# CLINICAL RESEARCH IN A HOSPITAL

## From the lone rider to teamwork

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Clinical research of high international standard is very demanding and requires clinical data of high quality, software, hardware and competence in research design and statistical treatment of data. Most busy clinicians have little time allocated for clinical research and this increases the need for a potent infrastructure. This paper describes how the Norwegian Radium Hospital, a specialized cancer hospital, has reorganized the clinical research process. This includes a new department, the Clinical Research Office, which serves the formal framework, a central Diagnosis Registry, clinical databases and multicentre studies. The department assists about 120 users, mainly clinicians. Installation of a network software package with over 10 programs has strongly provided an internal standardization, reduced the costs and saved clinicians a great deal of time. The hospital is building up about 40 diagnosis-specific clinical databases with up to 200 variables registered. These databases are shared by the treatment group and seem to be important tools for quality assurance. We conclude that the clinical research process benefits from a firm infrastructure facilitating teamwork through extensive use of modern information technology. We are now ready for the next phase, which is to work for a better external technical framework for cooperation with other institutions throughout the world.

Clinical research of high international standard is very demanding and requires clinical data of high quality, software, hardware and competence in research design and statistical treatment of data. Most busy clinicians have little time allocated for clinical research and this increases the need for a potent infrastructure. The Norwegian Radium Hospital (NRH) is a specialized cancer hospital with 400 beds and 1 500 employees (1). To facilitate clinical research, a special unit (the Clinical Research Office) was initiated in 1979 by Professor Herman Høst. Since then the special unit has evolved and today it serves the whole hospital in many fields related to clinical research (2). The main tasks of the NRH's Clinical Research Office are described: Diagnosis registry, clinical databases, multicentre studies, software and hardware, staff and costs as well

as formal framework. The costs and benefits of such an infrastructure are also considered.

### Diagnosis registry

In order to serve administrative needs as well as clinical research, the NRH started a central Diagnosis Registry in 1971. The Diagnosis Registry aims to cover the whole hospital including the out-patient clinic. Each year three data managers code approximately 3 500 new diagnoses and 12 000 referrals. The coding includes up to 30 variables for each new diagnosis and up to 20 variables for each new referral. The diagnosis table corresponds to the data in the Norwegian Cancer Registry, but includes more data. It follows international coding classifications such as TNM, ICD and SNOMED. In the referral table, diagnosis, reason for referral, extent of disease, treatment modalities, complications and codes for treatment such as radiotherapy, chemotherapy and surgery are registered. Every week administrative data for all referrals to the hospital are imported from the hospital's main administrative database.

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## Clinical databases

The first PCs were installed in about 1985. At that time the hospital had no common network and registering was done by each clinician on his/her own PC. Usually a new database was created for each publication, resulting in the existence of about 1 000 small databases (registries) in 1995. Naturally, data concerning many patients were duplicated in several databases. In addition, at least five different database programs were used, rendering operations such as data-matching difficult and time-consuming. After a testing period of five years the NRH's lymphoma group concluded that the sharing of databases by several clinicians ('the treatment group') was worthwhile. In 1995 it was decided to build up common diagnosis-specific, clinical databases for the whole hospital. Eventually, this will result in about 40 main clinical databases.

The designing of a new database can be accomplished in a few hours. The clinicians participate actively in this work with written proposals for the data fields (variables), coding and layout. In order to standardize and utilize earlier work as far as possible, the Clinical Research Office does the practical designing of most new databases. The first month after start-up is needed for making adjustments to the databases. However, the clinical databases are always undergoing changes such as addition of new variables and codes. The principle of using only one database program will be followed in order to standardize the databases as far as possible. This implies that older, important databases (up to 30) designed in other systems will be converted. The time needed for conversion is usually one day per database. The investment seems worthwhile as updating of databases takes much more time.

A main goal for the clinical databases is to have a complete inclusion of the actual diagnosis group and period. The establishment and updating of a database are based upon extraction of data from the Diagnosis Registry. This procedure gives a nearly 100% identification of the correct patient population treated in the hospital in the chosen period. About 30 variables are imported from the Diagnosis Registry. Then up to 200 variables are added in order to cover primary investigations, treatment and endpoints such as relapses and death. Students, secretaries, retired professors and consultants do the main data entry. Corrections and updates are performed by the treating clinicians in order to spread the work load and to assure the quality. Up to one hour is required for reliable and correct data entry of each patient. This procedure results in extensive information of high quality. It is not possible to delete patients in the databases, but patients who should be excluded (e.g. because of erroneous diagnosis), are indicated and can in this way be excluded from later statistical analyses. When a publication is prepared, a new data field is usually added which indicates patients who have been included in that paper. In this way we can later identify the

published population if necessary. Using a specially designed extract program, the data are rendered anonymous and can be exported to two different statistical packages or to spreadsheet format. Thus the original databases are stored in the hospital while the researchers can transfer anonymous copies to local PCs in the hospital or at home for statistical studies. In the Table the status of the clinical databases operative in June 1996 is summarized.

