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Long-Term Studies — A Challenge to Medical Informatics*)

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The paper describes the aims of long-term studies and the problems involved for medical informatics and shows ways to their solution.

Key-Words: Long-term Studies, Problems

LANGZEITSTUDIEN — EINE HERAUSFORDERUNG FÜR DIE MEDIZINISCHE INFORMATIK

Die Arbeit beschreibt die Zielsetzung von Langzeitstudien und die sich dabei für die medizinische Informatik stellenden Probleme und zeigt Wege zu deren Lösung auf.

Schlüssel-Wörter: Langzeitstudien, Probleme

Chronic diseases are the main concern of medicine in these days. One cannot investigate chronic diseases without long-term trials. For practical purposes, a long-term trial is defined as a study with an observation time per subject of more than 6 months. The trial must be prospective; however, a long-term study is not necessarily a randomized clinical trial. An observational study with one group of patients followed up for more than 6 months each would also be a long-term study.

A long-term trial is — at least partly — a not sufficiently defined open process which can be managed to give various different outcomes in various different ways. The world of long-term trials is rather complex and nearly everywhere there is a trap for the uninitiated investigator. Treating this wide field, my remarks are clustered around three questions: 1.) What are the essentials of long-term studies according to the present state of the art? 2.) What are the basic problems and challenges in long-term studies for medical informatics? 3.) What are the challenges for special subsystems for long-term clinical trials?

What are the Essentials of Long-Term Studies?

There are essentials in planning, performing and evaluating a long-term trial. First, the essentials in *planning*: The right question for a long-term study is a central point. How to find it and how to get the right people involved is more of an art than a science. The developement of the study protocol takes about one year. The study protocol is the manual of action for many people over years and it should be very specific. However, the weight of a protocol in kilograms is not an indicator of its quality. The study organisation is another central point. The organisation has to be clear and the responsibilities have to be defined. There are simpler and more complex organisational schemes. The inclusion and exclusion criteria have to be laid down. A patient logbook, also containing those patients not included in the study, must exist. Predetermined endpoints must be chosen very carefully. It is wise to separate primary and secondary endpoints and to limit the number of primary endpoints. The number of subjects must be estimated beforehand, attempting a delicate balance between various parameters like α, β, incidence, difference, dropout rate and observation time. The more subjects, the better one will know. The fewer subjects one needs, the better for ethical reasons. There is no clearcut escape from this dilemma by any statistical formula. One has to decide with responsibility and relying on judgement and experience. Randomization must be extensively planned in practical details. One has to decide on the control groups and whether blinding techniques will be required. The extent of variables covered requires careful attention. The details of the statistical evaluation must be laid down beforehand. Patient consent is necessary. A blind advisory group deciding on endpoints for individual patients might be a worthwhile instrument.

The essentials in *performing* a long-term trial are also numerous. Every participating hospital or medical doctor must adhere to the study protocol. They are responsible for the integrity of their data. Central monitoring is indispensable with multicenter trials. Continuous data entry and data correction must be provided for. Regular reports for the participating groups must be prepared. The information channels between partners must be kept open during the study. Interim evaluations require careful decisions and pose serious ethical problems. A strategy for the early termination of a trial is necessary. However, a trial should be stopped when the evidence is convincing and not when the statistical test says it should be stopped. Time is an essential factor in long-term trials. The arrow of a trial proceeding through time becomes slower and slower, missing its goal and sometimes falling to earth without reaching its aim. Performing a long-term trial is much of an organisational problem.

The essentials in *evaluating* the results of long-term trials are manifold. Determining the selection is a central point, coping with missing observation another. The baseline data must be analyzed and the treatment groups must be comparable. Compliance is a serious problem and should be evaluated. Statistical tests with a defined level of α should only be used in the strict sense when there has been randomisation. Using significance levels as descriptive values for generating hypotheses and using explorative procedures provides valuable information. The methodology and the medical content of a trial must be balanced.

Considering these and other essentials of long-term studies, one comes to the conclusion that such trials are complex, difficult and generate numerous problems. They are, however, the best and sometimes the only way we have to gain knowledge on chronic diseases.

What are the Basic Problems and Challenges in Long-Term Studies for Medical Informatics?

1.) The statistical test theory might not be a valid and sufficient paradigma for gaining knowledge. Knowledge is an

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entity which cannot be approached by Yes/No decisions. It is a wholeness, a »Ganzheit«. The present philosophy of randomized controlled clinical trials might not be the best philosophy, yielding, however, good results by using the data not for test purposes alone. Our main body of knowledge on drug effects does not rest on statistical tests. If it is true that classical statistical test theory is not a sufficient paradigma for gaining knowledge, then the challenge for medical informatics is to try other methods, for instance looking for the information content of a trial. A sensible question might be to design a system for localizing the maximum information content in a given trial with a given data set. This maximum information content could be defined within the trial or in comparison to the available knowledge outside the trial.

