistance (health economist, statistician, lawyer, etc.), for meetings, and travel expenses for members of the Board of Directors and members of the staff amounts an estimated DKK 600,000-700,000 a year.

Annual Total Cost

The following sums are estimations.

During the first year: Salaries DKK 0.8 million

Investments DKK 1.0 million

Running costs DKK 0.5 million

TOTAL DKK 2.3 million

During the second year: Salaries DKK 1.6 million

Investments DKK 0.5 million

Running costs DKK 0.8 million

TOTAL DKK 2.9 million

During following years: Salaries DKK 1.6 million

Investments DKK 0.3 million

Running costs DKK 1.0 million

TOTAL DKK 2.9 million

Space

As the staff may be expected to grow during the years, facilities should be flexible and leave space for expansion. During the first years about 150 square meters are needed, later doubling or tripling.

The CTU must be located in such a way that data can be secured. An additional location for back-up of data is necessary as the future health of patients is expected to depend on these data and the cost of assembling the data amounts to many millions.

As some trials may not be run using fax systems or telecommunication, space for filing under secure circumstances must be available.

The cost of space is assumed to be covered by housing of the CTU in the Copenhagen Health Services.

ORGANIZATION OF THE RANDOMIZED CLINICAL TRIALS

Each individual idea for an RCT (described briefly on 6-12 pages) received by the CTU should be critically evaluated by sending the idea out to 4-6 specialists within the field requesting them to evaluate the idea within 6 weeks. At least half of these specialists should be foreign international experts. On the basis of these evaluations the CTU should decide, possibly with the assistance of the Board of Directors, which RCTs they should mount.

In clinical trials run in collaboration with the drug and device industry, methods should be developed, which respect the interests of industry as well as the interests of the inhabitants of Copenhagen or other areas in which the trials are run.

PROJECTED PRODUCTIVITY OF THE CLINICAL TRIAL UNIT

With a core staff of 5-6 persons a CTU should be able to mount and launch 6 multi-centre RCTs during the first five year period, corresponding to a total cost for coordination per RCT of about DKK 2.6 million. However, with a larger staff (e.g. 10-15) about 12 studies could be coordinated during a five year period, reducing the coordinating costs per RCT by 10-20%.

COLLABORATION AND PUBLICATION POLICY

Any external collaboration should be based on explicitly negotiated agreements according to the particular aspects of the individual projects.

The publication policy should follow the recommendations laid down in 'Uniform requirements for manuscripts submitted to biomedical journals' (BMJ 1991; 302:338-341).

All manuscripts should aim at publication in international peer reviewed journals.

START OF THE CLINICAL TRIAL UNIT

During the first 1-2 years the CTU should:

1. Develop projects within the frame of the Objectives and Aims A, B and C.

2. Organize an educational program.

3. Select and install computer systems and software.

4. Develop Standard Operational Procedures (SOPs) for all details of trial coordination.

5. Develop marketing material for the CTU for the drug and device industry and develop an overview of the patient groups and specialties covered by the Copenhagen Health Services.

6. Develop a booklet for patients and relatives explaining how and why clinical research is being performed, to hand out to all patients in the primary and secondary health care sectors.

7. At a general level participate in the process of informing the inhabitants of Copenhagen of the value of clinical research.

Second year and onwards:

1. Further development as in first year (point 1-7).

2. Mounting and launching of RCTs when all systems and SOPs have been finally developed and tested in feasibility studies.

RESEARCH TOPICS FOR THE CLINICAL TRIAL UNIT

It does not seem proper to suggest specific research topics for the CTU at the present time, as the best science is probably developed by the free interactive communication of researchers. However, both within the primary and the secondary health care sectors a number of problems exists (e.g. to promote cessation smoking) reducing alcohol misuse, evaluating the beneficial effects of social networks, reducing mortality and morbidity of a number of diseases, etc.) which need further effective interventions.

PROPOSED DANISH NAMES FOR THE CLINICAL TRIAL UNIT

The name 'Clinical Trial Unit' may be misunderstood when translated into Danish ('Klinisk Forsrgs Enhed'). There are a number of possibilities, but 'Center for Interventionsstudier' (Centre of Intervention Studies) would cover both the preventive and clinical aspects. Another possibility would be 'Klinisk Forskningscenter' (Clinical Research Centre).

Chapter 5

WEAKNESSES AND DISADVANTAGES

No real disadvantages of establishing a Clinical Trial Unit in Copenhagen have been identified. Below, the weaknesses and potential and apparent disadvantages of forming the CTU in Copenhagen will be briefly discussed under the assumption of status quo.

WEAKNESSES

The CTU will be totally dependent on collaboration with physicians and other co-workers in both the primary and secondary health care sectors. However, the capacity for performing large RCTs in the primary health care sector seems far from being saturated and there is consensus that a number of studies need to be done in this field. Although the RCT activity in the secondary health care sector is much greater, there is also a great need for additional RCTs in this field. Moreover, if less than 5% of the present multi-centre activity was performed in collaboration with the CTU, then this work alone would saturate the resources of the CTU.

Further, the development of the CTU is dependent on the collaboration with the drug and device industry. There already exists close collaboration between this industry and a number of departments of the Health Service in which the CTU should not intervene. However, if a CTU does not create a critical mass of staffing with the appropriate education and skills and is not able to live up to the most critical quality control from industry, then it will fail.

POTENTIAL DISADVANTAGES

The CTU may be viewed as being able to provide a service to all aspects of clinical research at different levels of maturity. However, such a task will always be impossible, unless the CTU will grow to a considerable size - a size that will not be optimal neither from the clinicians, the Copenhagen Health Services, nor the CTU's point of view.

The fact that the CTU will only become involved in a limited number of projects of the total research activity may create problems. This 'non-service' will out-number the number of projects the CTU gets involved in. Therefore a negative attitude towards the CTU may be created, which could soon be turned into a real disadvantage for the CTU, unless there is an understanding of its limitations. This is, among other factors, the rationale for the necessity of a review process of the CTU before committing itself to further involvement in research projects.

APPARENT DISADVANTAGES

The CTU may be seen as an obstacle:

* creating a control mechanism for the possibility of continued free research;

The present proposal does not intend such a function. First of all such a function does not seem desirable for a number of reasons, and second the CTU will not have the sufficient staffing to fulfill such a task.

* creating competition for financial support from the drug and device industry and other resources;

It is a clear impression that the collaboration between industry and a number of investigators of the Copenhagen Health Services is at present functioning very well indeed, and that both sides in these collaborative efforts are not interested in intervention. Therefore, the CTU should only be viewed as a service to interested parties that themselves want to collaborate with the CTU. Moreover, the creation of the CTU should attract new projects and therefore new money.

* creating a new barrier for the drug and device industry;

This is not the case, as the CTU does not need to be consulted before a research project is mounted.

* demanding funding;

The CTU will create the need for an investment in the formation of a critical mass of the core staff, but taken over a longer span of time this investment may be sound as support from industry and private funds may be expected to increase and the results of the research may prove successful so that the investment may pay off. The survival of the CTU will depend on the success of the activities in free competition with alternative ways of organizing clinical trials.

CONCLUSIONS

The medical community has realized that progress in treatment is a stepwise process which can best be facilitated through the performance of multi-centre randomized controlled trials.

The international legislation and guidelines on how such trials should be performed has increased considerably in complexity during recent years.

During the last 30 years, an increasing number of non-specialty oriented organizations facilitating the performance of randomized clinical trials have successfully been established abroad, and more are under construction. However, such organizations do not at present exist in Denmark. The international organizations have during recent years refined the way in which randomized clinical trials can be performed in a more efficient - and hence more ethically acceptable - way.