## Multicentre studies

An important task of the Clinical Research Office is to administrate multicentre studies. These include mainly phase III randomized studies and a few phase I–II studies. A database and automated procedures for letters and reminders are made for every new trial in order to avoid any manual writing to the participating hospitals or patients. Several logs exist, and it is especially important to keep a log of all reports which have been sent. This is a quality assurance element which is used actively to monitor the management of trials. We have abandoned randomization performed from paper lists, and use only data entry with computer checking of inclusions- and exclusions criteria. These procedures may include techniques for balanced randomization. A complete computerization of all procedures is crucial in reducing the costs, but so far we have not started with optical reading of study forms. One data manager is able to handle the multicentre studies and only receives help for some randomizations and data-cleaning. At present our Office has eight open and seven closed trials (the latter still under updating) with about 2 200 patients in the follow-up. In addition, quality of life

### Table

*Some clinical databases at the Norwegian Radium Hospital*

| Diagnosis group | Start year | Variables | Patients |
|---|---|---|---|
| Non-Hodgkin's lymphomas | 1980 | 200 | 3.200 |
| Hodgkin's disease | 1971 | 210 | 1.700 |
| E-N-T tumours | 1970 | 190 | 1.200[1-2] |
| Sarcoma | 1980 | 160 | 2.200[2] |
| Benign bone lesions | 1980 | 60 | 640 |
| CNS tumours | 1980 | 110 | 1.400 |
| Breast cancer | 1975 | 90 | 9.000[2] |
| Vulva cancer | 1971 | 80 | 1.600[2] |
| Ovarian cancer | 1980 | 80 | 4.000[1-2] |
| Cervical cancer | 1980 | 150 | 4.400[1-2] |
| Oesophageal cancer | 1980 | 120 | 500[2] |
| Malignant melanoma | 1980 | 110 | 600[2] |
| Testicular cancer | 1980 | 120 | 2.300[2] |
| Bladder cancer | 1980 | 100 | 2.800[2] |
| Prostatic cancer | 1980 | 60 | 2.200[2] |
| Metastases origin unknown | 1980 | 120 | 1.100[2] |

[1] Not complete patient series at this time.
[2] Still under updating.

studies are linked to three of the trials and questionnaires are sent to the patients' home addresses for up to five years after inclusion. The Office has a close cooperation with the Scandinavian Breast Group and participates in multicentre trials either as a main-, national- or regional secretariat.

## Software and hardware

Before 1993 the clinicians had little software available on their local PCs. In 1993 we composed a software package with the aim of sharing all software on the network. This reduced the costs, made installation of new PCs faster and gave a consistent standardization. In Norway in 1996 the hospitals do not have Internet connections from their internal networks. Some hospitals, e.g. the NRH have access to Internet via a separate network. However, most users have only one PC and must give priority to the internal hospital network. Therefore we included literature retrieval on CD-ROM in the software package. The different software programs are presented in the Figure. As we seldom have two alternatives in each software group, this collection improves internal standardization, and very few users need to have additional soft-

ware installed. The clinicians get their PCs with the software package installed, ready for use. This saves both time and facilitates the learning and utilization process. Currently, about 120 clinicians, researchers and data managers are connected to this package. The Office gives the necessary support with short courses and seminars, production of minimanuals and, when needed, personal assistance. For the Office it is rather time-consuming to perform major upgrades of the software package for all users. Major upgrades will therefore be carried out about every second year.

The Office has four network servers for the different tasks. There is one SQL server (Structured Query Language) for the Diagnosis Registry, one file server for databases in clinical research, one software server, and finally a CD-ROM server. In addition, a scanner, a colour printer and a slide producer unit are installed in the Office in order to facilitate the producing of suitable material for presentations.

