Infections in Intraabdominal Surgery

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The EURESI Project

Summary: The situation of clinical research in Europe must be improved substantially according to statements of scientists, managers and politicians. The analysis of requirements is available; however, there are no indications that the conclusion of the analysis is being converted into actual facts. Government programs, although originally conceived to improve the situation of clinical research, are used to maintain the status quo. The European Research Network on Surgical Infections (EURESI) concept has been developed by scientists and clinicians from European institutions and university hospitals to make the first steps possible in a new cooperation in European research. With regard to the essentials for clinical research, formulated according to a survey among research-oriented pharmaceutical companies, EURESI was successful in the following objectives: 1) competence in clinical research, 2) capacity for clinical studies, 3) internal quality control, 4) special know-how relevant to clinical studies, 5) performance according to a time plan, 6) interdisciplinianism, 7) contract partnership, 8) organization of research meetings. This special addendum includes presentations at the EURESI meeting in Heidelberg/Weinheim with special reference to the requirements for clinical studies in intraabdominal infections to further stimulate contact with the network.

Introduction

Clinical research in Europe, including Germany, has been hampered by legislative, organizational and cultural imponderabilites for companies for many years. This had led to an investment of up to 80–90% of the budget for clinical research by European companies in the United States and Japan. Especially in Germany, the political discussion about cooperation between companies and universities in clinical research had contaminated the scene.

This brought on the discussion whether the situation in the United States could be a model for Europe. The conditions for clinical research there are quite different from Europe. Private and state universities coexist in this system and both types of universities are known to be excellent in clinical research (e.g., Stanford University, Harvard University, University of California). Grant and contract offices have been set up to support the scientists and clinicians in the business of fund raising. The funds acquired by clinical research are a major part of the income of American universities. Private initiative in this direction is supported and is part of the American philosophy of entrepreneurism. Furthermore, the Federal Drug Administration (FDA), which is responsible for the approval of a new compound, is very influential in the pharmaceutical-driven market and it also appears to be advantageous for European companies to apply for approval first in the USA rather than in Europe. In response to the Health and Human Services Secretary mandated review (1995) of the National Institutes of Health (NIH) management strategies in successful academic health centers include an active strategic planning process, close integration of hospital and medical school management, heavy investment in the information system and the establishment of revenue generating centers for clinical research and new relations with industry [1].

Another important aspect of the decision to perform clinical studies in the USA is uniform medical education, comparability of medical treatment and experience in the conduct of clinical studies. In European university hospitals for a long time a different culture was prevalent. Clinical research did not play a decisive role in medical education nor in the evaluation of clinical departments. Instead of having one ethical committee's decision for a study, each institution again asks for a decision by their ethical committee, which delays the start of the studies considerably. Also the time spent on clinical research seems to vary on both sides of the Atlantic. American professors devote 50–70% of their time to research, in Germany only 10–20%, according to a study by the Boston consulting group [2]. The image and acceptance of clinical research in Europe and Germany can be improved [3]. Therefore also meetings with scientists from the United States are