It is therefore proposed that the Copenhagen Health Services should establish a Clinical Trial Unit to facilitate and perform preventive and therapeutic randomized clinical trials in the primary and secondary health care sectors, function as a know-how centre on clinical trials, and help in the graduate and postgraduate education for the benefit of present and future patients of the health care sectors.

ACKNOWLEDGEMENTS

A large number of people have been crucial for the writing of this report, which has been produced during the period April to November 1993. In this period, I have drawn on the experience of a number of key persons and met a number of outstanding personalities within clinical research and other fields, who have taught me a number of fascinating aspects of organizing randomized clinical trials.

First, on the basis of the vision of certain scientists, the Copenhagen Health Research Council concluded back in 1991 that the international organization of clinical trials should be evaluated before the Copenhagen Health Services decided to form a Clinical Trial Unit. I am thankful for this decision.

Second, the Central Office of the Copenhagen Health Services decided to turn this evaluation into a more formal investigation of the international organization of clinical trials and to delegate the responsibility to the Institute of Preventive Medicine, Kommunehospitalet. I am very thankful for these decisions.

Third, the Director of the Institute of Preventive Medicine, Professor Thorkild I.A. Soerensen asked me to be coordinator of the planning of this investigation and to write this report. His constant interest, visionary abilities, and in-depth knowledge of the international research community as well as all aspects of clinical research, have been of pivotal importance for the completion of this report. I am most thankful for the support and help he has provided me together with perfect working conditions at the Institute.

Fourth, all members of the Planning Group (Jes Gerlach, Thomas Gjrrup, Ib Haurum, Fred Hirsch, Gorm Jensen, Jens Peter Kampmann, Ole Helmer Soerensen, Jens Aage Stauning, Thorkild I.A. Soerensen (Appendix 1)), chaired in the

most effective way by Deputy Director Ib Haurum, have shown substantial and constant interest and have presented sound critical attitude during the formulation of this report. I am most thankful for this collaboration.

Fifth, to the more than 60 outstanding researchers in Europe and North America (named in Appendix 3 and 4) with whom I have had enormously informative meetings, I can only say 'Thank You'. You devoted your time and huge experience, teaching me many interesting lessons, for which I am particularly indebted.

Finally, the staff of the Institute of Preventive Medicine is cordially thanked for creating charming working conditions and for providing excellent assistance in all aspects. Especially, I would like to thank Secretary Birgitte Bredesen and Administrator Vibeke Munk for correcting my bad English, and last, but not least, Secretary Anne Hee who transformed the diskettes into this elegant volume with an eye open to every inconsistency.

APPENDICES

Appendix 1

DEFINITION OF ASSIGNMENT

In April 1993, the Director of the Copenhagen Health Services, Dr.Med.Sci. Erik Juhl delegated the responsibility of forming an operational fundament to the Institute of Preventive Medicine, Kommunehospitalet, and a planning group was formed consisting of the Deputy Director of the Copenhagen Health Services, the Chief of the Department of Clinical Pharmacology, one clinician with experience in performing RCTs from each of the hospitals in the Secondary Health Care Sector, a representative from the Primary Health Care Sector, and the Director of the Institute of Preventive Medicine:

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During the period from April 1 to November 22, 1993 the Planning Group held five meetings (April 22, June 17, September 1, October 21, and November 16).

Appendix 2

CLINICAL TRIALS

TRIAL QUALITY - A HISTORICAL PERSPECTIVE

Pocock (1990) states that the first known medical trial was that of Lind in 1753. Lind took 12 patients with scurvy and assigned two patients to each of six different treatments. Only the two receiving oranges and lemons improved - and were appointed nurses to the rest of the sick. However, even at that time there were problems having a conclusion of a trial disseminated. Lind continued to advise 'pure dry air' as the first choice, with fruit and vegetables as the second recommendation.

In Denmark, Fibiger published a pseudo-randomized trial back in 1898 in 'Hospitalstidende'.

However, many years elapsed before medicine adopted the randomized trial, which in the meantime had been further developed within industry and agriculture. According to Pocock (1990, p. 17) the first clinical trial with a properly randomized control group was the British Medical Research Council (MRC) trial of streptomycin treatment of pulmonary tuberculosis. The first randomized placebo controlled double-blind trial also originates from the United Kingdom back in 1950, evaluating antihistamines for common cold (n=1550). There was no significant benefit from the antihistamines.

Since then there has been an enormous expansion of trial research in a number of fields, especially in the areas of cancer and myocardial infarction, but other areas have also demonstrated an increasing activity. This activity has not been flawless (Juhl et al., N Eng J Med 1977; 296:20-22).

DEFINITIONS

Clinical Trial

According to the Good Clinical Practice (GCP) guidelines, a clinical trial means any systematic study in human subjects, whether patients or non-patient volunteers, in order to discover or verify the effects of and/or to identify any adverse reaction to the investigational products or interventions, and/or to study (in the case of drugs) their absorption, distribution, metabolism, and excretion in order to ascertain the efficacy and safety of the products (GCP 1991).

There are various ways of classifying clinical trials. First, there is the type of treatment being examined: drug therapy, surgical procedures, forms of medical advice, or a new method of patient management. Clinical trials are also divided into certain phases, describing the 'maturity' of the product from the investigators' and sponsors' point of view. Although it is difficult to draw distinct lines between the phases, and although some diverging opinions about details do exist, these phases traditionally encompass (Pocock 1990, GCP 1991):

*** Phase I Trials**

Represent the first experiments in man, often healthy volunteers, to establish safety (i.e. how much can be given without serious side-effects) by performing dose-escalation experiments. Pharmacokinetics and -dynamics, and multiple doses will be examined. After these initial studies, small patient samples will be examined in a similar manner. Typically, less than 100 subjects and patients are required.

*** Phase II Trials**

Represent studies in patients with the main objective to assess short-term safety in patients suffering from the disease for which the product or method is intended. However, one also wants to estimate the potential impact on the disease process and at a later stage a comparative (e.g. placebo controlled) design is employed. This phase also aims at the determination of appropriate dose ranges/regimes and, if possible, clarification of dose/response relationships. Seldom more than 200 patients enter this phase.

*** Phase III Trials**

After a product or intervention has been demonstrated to be reasonably safe and seems to be effective, its overall therapeutic value and short- and long-term safety has to be examined. In order to do this, randomized studies have to be performed. The randomization process is essential in order to create comparable groups. Studies have shown that the use of historical controls will lead to an overestimation of the effect of a new product (Sacks et al., Am J Med 1982;72:233-240, Pocock, 1990). In order to reduce or eliminate bias (Pocock, 1990) these trials are best performed as a double-blind study. The pattern of the more frequent adverse effects must be investigated and special features of the product must be explored (e.g. clinically relevant drug interactions, different responses to the product in gender, age groups, and ethnic groups). In case of prevalent diseases even minor therapeutic benefits (e.g. 5% reduction of mortality in myocardial infarction) are relevant, which necessitates the large groups to estimate such differences with certainty (mega-trials). This has fostered the necessity of collaboration - national as well as international. In the wake of this collaboration, systems for faster randomization and data management systems have been developed. This development will not only be of interest for the mega-trials, but could also substantially shorten the duration of smaller RCTs.

Although RCTs are accepted as the most powerful tool available to assess the effectiveness of a medical procedure, doctors are reluctant to participate in clinical trials, despite such participation being one of their duties, and governmental agencies have until recently rarely funded clinical trials (Boissel, 1989).