## Staff and costs

In 1996 the Clinical Research Office employs seven full-time persons. The Office is directed by a consultant in
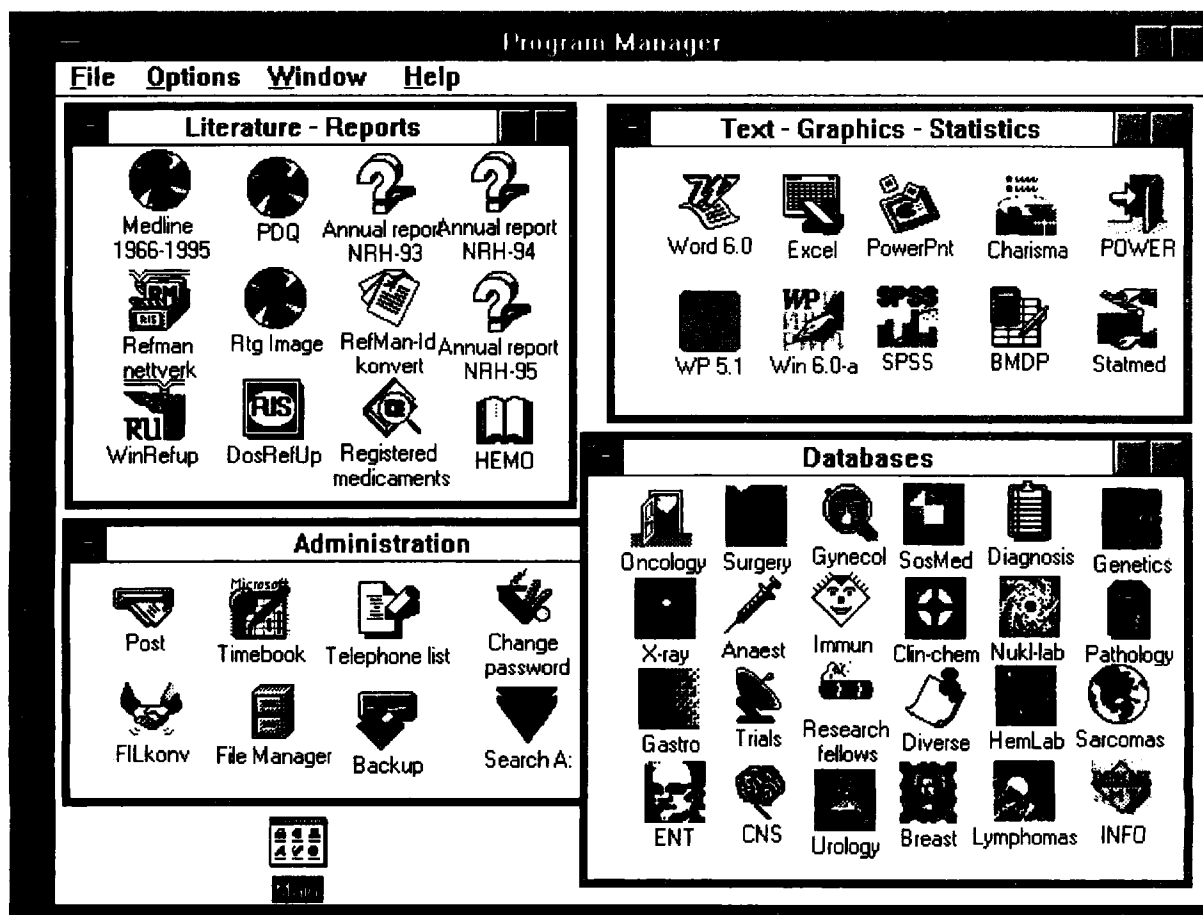


Figure. The network users' start-up screen.

oncology with special training in computing and statistics. A professor in medical statistics serves as an adviser in trial design and statistical methods for both the NRH and the other university hospitals in Norway. Three data managers handle the Diagnosis Registry, one deals with multicentre studies and one takes care of the software package. In addition, three students and two retired data managers work parttime in building up the clinical databases.

The cost of the four servers was about USD 70 000. The Office has bought software licences for about USD 50 000. The annual fees for some software and CD-ROMs are about USD 20 000. The annual budget for the Office (excluding salaries) is about USD 30 000. The main external sponsor is the Norwegian Cancer Society, which supports the annual budget and pays the salaries of the professor and two of the data managers.

## The formal framework

In Norway all testing of new drugs must be approved by the Norwegian Medicines Control Authority and the Regional Committee for Medical Research Ethics. In addition, the NRH has an internal 'protocol committee' which evaluates and approves all plans for clinical investigations and treatment protocols. In this way the NRH administration is updated on all activities and can adjust the use of research resources accordingly. The Clinical Research Office participates as a secretary in the protocol committee and keeps a database over all internal clinical research. The database has been complete since 1992. In studies involving industrial partners, the hospital's Research Foundation prepares the contracts. According to the National Data Inspectorate, all hospitals in Norway should have a survey of all their databases (registries) containing personal and medical information. Accordingly, the Clinical Research Office keeps a database over all the registries in the hospital. This is of increasing importance also in order to identify older special registries containing data which may be very valuable. The documents of the NRH's Internal Control describe how the clinical and laboratory departments should collaborate and share the data in clinical research. In addition, written agreements are often set up with research fellows. These agreements enable the hospital to ensure that the data can be utilized later in other projects. Earlier, many databases created during research were considered somewhat 'private', resulting in loss of important registries for the hospital. Today one of the main tasks of the Clinical Research Office is to survey and preserve important research registries. In addition, the Office is responsible for obtaining the necessary national permission for research registries with personal identification.