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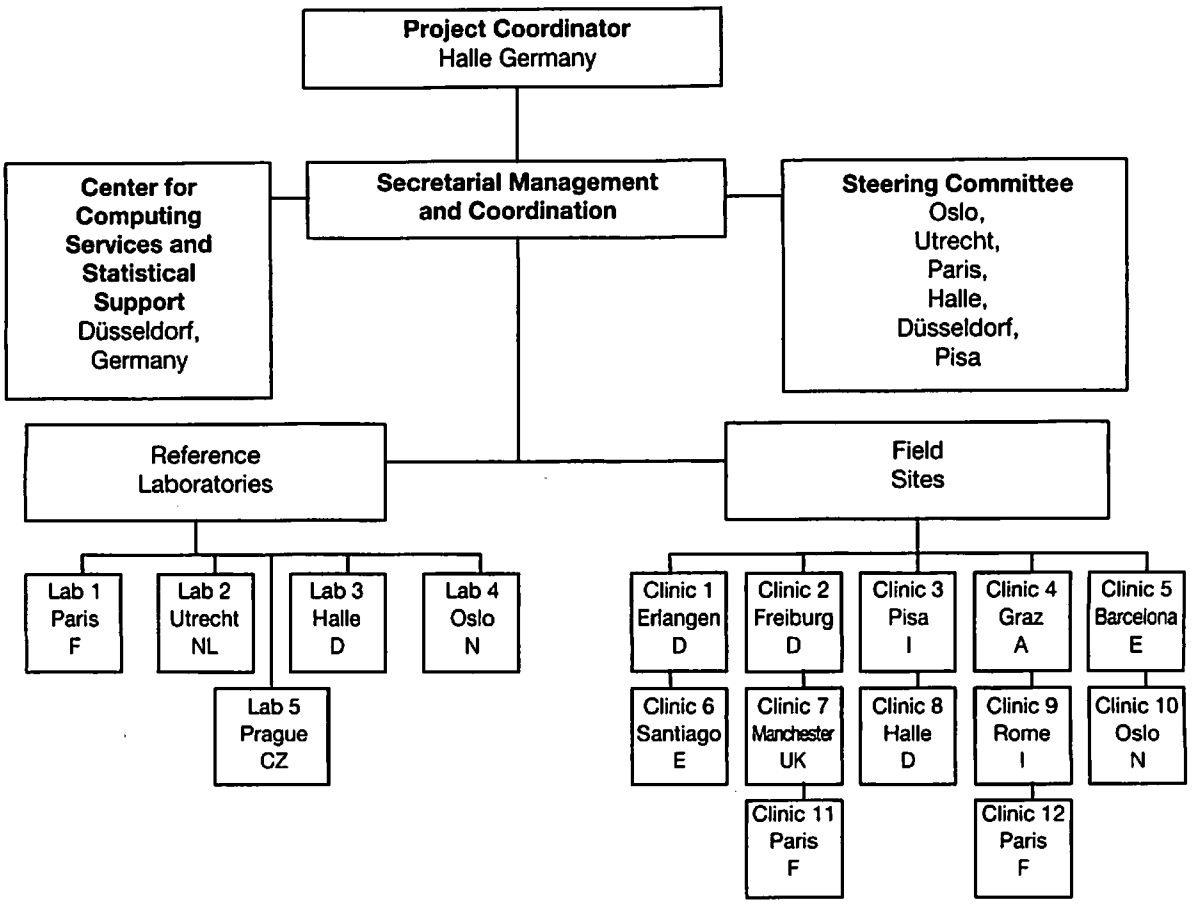

Figure 1: Organizational structure of the European Research Network.

helpful to define the requirements for clinical research, e.g., Consensus Conference of the Surgical Infection Society of North America, May 1998, on "Source Control in Intraabdominal Infections." While "globalization" becomes more than a description for industrial cooperation and competition, the universities seem to maintain their traditional role. Clinical research is mainly a one-institution business [4]! However, it should be remembered that clinical studies are in need of larger populations and that the reduction of a phase III study by 1 month may have important implications for the study budget of a company. Although several programs were set up by the European Community, General Direction XII, to improve the situation of clinical research, the intention and reality differed as far as the board of reviewers and the administration were concerned. Sometimes information on the objective of the program may have been misleading if not even false. This may, furthermore, help to keep the status quo.

Essentials for Cooperation in Research between Academic Research and Companies

There are good reasons for cooperation between universities and research-oriented companies [5]. For companies, rapid access to know-how, the identification of new research targets and their validation and specific methods would be available. Cooperation with universities would enable a company to cover most of the important aspects of a research project at reduced cost compared to setting up their own laboratories and clinics. Outsourcing of research may have beneficial implications, e.g., reduction of cost for research, presentation of results by independent experts, more flexibility by time-limited extension of research capacity and a lower threshold for entrance into the market with new products [6]. For the cooperation between academic institutions and companies to succeed, some fundamental facts about the interest in research should be understood. University-based research mainly is interested in a better understanding of pathophysiological pathways in disease; in the era of "share holder value" a company will always think of the return of investment. This also influences the selection of research topics. Company research is time and product oriented. This is criticized by universities who consider the clinical research of companies as minor. Integrity and credibility in industry-sponsored clinical research has been questioned [7]. Companies are afraid of university bureaucracy, sudden changes in the direction of research and a conflict of interest when universities cooperate with other companies [6].