*** Phase IV Trials**

After a product or an intervention has been approved for a certain indication - typically after 2-4 Phase III trials - postmarketing longterm studies for surveillance are necessary to monitor for rare or late adverse effects. As these Phase IV trials do not involve randomized control groups, however, it is difficult to conclude from them with certainty, unless strict pharmaco-epidemiological criteria are applied. The Phase IV trials are also viewed by many as 'seeding' trials, which educate the physicians to use the new product or intervention.

A similar, but more detailed, subdivision of trials is given by Spilker (1991).

RECENT DEVELOPMENT OF PHASE II-IV TRIALS

During recent years there has been an increasing understanding of the advantages of condensing Phase II to IV trials into large RCTs. The patients are randomized into e.g. four groups (placebo or standard treatment, low dose therapy, intermediate dose therapy, and high dose therapy) in an unblinded trial, and after initial evaluation, the trial continues randomizing new patients into the trial with a double-blind design. Moreover, a factorial design (e.g. 2 x 2) is more often used, combining two treatments in one arm of the trial. This facilitates the study of additive or supra-additive efficacy and unwanted adverse effects due to unrecognized interactions of the interventions.

Appendix 3

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Appendix 4.1

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

1	April 13	Ospedale V. Cervello Palermo, Italy Hepatology	Luigi Pagliaro et al.	Meta-analyses Trials in Primary Health Care Sector
2	April 14-15	Mario Negri Milan, Italy Cardiology	Gianni Tognoni Maria Grazia Franszosi	Mega-trials Coordination Involvement of nurses

				Quality control
3	April 16	Istituto Sup. di Sanita Rome, Italy AIDS	Stefano Vella	Quality control Fax randomization INTERPAC Network of Clinical Research Centres
4	June 4	Data & Analysis of Research Ltd. Cambridge, UK CRO	Roy Shentall	Standard Operational Procedures Quality control Network of general practitioners Triple market in year 2000
5	June 7	Medical Research Counsil Solid Cancer Clinic Cambridge, UK	David Machin	Working groups Protocol development Phone randomization EuroCODE COMPACT data management Register of trials
6	June 8	Medical Research Counsil Clinical Trial Services Unit Oxford, UK Cardiology etc.	Richard Peto Rory Collins	Mega-trials Organization International trials Fax & Phone randomization Simple trials Essential trials

Appendix 4.2

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

7	June 8	Perinatal Trials Service Oxford, UK	Adrian Grant	Mega-trials Organization

				International trials Simple trials Relevant trials Register of RCTs
36	June 8	Cochrane Collaboration Centre Oxford, UK All specialities	Iain Chalmers	Meta-analyses Consumer influence International cooperation Cochrane Collaboration Dissemination of RCT results
8	June 9	Royal Free Hospital London, UK Hepatology	Marsha Morgan	Phase II trials
9	June 9	London School of Hygiene and Tropical Medicine London, UK Cardiology	Simon Thompson	Mass allocation Community trials Meta-analyses
10	June 10	London School of Hygiene and Tropical Medicine London, UK Infectious diseases	Keith P.W.J. McAdam	Vaccine trials Marketing International trials Education
11	June 10	Royal Infirmary Glascow, Scotland Gyn. & Obstet.	James J. Walker	Press button phone randomization Trials comparing Primary vs. Secondary Health Care Sector Mega-trials Organization International cooperation Randomized when in doubt

Appendix 4.3

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

12	July 22	Epidemiology Research Unit Barcelona, Spain All specialities	Pedro Alonso	International trials Malaria vaccine trials Trial services Meta-analyses Marketing to the pharmaceutical industry
13	July 21	Hospital Clinic i Provincial de Barcelona, Spain Hepatology	Joan Caballeria	Multi-centre trials Marketing to the pharmaceutical industry
14	July 28	Biofield Corp. New York, USA	Robert Yocher	Marketing to the pharmaceutical industry Quality assessment FDA/EU-GCP
15	July 29	Schering-Plough Research Institute Kenilworth, New Jersey, USA Cardiovascular diseases	Roberto Casareto	Marketing to the pharmaceutical industry Quality control FDA/EU-GCP Quality-of-life Pharmacoeconomics
16	July 30	Maryland Psychiatric Research Center Baltimore, USA	Robert Conley Carrol Tamminga William Carpenter	Combination of basic and applied research Inter- and intraobserver assessment Basic and applied science Pharmacoeconomics
17	August 2	Maryland Medical Research Institute Baltimore, USA	Genell Knatterud Michael Terrin Knut Ra	Press button phone randomization including fax Data management Community trials

				NIH

Appendix 4.4

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

18	August 3	Food and Drug Administration Rockville, USA	Paul Leber	Pharmacoeconomics Quality-of-life Surrogate endpoints Missing data FDA requirements
19	August 3	NIH Bethesda, USA	John Ferguson	NIH consensus conferences Definition of clinical trials Dissemination of the results of RCTs FIRMS Register of RCTs
20	August 4	Tufts New England Medical Center Boston, USA Meta-analyses	Thomas Chalmers	Sequential meta-analyses Combination of small trials
21	August 5	Veterans Affairs Medical Center Cooperative Stud. Program Boston, USA	Daniel Deykin	RCT organization RCT evaluation Pharmacoeconomics Management Marketing to the pharmaceutical industry Health services research
22	August 5	Harvard School of Public Health Boston, USA	Fredrick Mosteller	Quality control Lawyers Malpractice

		Meta-analyses		Register of RCTs Small RCTs Meta-analyses
23	August 6	Harvard Medical School Infectious Disease Unit Boston, USA AIDS	Martin Hirsch	Trial marketing to community incl. of patients RCT management E-mail International trials

Appendix 4.5

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

24	August 10	Women's College Hospital Toronto, Canada	Mary Hannah	Press button phone randomization Organization of multinational mega-trials Economics National network Register of trials
25	August 11	McMaster University Dept. of Clinical Epidemiology Hamilton, Canada	Wayne Taylor	DataFax Data management Quality control Organization Mega-trials Clinical Trial Simulator
26	August 11	McMaster University Health Services Center Hamilton, Canada	George Browman	Organization of research Management Marketing Pharmacoeconomics Quality-of-life

				Health Policy Dissemination af RCT results
27	August 11	McMaster University Dept. of Family Medicine Hamilton, Canada	Ron McAuley Brian Hutchison Brian Haynes	Trials in Primary Health Care Sector Pay vs. non-pay trials
28	August 12	McMaster Clinic Hamilton General Hospital Hamilton, Canada Cardiovascular diseases	Salim Yusuf	Mega-trials DataFax National network Marketing Patient newsletter Preventive trials Preventing doctors from industry
29	August 12	Henderson Research Centre Hamilton, Canada Thrombolysis	Mike Gent	Simple trials Mega-trials International trials Industry cooperation

Appendix 4.6

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

30	August 12	McMaster Clinic Hamilton, Canada Internal medicine	David Sackett	Consultative service DataFax Mega-trials Organization Surgical trials
31	August 16	Cleveland Clinic Foundation Cleveland, USA	Valerie Stosik	Mega-trials Data management

		Cardiovascular		International trials Weekly posters Economy Standard Operational Procedures
32	August 16	University Hospital of Cleveland Case Western Reserve Cleveland, USA	Peter Buckley Myung Lee Philip Cola	Mega-trials Organization International trials Pharmacoeconomics Data management
33	August 19	Pharmaco::LSR Maryland, USA CRO	Melany Adamico	Data management Quality control Phase I-IV trials Standard Operational Procedures Marketing
34	August 19	University of Maryland Baltimore, USA Ophthalmology	Kay Dickersin	Surgical trials Multi-centre trials Marketing Meta-analyses Register of RCTs
35	August 12	McMaster University Hamilton, Canada	Gord Guyatt	Quality-of-life