2.) A consistent theory for gaining knowledge in the medical field is missing. The resulting challenge for medical informatics might be to try to develop such a framework for gaining knowledge, for instance with the aid of long-term trials.

3.) Getting consensus for research is very difficult with long-term trials, considering, for instance, ethical problems. Medical informatics might provide better means and ways of getting consensus, making goals and means for their achievement more transparent and more intellegible to all participants.

4.) A basic problem in the philosophy of long-term trials is that they rely on a preconceived frame of reference which must not be altered during a study. The corresponding challenge for medical informatics might be to consider the trial as an open process with several moving targets, looking for an adaptive system, some automated target finding system within a long-term trial, comparable to missile interception, a system which is guided by the incoming data, aiming at the point of maximum information content, not at a preconceived null-hypothesis which might be ill-defined.

5.) Using clinical data bases and registers as alternatives and as reference points for long-term trials is a basic challenge. Improved data collection and data analysis systems combined with reference data bases and reference registers regarding treatment regimens could put individual trials in proper reference to other sources of knowledge. It might be conceivable in certain cases that, by repeating several times the careful observation and detailed follow-up of a number of subjects over longer periods of time, registering the outcome, without intervention and without missing observation, the evidence could approach the quality of the evidence we can get by controlled randomized trials. The price of this might be even higher, also in terms of human suffering.

6.) Using new technical devices for collecting individual information on the natural medical history of human beings without central storage of information might be a way out of present problems with data security. A small individual information storage device, a small dedicated personal computer like a wrist watch, easy to handle, might be a challenge for medical informatics regarding data acquisition for chronic diseases.

7.) Making data collection simpler and the data more usable in a direct way by the medical doctor and by the patient is a challenge to long-term trials. To have all information of a certain point in time available to all participants with the comments of the responsible physician is a challenge to medical informatics.

What are the Challenges for Special Subsystems for Long-Term Clinical Trials?

1.) Improved subsystems for estimating the number of subjects.

This is usually done by hand. There are a variety of formula available depending, for instance, on the type of data. Various calculations are performed, varying the input — for instance α, β, incidence, difference, dropout rate, observation time — and assembling the output in a table. The final decision is made by a human reasoning process. Subsystems for supporting the estimation of the number of subjects in an interactive way can be developed including, for instance, simulations.

2.) Improved subsystems for randomization.

Various randomization procedures are described in the literature. A subsystem providing all methods in a user-oriented way does not exist.

3.) Improved subsystems for data entry and data correction.

Such systems can reduce the amount of work connected with data collection und can improve the quality of data.

4.) Improved report systems.

Automated report systems can contribute to the motivation of the participants and to the central monitoring of long-term trials.

5.) Systems for interim evaluation and early termination of trials.

These are performed today with the same methods as the final analyses. By considering the problems of interim evaluation and early termination of trials on their own and by implementing interactive systems, interim evaluation could be improved.

6.) Improved systems for baseline data evaluation and for checking the comparability of treatment groups.

These tasks are usually performed by standard statistical software packages. Special systems dedicated to these questions might be easier to handle and can give more condensed information, speeding up the process of analysis and making it more precise.

7.) Improved systems for hypothesis generation, using various explanatory procedures.

8.) Improved systems for finding the relevant predictor variables within a given material.

9.) A system for the analysis of the individual course of disease, looking through the data of the individual patient, analysing, for instance, periods with omitted treatments, considering on/off-effects or other relevant information.

Going through this variety of challenges to medical informatics in the field of long-term trials, there appears the fundamental impact which could come to this field from medical informatics. Developing new paradigmas for gaining knowledge in medicine, getting better consent for research, developing automated target finding systems within long-term studies, using new technical devices, clinical data bases and registers, trying to make the information directly usable by the physician and improving various subsystems might overcome the present stalemate which we have with long-term studies for various reasons. Shifting the importance from classical statistical test theory to methods of informatics might change our view and our results considerably. Such new ways of looking at old things might be stimulating and rewarding. Long-term studies are indispensable from a scientific point of view and they can be improved by various approaches from medical informatics.

We can no longer retire to classical statistical methods alone. We as methodologists will have to become involved with the medical content, with new instruments and with the power play of the field if our methodology is to unfold its complete usefulness.

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