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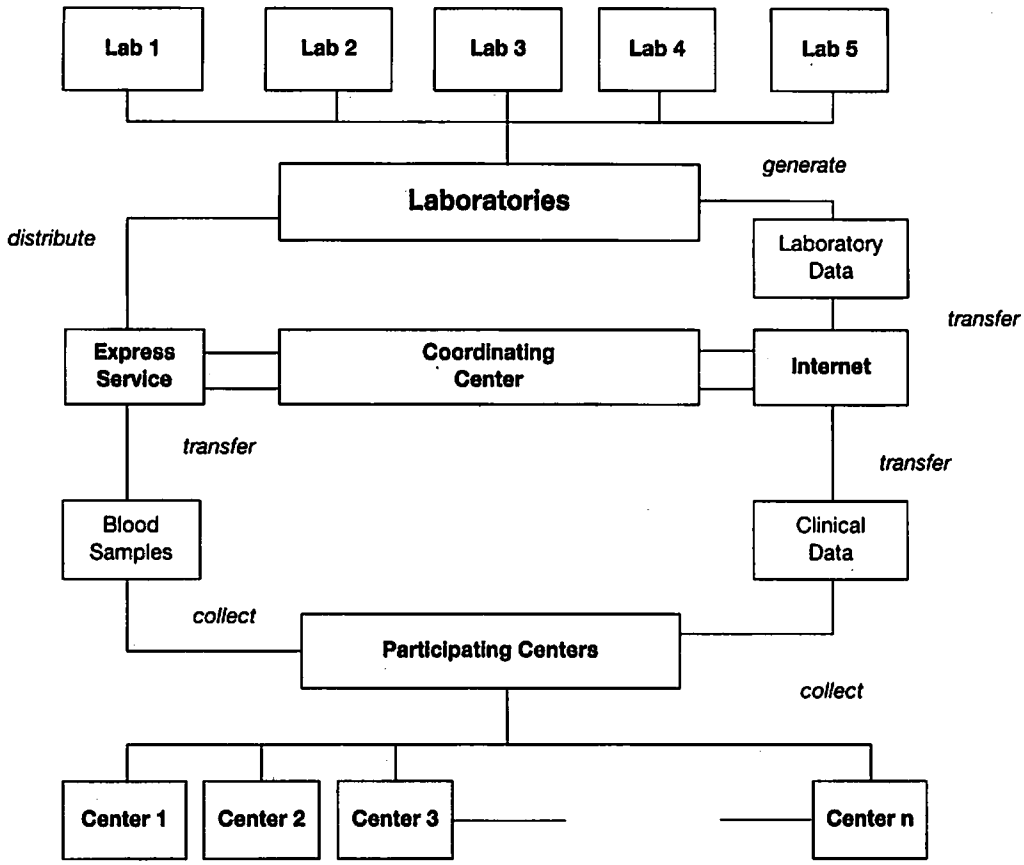

Figure 2: Flow of information, material and data in the European Research Network.

Most important, however, is the missing consensus of society on the value of research. This fact is underscored by decreasing public support for research in Germany and other European countries. The consequence is a decrease of experienced personnel and a withdrawal of company support which leads to a reduced perspective of research personnel. Fewer scientists will increase this vicious circle. The deficiencies of the system are well known, but no firm action is taken.

This situation has stimulated the cooperation of scientists and clinicians from European scientific institutes and university hospitals to form a research network – European Research Network on Surgical Infections (EURESI) – in 1994. The topic of infection was chosen for the start because most of the partners had a record of experience in this field. First a survey among leading research-oriented pharmaceutical companies (Verband forschender Arzneimittelhersteller, Germany) was conducted by the coordinator of the network to analyze the requirements for EURESI. The following companies participated: Pfizer, Schering, Glaxo-Wellcome, Knoll, Byk-Gulden, Smith Kline Beecham, Bayer, Pharmacia & Upjohn, ASTA Medica, Boehringer Ingelheim, Grünenthal, Janssen Cilag. Two questions were important for the setup of the network:

I. What qualifications are required for university research?
II. What are the possible tasks for a European research network?

I. Essentials for cooperation with a research-oriented company according to the survey are:
1. Competence
2. Capacity for studies and sufficient number of patients
3. Quality assurance and internal quality control
4. Special know-how in research important for clinical studies
5. Performance according to a time plan
6. Interdisciplinarianism
7. Option for a formal contract

II. Tasks for the European Research Network according to the survey could be:
1. Coordination of clinical studies
2. Assurance of comparability and communication to pool data
3. Clinical phase II and III studies
4. Design of protocols
5. To provide competent centers
6. Organization of research meetings
7. Consensus conference
8. Multi-center clinical trials