Appendix 4.7

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

37	September 24	Center for Osteoporosis Department of Medicine 331	Ole Helmer Soerensen	Combination of basic and applied research Marketing to the pharmaceutical industry

		Kommunehospitalet, Copenhagen, Denmark Osteoporosis		Osteoporosis research
38	September 20	EORTC Brussels, Belgium Cancer	Francoise Meunier & Richard Sylvester et al.	Data management Quality control Phase I-IV trials Marketing Register of RCTs Pharmacoeconomics Quality-of-life EuroCODE
39	September 22	H^pital Neuro-Cardiologique DJpartement MJthodologie et Essais ThJrapeutiques Lyon, France Cardiovascular	Jean-Pierre Boissel	Data management MINITEL Mega-trials International trials Trials in Primary Health Care Sector Marketing to the pharmaceutical industry Register of RCTs

Appendix 4.8

Highlights from Meetings in Organizations performing Multi-centre Randomized Clinical Trials.

Report No. Date Institution Representative Highlights

1993

40	September 9	The State Serum Institute Copenhagen, Denmark	Nils Strandberg Pedersen Pia Lading Birgitte W. Knudsen	Marketing towards industry Organization of Primary Health Care Sector Education of physicians
41	September 13	LEO Ballerup, Denmark	Hans Jessen Jhrgensen	Marketing towards industry Organization of Primary Health Care Sector

				Education of physicians Data management
42	September 4	Novo Nordisk A/S BagsvFrd, Denmark	Lars Nellemann Jrrgensen	International RCT coordination Marketing towards industry Meta-analysis service Data management Pharmacoenonomy
43	October 11	H. Lundbeck A/S Valby, Denmark	Vagn Pedersen	Phase II studies Marketing towards industry Organization of Primary Health Care Sector Broker function
44	November 15	Perinatal Epidemiology Research Unit Crhus, Denmark	Jacob Hjort	Press Button Phone Randomization

Appendix 5

Interview No.: 7 (Accepted July 2, 1993)

Report from meeting in: Oxford

Date: June 8, 1993

Between: Honorary Director

Adrian Grant MA, DM, BCh, MSc (Epid), MSC (Med Dem), FRCOG

Perinatal Trials Service

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and Christian Gluud for The Copenhagen Health Services.

STRUCTURED INTERVIEW QUESTIONS OR QUESTIONNAIRE CONCERNING CLINICAL TRIAL UNITS

1. Name of institution?

Perinatal Trials Service.

Formed under the National Perinatal Epidemiology Unit (NPEU) in 1990. The former Director of the NPEU, Iain Chalmers, set up the NPEU in 1978. In 1980 Adrian Grant joined the NPEU with the remit to mount a programme of perinatal trials. In the beginning they were doing small trials, but during the 1980's the balance shifted to multi-centre trials, and the basic idea of forming a Trials Service Unit was formed. In the late 80'ies international collaboration was started and Adrian Grant was appointed Honorary Director of the Perinatal Trials Service Unit (PTS) in 1990.

2. Date of Foundation?

1990.

3. Basic idea?

The unit's programme of randomized trials has involved studying the effects of social and clinical interventions, and these have been evaluated in terms of social, psychological, and economical, as well as clinical, outcomes. The programme of trials has included many individually important trials. Some of these, e.g. those concerned with finding ways to reduce postpartum maternal morbidity, have tackled problems, which previously have been largely ignored by researchers. The achievement of the Unit's work in controlled trials is greater than the sum of the individual trials within it. The Unit has helped to foster a culture, in which it is accepted that randomized trials are the appropriate response to uncertainties about whether a particular form of perinatal care does more good than harm, than an alternative. This new culture has been reflected in the Unit's programme of work in a number of diverse ways:

* Representatives of voluntary organisations were involved in planning and actively promoting the successfully concluded Medical Research Council sponsored European Chorion Villus Sampling Trial.

* The MAIN trial represents the first international collaborative trial run by midwives.

* The OSIRIS trial is the largest trial of neonatal intensive care ever conducted and has involved nearly 7000 babies recruited in over 200 hospitals in 21 countries.

* The CLASP trial represents the largest collaborative obstetric trial ever conducted, recruiting more than 9000 women in 226 centres in 17 countries.

* Multi-centre trial of alternative treatments of eclampsia, recruiting patients from Latin America, Africa, and Asia.

4. Objectives and aims?

The aim of the Perinatal Trials Service is to provide a service to busy clinicians who wish to evaluate their care in randomized controlled trials. The service coordinates a programme of randomized trials in perinatal medicine, and the expectation is that any one-time there will be about two trials at each stage of development over a 5-year cycle. The PTS has three main areas of research:

1. Prevention and treatment of neonatal immaturity and its consequent morbidity.

2. Identification and management of the compromized fetus or new-born baby.

3. Prevention and treatment of maternal morbidity.

See Appendix A.

5. Specific tasks?

In addition to doing randomized clinical trials, the PTS is involved in meta-analysis (now collected in the Cochrane Centre), and the development of trials technology. Furthermore, we are involved in education -mostly postgraduate. In addition, cost-effectiveness analyses, social science aspects of evaluation, and doing a long-term follow up of studies in childhood, in order to examine late effects of interventions are increasingly important aspects of the trials programme.

6. Should one have a specific therapeutic area?

No, but one should collaborate with experts in the particular field. It is the PTS' experience that one can work in a couple of fields.

7. Or should one have the expertise of doing randomized studies?

Yes, definitely. It is sensible to plan to mount a programme of trials. The reason is the life cycle of a trial. Trials are very work intensive for a Trials Service Unit in the beginning of a trial and at the end of a trial. In between, when the trial is running smoothly, the work load is mostly on the clinician. Therefore, one should adopt a strategy for developing and running different trials at the same time. It is essential that this strategy is very coordinated, otherwise the Trial Unit will have periods with over-work and others with very little to do. This strategic planning is quite difficult, because a number of problems always arise. However, with some experience it is possible to make it work.

8. Owner of unit?

The Department of Health.

9. Controller unit - board of unit?

The Dept. of Health - represented by the National Perinatal Epidemiology Unit's Steering Committee which meets every 6 months.

10. Name of present leader?

Adrian Grant**.**

11. Educational background of present leader?

Medical Doctor with basic training in obstetrics and gynaecology. Specialist in Epidemiology.

12. Name of previous leaders?

None.

13. Educational background of previous leaders?

Vide supra.

14. Reason for change of leader?

Vide supra.

15. Academic staff at the foundation?

Five.

16. Non-academic staff at the foundation?

Eight.

17. Present academic staff?

Five.

18. Present non-academic staff?

Eight.

The organisation of the PTS can be divided into a group of core-persons represented by:

A Medical Trialist

A Statistician

A Programmer

An Administrator

A Secretary

This core group runs and supervises all the projects. Further, the individual projects should be staffed with varying combinations of: A Coordinator

A Programmer

A Data-clerk

A Secretary

The PTS draws heavily on the Economist and Developmental Paediatrician within the NPEJ.

RELATION TO THE PUBLIC HEALTH SERVICES

19. Clinical departments?

The PTS has a great advantage by being a National, even an International Service Unit. This is a big advantage when approaching clinicians. The Trial Unit looks upon itself as very neutral, and we are not connected to any clinical departments.