## Discussion

There are many good reasons for developing a common infrastructure for clinical research within a hospital. Other hospitals have utilized the PC revolution in clinical research earlier than the NRH (4, 5). Furthermore, different parts of the infrastructure described in this paper have been established in other institutions (6–8). However, to our knowledge no other hospital in Norway or in Scandinavia has succeeded in establishing a similar standardization project for clinical research covering an entire hospital. After five years of hard work and with some conflicts, we can understand this hesitation. This new infrastructure met with considerable scepticism, expressed in questions such as: Doesn't each department or the individual researcher work faster and more flexibly on their own? Shouldn't all users have the freedom to select their own software? Can we trust the current information technology to be sufficiently developed to meet all our challenges in clinical research? Do the hospitals have sufficient resources to serve many different users quickly, securely and satisfactorily in many different programs and procedures?

Perhaps there will always be conflicting interests between the clinical researcher and the administration of a hospital. A hospital may consider clinical research as a banking activity; every project requires new data and thus new, possible deposits in the registry bank. On the other hand, some researchers argue that an individual approach is more time- and cost-effective. Our standardization process had two critical stages. First, we decided to establish as soon as possible a broad and useful software package. As the possibilities for literature retrieval had been limited earlier, this has had a very high priority within the package. In this way the scepticism of many doctors declined markedly. Secondly, we used patience and several years in converting the older databases to a common structure within the same database system. When the staff finally were able to use and search in a single database containing all relevant data for a particular diagnosis group, instead of labouring with many different databases, this usually demonstrated that the investment had been worthwhile. Examples of other clinical databases can be found in the literature (9–12).

Quality assurance in clinical research is of general interest. The choice of study objects, design, selection of patients, statistical analyses and forms of presentation are some relevant parts in the research process. The hospital can influence the choice of study objects through its research strategy and the internal protocol committee. The study design and study plan should be presented before a consultant in medical statistics before start-up, and this checkpoint is important in allowing for possible improvement. The selection of patients in clinical research presents two problems. First, the hospital itself may represent a significant selection bias due to different referral of patients. Secondly, the researcher may use a patient population selected within the hospital, and this can influence the results published. It should be realized that by omitting or adding as little as 10 to 20 patients in a statistical analyses

of some hundred patients, the results ('p-values') can be markedly changed. Shared clinical databases where several investigators check the same data combined with marking of records (patients) used in different publications should improve the data quality. Several publications with complete patient series from these clinical databases have appeared (3).

In the software collection we regret not having the possibility of using electronic mail in the communication with other institutions throughout the world. In Norway the hospitals are not yet (1996) allowed to connect their internal networks to the Internet. However, we believe and hope that within 1–2 years some technical solutions will allow users to access at least some of the resources of the Internet. We intend to build up 'home-pages' on the Internet with a description of the Clinical Research Office, listing of ongoing trials with inclusion- and exclusion criteria and other relevant information.

Perhaps the most critical choice of software in the package is the database system. Today we have a reliable database system which is easy to use. However, in the future we want a closer integration of our clinical databases with the large laboratory databases, e.g. pathology, radiology and clinical chemistry. The aim is to pick up as much relevant information as possible without new data entry. With modern database standards such as SQL this is a realistic and not too expensive option. Because of these new challenges, we will reconsider our choice of database system next year.

The infrastructure for clinical research described here seems to improve the standardization and quality in clinical research. But what are the costs? Buying software network-licences is much cheaper than several single licences. Several program licences are sold for concurrent users, i.e. number of users at one time. For some programs we have only five concurrent user licences, but 120 potential users. The Office uses only one data manager and half the time of a consultant to administer the network package for 120 users and serve about 200 databases. It saves much time for clinicians, researchers and even for the hospital's computer department. We conclude that a small staff or department dedicated to organizing the clinical research process is an extra cost only in the start-up phase.

Soon the last lone rider in clinical research at our hospital will ride into the sunset. The increasing demands in clinical research with extensive use of information technology have made this disappearance a natural outcome.

Instead, we have contributed to teamwork in clinical research within the hospital by building a firm infrastructure. However, teamwork in clinical research also includes extensive, external collaboration. We are now ready for the next phase, which is to work for a better external technical framework for cooperation with other institutions throughout the world.

## ACKNOWLEDGEMENTS

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