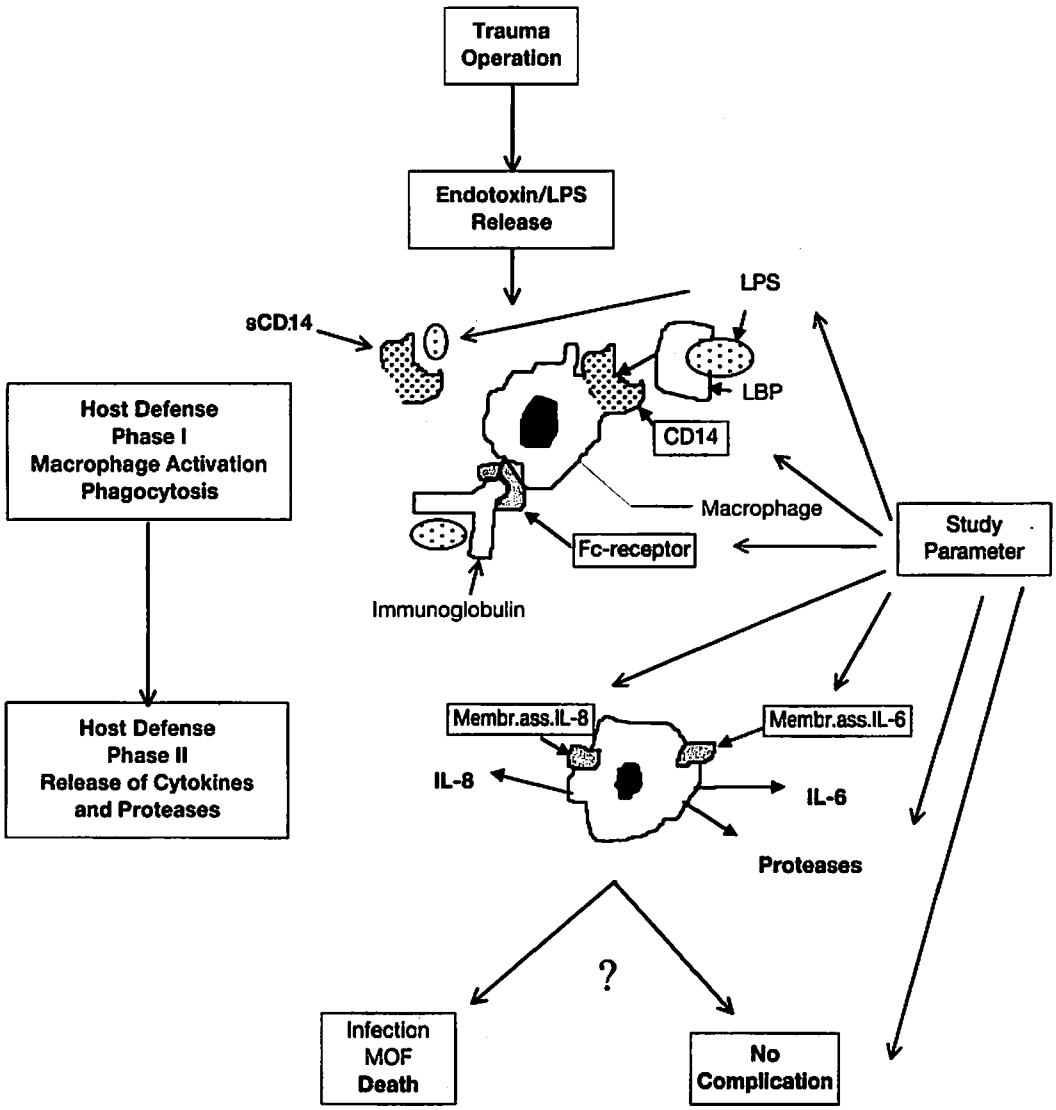

Figure 3: Host defense and postoperative infection – scientific objectives of the proficiency study.

Start of EURESI

The European Research Network was set up in accordance with the essentials provided by the survey among the pharmaceutical companies.

I.1. Competence: With regard to clinical research there can be competence in a single institution or competence of a network to perform a multicenter study. Consequently a "Proficiency Study" was begun in 1996 and terminated in August 1997. To conduct this study an organizational structure was created with a coordinator, a steering committee, a center for statistical support, study sites and reference laboratories (Figure 1). A flow of information, material and data had to be organized and supervised by the coordinator (Figure 2). The scientific objectives of the trial were to study the impact of cell-associated cytokines (Paris), Fc-receptor polymorphism (Utrecht), CD14 receptors (Oslo) and endotoxin/endotoxin neutralizing capacity (Halle) in surgical intensive-care patients treated with antibiotics (Figure 3). The coordinator's task is quite complex and has been discussed in a recent report [8]. The clinical part of the study ended in August 1997 and statistical evaluation is nearly complete. First reports on the proficiency study were presented at the International Congress on Immune Consequences of Trauma, Shock and Sepsis, Munich, 1997, and the Vienna Shock Forum, 1997 [9, 10].