The basic philosophy of our trials is to run them very simply. Accordingly, we are also very open, and, in principle, any clinical department can join our studies. We ensure safe and sound randomization. In our experience it is very good to collaborate with county hospitals. Usually, they are more easy to cope with than many university departments. Furthermore, the results of the research can be extended to the whole hospital community, when the basic research is done so broadly.

- Criteria for collaboration?

The protocol is the basis of the collaboration between the perinatal trial service and the clinical department.

20. Paraclinical departments?

We do not normally work directly with them.

- Criteria for collaboration?

Vide supra.

21. Primary Health Care Sector?

Up till now, we have no experience in co-working directly with the general practitioners. However, we have a very good experience, indeed, in midwifery trials.

- Criteria for collaboration?

See 19.

22. Statistical departments?

Again, our basic philosophy is to apply very simple statistical techniques. However, we have statisticians in the core staff of the trials service, and in addition we sometimes seek external help.

In the randomization process, we always involve minimization by computer.

- Criteria for collaboration?

RELATION TO THE PRIVATE HEALTH SERVICES

NO EXPERIENCE.

23. Clinical departments?

- Criteria for collaboration?

24. Paraclinical departments?

- Criteria for collaboration?

25. Primary Health Care Sector?

- Criteria for collaboration?

26. Statistical departments?

- Criteria for collaboration?

RELATION TO THE PHARMACEUTICAL INDUSTRY

27. In general terms

We do not have very much experience in working with the pharmaceutical industry. It is due to the fact that the pharmaceutical industry is quite anxious about entering the perinatal field because of fear of litigation. However, the experience that we have had, has been very good. What we seek is independence.

- Criteria for collaboration?

Reasonable degree of independance.

28. Collaboration with one or more companies?

More.

- Criteria for collaboration?

Should be decided from case to case.

CLINICAL PHASE III-TRIALS

29. Description of the logistics?

In every project the Trial Service Unit should co-work closely with a Steering Committee of the individual study. This Steering Commitee is usually headed by a clinician, and normally composed of between 3 and 7 people and meets about 4 times a year.

This Steering Committee refers to a Steering Group, which is ultimately responsible for the trial, and consists of the national coordinators of the study in international studies or the coordinators of the different clinical centres in a national study. They meet about once a year during a trial.

In addition to the Steering Committee and the Steering Group, it is also important to have collaborators' meetings. One doctor and - importantly - one nurse or midwife should attend annual meetings of preferably two days duration. One should compose a good scientific programme for such meetings. In addition, it is also very useful to be able to fund a good dinner, where people can feel more free to speak, and are able to present their problems and complaints in a relaxed atmosphere.

In addition to these groups, the Data Monitoring Committee (DMC) is essential. It should be composed of highly respected people, who are able to interpret accumulating data. In UK we normally speak of two different schools in monitoring trials. The first one is that of Peto, who thinks that the DMC should ask for as many interim analyses as seems desirable, but one should only react if there is a difference of 3 standard deviations or more and there is the likelihood that the results would change clinical practice. The other is the school of Professor Pocock, who normally advises the use of adjusted p-values in interim analyses.

30. Function of the Steering Committee?

Vide supra.

31. Function of other Committees?

Vide supra.

32. Description of daily operational procedures?

Vide supra.

33. Quality control?

We take great trouble to ensure a complete dataset and to check for internal consistency. We do not cross-check against the hospital case notes.

34. Local randomization?

We are reluctant to set up local randomization unless there is no alternative.

35. Central randomization?

Yes, and here it is essential to have good programmers able to develop minimization programs for the randomization. In that respect we have had very much delight in co-working with the Danish programmer Jakob Krog. He is very talented,

and he will soon be returning to Denmark. I would advise the Copenhagen Health Services very much to co-work with him.

36. Phone-randomization?

Yes, we do that, and it is working very well.

37. Fax-randomization?

We also offer that, where feasible, and this is also working well.

38. Data-communication systems?

In a trial in Barbados we are using de-centralized computers, but I think the data communications systems will be used much more in the future. In France they have developed MINITEL, and as far as I am informed, it is working very well.

39. Type of projects completed - including reference list?

Please see Appendix B.

40. Type of current projects?

Please see Appendix B.

41. Planned projects?

Please see Appendix B.

42. Market development during the past?

The market has definitely been growing, and will definitely grow in the future.

43. Major mistakes?

Insufficient funds for some early trials, too small trials, and not chosing questions that were of sufficient importance.

44. Major selling-points?

That we now have demonstrated over a number of years that we are able to coordinate large trials in an international setting.

45. Present market situation - competitors?

Other groups are trying to coordinate similar trials, but are relatively inexperienced.

46. Main competitors inside the country?

Vide supra.

47. Main international competitors?

Vide supra.

48. Future market situation?

I think the future market is looking very good. We intend to:

- break new ground in perinatal follow up;

- break new ground in relation to consumer groups;

- break new ground on cost effectiveness, we find that the economic analysis should be a natural part of a trial;

- break new ground in ascertaining the views of participants in trials.

49. Strategy of coping with problems?

We always try to use at least 2 x 2 multifactorial design. This certainly increases the likely value of the trials results.

50. Economical background?

Partly, or mainly public money.

51. Public funding?

60% of our budget is covered by the Dept. of Health, of which 50% cover core expenses and 50% cover project expenses.

52. Private funding?

Private funds provide roughly 20% of our budget.

53. Funding from pharmaceutical industry?

20%, mainly from one big grant.

54. Funding from EU/NIH?

Yes, we have got money in connection with a concerted action.

55. Average cost (per patient/per project/duration of project)?

Phase II-trials: Not answered

Phase III-trials: Substantially less than North American trials

56. Range of costs (per patient/per project/duration of project)?

Phase II-trials: Not answered

Phase III-trials: Not answered

57. Average time (person months) invested per project?

Not answered.

58. Cost of a new placebo-controlled study on easily accessable patients receiving treatment for 12 months with a total of six clinical evaluations encompassing clinical examination and 12 routine blood samples (e.g. hemoglobulin, creatinine etc.)?

Not answered.

59. Should a CTU do meta-analyses?

Yes, definitely.

60. Other tasks?

See question 5.

61. Do you have guidelines for sorting out new projects and in this case which?

The Perinatal Trial Service's criteria for deciding whether or not to mount a particular trial encompass:

1) **Importance of the underlying problem** - the number of pregnancies or babies affected, the number developing major problems, and the health service implications.

2) **Plausibility** - the existing evidence that the proposed intervention would be likely to be beneficial, medically, economically, and socially, particularly as judged from the results of any previously conducted randomized trials, where appropriate, considered in the context of formal overviews.

3) **Hazards** - the potential for harmful effects.

4) **Clinical interest** - sufficient clinical interest to secure recruitment of large numbers of participants.

5) **Timing** - sufficient current clinical uncertainty for randomization.

6) **Funding** - the likelihood of attracting top-up project funding.

7) **Feasibility** - the possibility of answering the questions within a reasonable period of time.

8) **Necessity of Perinatal Trial Services coordination** - the possibility that the trial could be effectively and efficiently coordinated by another research group.

We have a **Scientific Advisory Committee.** In particular we seek their advice when trying to agree on which trials to mount and which not to. This Committee includes a consumer representative. We have found that representatives of the users of the health services are very helpful when developing patient information.

62. Are you connected to data-base of on-going or planned clinical trials?

Yes, the International Registry of On-going and Planned Perinatal Trials (IROPT)

63. How do you consider the future of randomized clinical trials?

It is certainly a rising market.

64. How do you consider the future of Clinical Trial Units?

Certainly rising as well.

65. The advantages of mega-trials are evident. Could you isolate the major draw-backs apart from money and time, and organisational mega-energy?

Must be kept very simple and well-organized or will collapse.

66. Do you have suggestions for further Institutions/Clinical Trial Units around the world that the Copenhagen Health Services should consult regarding this matter.

You should definitely talk to Finn Brrlum Christensen in Denmark, who has an interest in running trials in general practice.

In addition to that, I can advise you to see the Cancer Research Campaigns Clinical Trials Centre, Kings College School of Medicine and Dentistry, Royal Institute, 123 Coal Harbour Lane, London SE5 9NU. Phone +44 71 737 3642 or 3048 (Hon. Director, Professor Michael Baum and Assistant Director Joan Houghton).

Professor Stuart Pocock, Clinical Trial Research Unit at the London School of Hygeine and Tropical Medicine.

And, naturally, Richard Peto, Rory Collins, and Iain Chalmers of Oxford.

67. Do you know any CTUs that have failed, - and if so, why?

Not answered.

68. Do you have suggestions for further relevant questions?

Not answered.

69. Which of the questions did you find irrelevant?

Not answered.

Appendices:

Appendix A: Adrian Grant. Rationale for and work of the Perinatal Trials Service, Early Human Development, 1992; 29:305-308

Appendix B: National Perinatal Epidemiology Unit - Annual Report 1991.

Christian Gluud for The Copenhagen Health Services

April 2, 1993 (revised June 16, 1993)

Appendix 6

METHODOLOGIC ADVANCEMENTS IN RANDOMIZED CLINICAL TRIALS

PRESS BUTTON PHONE RANDOMIZATION

In Europe (I: 11, 44) and in North America (I: 17, 24), Press Button Phone Randomization has been developed during recent years. The clinical investigator calls a (toll free) number, and through a personal code the investigator is welcomed to a particular trial by a recorded voice and asked to enter the randomization variables of the patient. When these data have been entered, and after the investigator approves the data, the system randomizes the patient and informs the investigator about which treatment the patient is going to receive. All these systems seem to function at the same high level of efficacy, facilitating randomization within few minutes. In Maryland (I: 17), the system was further refined as a fax was automatically sent to the clinical investigator, the coordinating centre and the industry involved in the trial. Some of the systems are commercially available (I: 24, 44).

DATA MANAGEMENT SYSTEMS

A number of data management systems have been developed during the last 10-15 years, constantly gaining in capacity and flexibility. A number of these systems are available commercially and are marketed, e.g through the Drug

Information Association's publications. A number of systems have also been developed at some of the CTUs visited, and they will be briefly described below.

*** COMPACT**

COMPACT (**COM**puter **PA**ckage for **C**linical **T**rials) was developed with the support of the UK Medical Research Council in Cambridge (I: 5). COMPACT

- facilitates interactive data entry and correction for clinical trials;

- allows detailed checking of consistency and accuracy of data;

- maintains a list of any inconsistencies in the patient data, together with the status of any queries and the action taken;

- assists the daily administrative work involved in running trials;

- produces displays and printed listings required for interim data review;

- generates files in a form readily accepted by most statistical packages (SPSS, SAS, BMDP, or Minitab);

- runs on any micro- or mini-computer capable of reading Fortran (e.g. Digital VAX or IBM PC).

The COMPACT seems to be an advanced software package with good flexibility allowing text entry. It can be obtained at a very low price by contacting the Cancer Clinical Trials Office in Cambridge, UK (I: 5).

*** SMART**

The European Organization for the Treatment of Cancer (EORTC) has developed a data management system called SMART (**S**oftware for the **M**anagement and **A**nalyses of **R**andomized **T**rial). A whole set of data forms for a RCT can be set up on SMART in a few days or less with direct checking of illogical data, warning about missing data, and the system can automatically send out warning variables (e.g. if leukocytes become too low). When the data manager is sure that all entered data are correct, the data can be transferred into files for subsequent statistical analyses.

The system seems to be an advanced software package with good flexibility, but does not allow entry of text. The price is unknown.

*** MINITEL**

In France, the introduction of a national electronic communication system (MINITEL) has proved to be a revolution in the fast transfer of small data samples (I: 39). Most French doctors are now able to successfully use the system, which has proved valuable in performing RCTs both within the Primary and Secondary Health Care Sectors. Although MINITEL works well in France and other centres (e.g. the AIDS centre in Rome (I: 3) had good experience in using Electronic Mail in the running of RCTs), other CTUs report substantial difficulties. In Canada a number (20-40%) of physicians had difficulties entering data into Electronic Mail, and the system has now been abandoned in certain centres.

In Denmark the Electronic Mail systems have just been introduced and it will take 5-10 years before the system is fully integrated in the Danish society. However, in the future, Electronic Mail systems represent an attractive solution for many purposes, including trial management.

*** DataFAX**

DataFAX was developed in Canada, among other factors due to the bad experience in using Electronic Mail for RCTs. The system only requires that the clinical investigator fills in the trial data form and faxes it. The trial data form has a bar code and the moment it enters the fax at the CTU, the bar code is read by a computer which brings the fax to its file. The next day the data manager can check the data of the fax in its file, transfer the data to an intermediary file (looking exactly like the fax), and missing data and illogical data are identified. The moment these problems are identified a fax is prepared and sent back to the clinical site requesting action. When the response has been received at the CTU, the

intermediary file can be corrected and up-dated, and a final file is formed. The data in the final file are prepared for statistical analyses. The DataFAX system runs well, a data manager may go through 500-600 trial forms per day, and there is no paper at the CTU, which reduces the filing space substantially. The DataFAX system is further described in interview 25.

For Universities the price (with a 50% reduction) is USD 75,000 the first year (including 30,000 for consulting in setting up the first data-base), and thereafter the license is 22,000 a year (without consulting fee). The system seems very attractive as it is easy to use for both the clinical investigators and the CTU, and experienced trialists have adopted it for several RCTs (I: 25, 28).

*** Padcom Clinical Data Management System**

The German firm Padcom has developed a series of trial software packages for the new generation of pen-based computers. On a portable computer, one writes with a special pen and the handwriting is transformed into characters and numbers. In PadTrial the computer will check the data for correctness and completeness, and will when validated enter the information into a database. According to the firm this should increase data quality and reduce the complicated cleaning of data (Beinlich et al., Drug Research 1993; 43:399-404). Using fax or telecommunication, the validated data can be transferred from the investigator to the CTU. The firm offers to develop the design of databases etc. Padcom has also developed PadMonitor and PadTrial Manager software in an integrated Clinical Data Management System.

As the system allows for capturing the handwritten data, the system lives up to the rules of GCP which require that there is a validated print-out and back-up record (dated and signed) if trial data are entered directly into a computer. The price is not known.

Appendix 7

HEALTH ECONOMICS

Introduction

There will never be sufficient resources to satisfy all the demands for which some kind of medical, surgical or rehabilitative intervention is feasible. In many industrialized nations, health care expenditures increase by 6-9% annually, while the Gross National Product only increases by 2-4% annually.

In order to maximize productivity of available resources by investing in the most cost effective treatment and intervention options, health economic evaluation is a technique developed during the last 30 years (Robinson, BMJ, 1993; 307:670-673). As pharmaceuticals belong to the high profile items of health costs (10-20%), a similar technique called Pharmacoeconomics has been developed for drawing up a balance sheet of the advantages and disadvantages of pharmaceutical interventions.