I.2. Capacity for studies: The participating clinics can provide approximately 1,800 surgical beds with approximately 200 intensive care beds.

I.3. Quality assurance: The quality control of clinical studies is a major factor for the success of a study [11, 12]. The participating clinics were in favor of the internal quality control provided by the Institute for Surgical Research, University of Oslo. The task included the visit to all centers, inspection of laboratories and clinical facilities according to a checklist, report to the coordinator and steering committee. The quality of shipment of samples was re-

Table 1: Clinical and basic research potential of EURESI.

Clinical specialities	Topics of clinical research	Basic science research	Test methods and equipment	Animal models	Recent clinical trials
Oncological surgery	Surgical infections	Sepsis	Cell cultures and cell lines	Cecal ligation puncture (CLP) – rat	Cytokine production in sepsis
Sepsis	Peritonitis	Peritonitis	PCR	Zymosan peritonitis – rat	Plasma effect on cytokine production
Liver transplantation	Bacterial translocation	Surgical infections	ELISA	Sepsis – pig	Preoperative risk assessment
Cardiovascular surgery	Sepsis	Nutrition	FACS (fluorescence-activated cell sorter)	Septic shock – rat	Antibiotic therapy in intraabdominal infection
Trauma surgery	Nutrition	Trauma	Immunohistochemistry	Septic shock – rabbit	Antibiotics in clean surgery
Plastic surgery	Cancer of the GI tract	Gastrointestinal physiology	Cell signalling	Single lung transplantation – pig	Free radicals in trauma and sepsis
Thoracic surgery	Gastroesophageal reflux	Lipidperoxidation in Tx and trauma/sepsis	Receptor analysis	Laparoscopy – pig	Factor VIII in trauma, sepsis, multiorgan failure
General surgery	Wound healing	Lymphocytes and PMN in sepsis	HPLC (high pressure liquid chromatography)	Liver/kidney transplantation – pig	MCT as substrate in trauma and sepsis
Laparoscopic surgery	Anal physiology	Signal transduction	Fluorescence spectrophotometer	KO, SCID, nude mice	Risk factors in aspiration pneumonia
Gastrointestinal (visceral) surgery	Jaundice and anergy	Membrane receptors	DNA sequencing		Tracheotomy for weaning
		Endotoxin and endotoxin neutralizing capacity	Northern, Western, Southern blots		Immunglobulin in trauma and intraabdominal infection
		Proteases	Microsurgery		Antibiotics in pneumonia
		Mucosal immunology	GI physiology		Antibiotics in soft tissue infection
		Endothelial alteration in organ failure			AT III substitution therapy

corded; samples were excluded if in bad condition. The coordinator visited most of the centers to give detailed information on the study protocol. Statistical evaluation is performed at an institute with professional experience (Düsseldorf). The coordinator and the steering committee are aware of the continuous efforts to improve the quality assurance system of the network.

I.4. Special know-how: The development of clinical research is a fast growing process. A single institution may not be able to provide all the know-how required for clinical studies. EURESI has accumulated special know-how in basic research and clinical research. This includes sophisticated equipment for research (Table 1). The cooperation among these institutions has created a European laboratory without walls. This laboratory has provided special know-how, e.g., DNA isolation procedures for Fc-receptor analysis, to participating clinics. The distribution of know-how is also supported by publications of the network [13, 14].

I.5. Performance according to a time plan: The proficiency study was performed to demonstrate that EURESI can conduct a multicenter study according to a time plan. This

is an important record for further cooperation in the field of clinical research.

I.6. Interdisciplinarianism: The inclusion of renowned scientists in basic research established the basis for an interdisciplinary research network. This opens up new research perspectives for both clinicians and basic scientists by offering expert advice and the potential for specific studies to pharmaceutical companies. This part of the network will be extended according to the needs of the partners.

I.7. Contract partnership: Cooperation in clinical studies requires a formal contract. To better support the cooperation of EURESI with pharmaceutical companies a "European Clinical Research Foundation" was created.

II.6. Organization of research meetings: EURESI has organized four research meetings since 1994 in Germany, Italy and France. Purpose of the meetings was the exchange of scientific expertise and the organization of the proficiency study. The meeting in Weinheim/Heidelberg, in 1997, had the objective to form a consensus within the group on requirements for clinical studies in intraabdominal infections.

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