There are a number of ethical problems related to health economics. However, one should realize that health economic evaluations are an everyday phenomenon in our life. For a number of years, traffic safety has been considered when money is allocated for road building. Moreover, physicians consider the costs of a treatment every day when treatment is given to specific patients. However, this evaluation is often performed in an unsystematic way, subjected to personal bias, and without sufficient clarity in the fundament for decision making.

DEFINITION OF HEALTH ECONOMIC TECHNIQUES

The four main approaches currently in use for health economic evaluation are:

*** Cost-minimization analysis**

It simply compares the cost of treatment (cost of products and cost in connection with administration), and should only be used in connection with interventions where there is good reason to believe that the outcomes of the interventions under consideration are the same (Robinson, BMJ 1993; 307:726-728).

*** Cost-effectiveness analysis**

This is an appropriate method to use if the outcomes of different interventions for a specific disease are expected to vary, but these outcomes can be expressed in common natural units ('positive cases' detected by screening procedures, 'mmHg reductions in blood pressure obtained', 'healthy days', or 'life years gained' achieved through treatments). With a common unit of outcome, different interventions can be expressed in terms of cost per unit of outcome (Robinson, BMJ 1993; 307:793-795).

Cost-effectiveness analysis is limited, however, when one wants to compare cost-effectiveness of different diseases having different outcome measures.

*** Cost-utility analysis**

Since a cost-effectiveness analysis is not able to combine reductions in morbidity or mortality into a single index, considerable efforts have been invested in the development of 'utility' based measures of outcome during recent years. In the health care context, 'utility' refers to the subjective level of well-being that people experience in different states of health (Robinson, BMJ, 1993; 307:670-673).

To measure utility, various quality-of-life scales have been developed. Quality Adjusted Life Years (QALYs) combine quality-of-life with a quantitative measure of life years in order to obtain a single measure of lifetime utility. Hence, cost per QALY gained can be calculated and compared.

Such comparisons demonstrate that the cost per QALY for cholesterol testing and treatment by diet (adults aged 40-69) is , 220 compared to the cost per QALY of erythropoeitin for anaemia in dialysis patients of , 126,290 (Mason et al., BMJ, 1993; 306:570-572). It should, however, be realized that cost-utility analyses are still at a fairly early developmental stage and conclusions should be treated with care (Robinson, BMJ, 1993; 307:859-862).

*** Cost-benefit analysis**

Cost-benefit analysis is often used as a general term to cover all types of economic evaluations, but with regard to health economics it compares the costs of an intervention with a monetary output. Cost-benefit analysis forces an explicit decision about whether the cost is worth the benefit by measuring both in the same units.

The costs can be hard to evaluate, and one may often rely on 'shadow' prices. It is necessary to include direct costs, indirect costs, and intangible costs, and due to the uncertainties sensitivity analyses must be performed. However, cost-benefit analysis may give valuable information. Suppose intervention A costs , 200 and has a benefit of , 300 and can help 1000 people, then the net benefit is , 100,000. Intervention B costs only

, 100 and has a benefit of , 300, but will only help 100 people, then the net benefit is , 20,000 (Eisenberg, JAMA, 1989; 262:2879-2886).

HEALTH ECONOMICS AND CLINICAL TRIALS

Due to the fact that the precise estimation of costs becomes increasingly difficult when performed retrospectively, it is generally accepted that health economic evaluations increase their validity and reliability when performed in a prospective manner. As health economic evaluations may have importance, irrespective of the efficacy and rate of adverse effects of interventions, it is generally considered that health economic evaluations should be included in many more clinical trials, especially from phase III and onwards. However, only 121 of over 50,000 published randomized trials during the 1966-1988 period (0.2%) included economic analyses and these varied considerably regarding quality (Adams et al., Medical Care 1992; 30:231-243).

In a number of countries (Australia, Spain, Portugal) economic analysis is already required for government approval and pricing of new pharmaceuticals, and a number of countries (Canada, UK) are developing guidelines for pharmacoeconomic data. Due to the competitive market, the drug and device industry is increasingly trying to demonstrate the cost-effectiveness of their products.

Therefore, in the future one will see the development of international guidelines which will increase the validity and comparability of health economical analysis (Hillman et al., N Engl J Med 1991; 324:1362-1365), and these analyses will become an integrated part of more randomized clinical trials.

Appendix 8

QUALITY-OF-LIFE

Introduction

Health related Quality-of-life (QOL) is increasingly becoming an accepted measure of the efficacy of a drug or device, or other interventions in clinical trials. Although the methods of measuring QOL have been employed for more than 30 years, the methodology still needs refinement and so does the way of analyzing the results of QOL measurement.

As the limitations of traditional indicators of health have been increasingly recognized (a physician's evaluation of the function of a given patient has repeatedly been shown to differ from the patient's evaluation, and physicians may also vary substantially in the evaluation of a single patient), QOL has become an important outcome of medical care (Wiklund et al., Controlled Clinical Trials 1990; 11:169-179). QOL is not a surrogate endpoint, but represents in itself the ultimate goal of any intervention, i.e. to see how patients feel, act and behave. However, QOL is not the physicians' evaluation of the patients QOL. By measuring QOL one obtains the patient's values, judgements and beliefs. It should be realized that measuring QOL is a difficult task still needing refinement.

HEALTH RELATED QUALITY-OF-LIFE MEASURES

About 600 QOL measures have been developed over the years (Spilker et al., J Clin Res Pharmacoecon 1992; 6:205-266). However, only a minority has been properly validated (Guyatt. Personal communication). The QOL measures may be divided into non-disease specific (global, general or generic) and disease specific QOL measures (Brooks, 1991; Guyatt GH et al, Ann Intern Med 1993; 18:622-629).

Global Quality-of-Life Measures

Global QOL measures purport to be applicable across types and severities of disease, across different interventions, and across different demographic and cultural subgroups (Brooks, 1991).

Global QOL measures cover the following aspects of life:

* Physical capabilities

* Psychological capabilities

* Social status

* Economic/Employment status

These aspects can be presented as a profile of the dimensions or be condensed into an aggregate measure, e.g. Quality Adjusted Life Years (QALYs).

Typical examples of a global QOL profile is the Nottingham Health Profile (NHP) (Brooks, 1991), consisting of 45 yes/no answers. Another example is the short form 36 health survey questionnaire (SF-36) developed in the USA. The SF-36 has recently been validated against the NHP in UK (Brazier et al, BMJ 1992; 305:160-164), and it was demonstrated that SF-36 fulfills criteria of reliability, validity and sensitivity. A recently developed EuroQol demonstrates a striking similarity in relative valuations attached to 14 different health states in three European countries (Sweden, UK, and the Netherlands) (The EuroQol Group, Health Policy 1990; 16:199-208).

The aggregate measure of QOL, e.g. QALYs, weights years of life by the quality of those years, which is determined by the presence of intangible outcomes such as disability and pain. For example, a year of life with hemiparesis might be equivalent to 0.5 years of life in perfect health, thus equaling 0.5 QALYs (Ei-

senberg, JAMA 1989; 262:2879-2886). Rosser et al. have developed a numeric scale extending from 0=dead to 1=perfect health, by interviewing people about their attitude to two dimensions: disability and distress (Robinson, BMJ 1993; 307:859-862). By using such tabulations, QALYs may be calculated. It should be realized that the method has been severely criticized and must still be considered not fully developed (Brooks, 1991).

Disease Specific Quality-of-Life Measures

These measures are designed to assess specific diagnostic groups, measuring responsiveness to interventions. Disease specific measures are available for arthritis, back pain, cancer, diabetes, cardiovascular diseases, lung diseases, digestive diseases, mental health, etc. (Brooks, 1991). The rationale for this approach is the increased responsiveness that may result from including only important aspects relevant to the patient. Moreover, specific measures relate closely to areas routinely analyzed by clinicians.

Quality-of-Life and Clinical Trials

Government regulatory agencies, such as the USA FDA and the Canadian agency, are beginning to consider QOL assessments of new drugs as part of the drug approval process (Reviki et al., PharmacoEconomics 1992; 1:394-408). Only a small part of clinical trials at present include QOL assessments. For example, among 75 RCTs from major medical journals in 1986, 32 used at least one QOL measure (often of untested validity). However, QOL should have been assessed in 25 out of the remaining 43 RCTs (Jaeschke et al., PharmacoEconomics 1992; 1:84-93).

The assessment of QOL may be especially important in case certain drugs are equivalent regarding efficacy and adverse effects. As this is not known before trials are launched, it may be wise to consider the inclusion of QOL measures in some late phase II trials and in more phase III trials. In the future, one will see QOL measures in many more RCTs, especially in highly competitive therapeutic areas, therapeutic areas where data may help speed regulatory approval (e.g. cancer), and in 'me-too-drug' areas.

The evaluation of QOL assessments should be undertaken paying special attention to the following:

* Have validated QOL measures been used?

* Have the measures been validated in the country in which they have been used?

* How many QOL measures have been included?

* What was used as the control regimen?

* Has a proper design been used allowing for the often larger number of patients required in RCTs evaluating QOL?

* Has proper statistical analysis been employed?

* Were the conclusions drawn from the results valid?

Although QOL is soft data, the precision in the estimation of QOL is expected to grow considerably during the next couple of years.

Appendix 9

Drug Information Association-Forum on EUROPEAN BIOSTATISTICS GUIDELINES

London, UK, October 6-7, 1993

The Drug Information Association (Committee of Proprietary Medicinal Products Working Party: Biostatistical methodology in clinical trials in applications for marketing authorizations for medical products) held a meeting on the draft for the new European Biostatistics Guidelines chaired by Dr Jrrgen Seldrup, ITEM, France, and Professor John Lewis, University of Kent, UK. The guidelines had been produced by Professor David Jones, University of Leicester, UK, and Professor Joachim R`hmel, Bundesgesundheitsamt, Germany, under the auspices of the CPMP (The EU Committee on Proprietary Medicinal Products).

There was a free discussion about the guidelines divided into six sessions:

Session 1 concentrated on the intended purpose, format, and general approach of the guidelines.

Session 2-5 examined in sequence approximately one quarter of the guidelines.

Session 6 attempted to evaluate the relative importance and degree of agreement attached to the points raised.

The guidelines - in slang 'Good Statistical Practice' - were generally seen by the 50 participants as a set of guidelines that could be recommended if certain improvements were included. However, the next set of guidelines should be changed in a way so it was clearer to whom the guidelines were written and the intentions of the guidelines. Further, the evaluation of cross-over-trials should be less critical, it should be defined more clearly what was meant with 'intention-to-treat' analysis, the estimation of sample size should be better described, and it should be stressed that confidence intervals were better than simply reporting P-values.

Moreover, it was stressed that it was necessary to harmonize the present guidelines with the guidelines of Japan and the US FDA-guidelines.

Although the present guidelines will have to be amended before general acceptance, it seems to be clear that the introduction of the present set of guidelines in an amended version will increase the complexity of performing randomized clinical trials and will substantially increase the necessity for collaboration with statistical experts in the future.

Appendix 10

CURRENT RANDOMIZED CLINICAL TRIALS ACTIVITY WITHIN THE COPENHAGEN HEALTH SERVICES

THE CITY OF COPENHAGEN

The City of Copenhagen represents the central area of Copenhagen, encompassing about 465,000 people. The Copenhagen Health Services are a public organization providing health services to more than 97% of these people. In addition, the Copenhagen Health Services have the responsibility of a number of other closely related functions, e.g the care of the elderly. There are about 30,000 people engaged in the Copenhagen Health Services and the annual turnover is about DKK 8-9 thousand millions. Almost 1.5 million people live within a 45 minutes drive from the centre of Copenhagen. However, the health services to this extra million is taken care of by other public health services, with which the Copenhagen Health Services have a close cooperation.

The Copenhagen Health Services are organized into a Primary Health Care Sector and a Secondary Health Care Sector, organized under the Central Office of the Copenhagen Health Services.

THE PRIMARY HEALTH CARE SECTOR

The Primary Health Care Sector consists of nurses, home assistants, dentists, and general practitioners (GPs). As of April 1991, 274 GPs were working in the Primary Health Care Sector, of which 159 are working solo. In non-acute situations the GPs represent the first contact between the inhabitants of Copenhagen and the Health Service.

The research activity within the Primary Health Care Sector in Denmark has been steadily increasing during recent years. However, more research in the Primary Health Care Sector is needed, by allocation of more economic support and securing increased activity centrally as well as locally, and there is a need for better organization of the research within the Primary Health Care Sector (Pedersen, Ugeskr LFger; 1993; 155:502-505).

There are at present two large controlled clinical trials going on in the Primary Health Care Sector involving GPs in the Primary Health Care Sector of the Copenhagen Health Services (Stauning, personal communication 1993). One national study (Diabetic Care in the Primary Health Care System) deals with the control of diabetics (> 40 years). In that study the GPs are randomized to intensive postgraduate education or to a control group, and the effect variables encompass the clinical progress of the patients. The other study also randomizes the GPs to educational intervention and a control group, but here the patient group encompasses children with asthma.

THE SECONDARY HEALTH CARE SECTOR

The Secondary Health Care Sector consists of five hospitals, Hvidovre University Hospital (1,028 beds), Bispebjerg Hospital (980 beds), Kommunehospitalet (432 beds), Sundby Hospital (436 beds), and St. Hans Hospital (psychiatric, 525 beds).

The Copenhagen Health Services are affiliated with the University of Copenhagen.

Table 1 shows the numbers of RCTs (total number and the number of multi-centre studies (M)) performed at the hospitals and presently running at the hospitals of the Copenhagen Health Services.

In total, 123 RCTs were completed during 1991 and 1992, and at present about 147 RCTs are actively recruiting patients or are in a mature planning phase. Only about a third of the RCTs are run as multicienter trials. Among the multi-centre trials , the majority is run from other centres, either in Denmark or abroad.

As demonstrated in **Table 1**, more than half of the RCTs are run at Hvidovre Hospital, encompassing both single centre activity and multi-centre activity.

At all hospitals, the activity varies considerably among the clinical departments. Generally at all hospitals, the highest RCT activity is found at the departments of abdominal and general surgery.

Table 1 Estimated activity of randomized clinical trials in the Secondary Health Care Sector of the Copenhagen Health Services.

The figures represent the total number of randomized clinical trials (single and multi-centre) and the number of multi-centre randomized clinical trials (M).

COMPLETED ACTIVE

(1991 and 1992) (1993)

S))Q

HVIDOVRE HOSPITAL 68 / 26 M 82 / 27 M

BISPEBJERG HOSPITAL 38 / 8 M 36 / 19 M

KOMMUNEHOSPITALET 2 / 2 M 11 / 9 M

SUNDBY HOSPITAL 4 / 2 M 10 / 4 M

ST. HANS HOSPITAL 11 / 2 M 8 / 6 M

S)))Q

TOTAL 123 / 40 M 147 / 65 M

Appendix 11

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