Internet based clinical trial protocols – as applied to a study of warfarin pharmacogenetics

Jonatan D. Lindh,¹ Marius Kublickas,² Magnus Westgren² & Anders Rane¹

¹Division of Clinical Pharmacology and ²Division of Obstetrics and Gynaecology, Karolinska University Hospital Huddinge, Stockholm, Sweden

Correspondence

Jonatan D. Lindh, Department of Clinical Pharmacology, C1 68, Karolinska University Hospital Huddinge, S-141 86 Stockholm, Sweden.

Tel: + 46 8585 81201

Fax: + 46 8585 81070

E-mail: jonatan.lindh@labmed.ki.se

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Aims

To describe and evaluate the use of an Internet-based study protocol in a multicentre study of genetic risk factors in anticoagulant treatment.

Methods

A web-based study protocol, similar to existing anticoagulation medical record systems, was developed for entry of clinical data. It was also supplied with a separate interface for study monitoring. Measures were taken to assure the confidentiality of transferred data. In addition, software modifications were made to enable automated transfer of clinical data from an existing medical record system to the study database.

Results

The system has been in use since March 2002, and at present 39 centres have included 909 patients with a dropout rate of 2.8%. The need for education of participating clinicians has been satisfactorily provided for by means of written instructions and telephone support.

Conclusions

Our study demonstrates the usability of Internet-based data acquisition techniques in a full-scale multicentre clinical trial. The main advantages of such a protocol are automated data validation and standardization, fast data transfer independent of geographical distance, user feedback, synchronization of protocol updates and automatic data formatting facilitating statistical analyses. Safety and accessibility are possibly cumbersome areas and should be addressed duly.

Introduction

A multicentre clinical trial is a project of great logistic complexity. Employing tailor-made Internet solutions in such trials would potentially be of great value by facilitating data acquisition, validation, transfer and formatting. Although the Internet has proven very efficient in other fields of medical communication, there are yet but a few examples of its use in clinical trials [1–10]. In this report, we describe the use of an Internet study protocol in the warfarin genetics (WARG) study addressing genetic risk factors in anticoagulation therapy.

The main aims of the WARG study are to assess the true incidence of severe bleeding complications during treatment with the vitamin K antagonist warfarin, and to investigate the impact of different genetic factors on the risk of such complications. When a sufficient number of patients have been included, the results of this main analysis will be presented in a separate report. In this article, we describe two different Internet-based data acquisition tools and evaluate their usefulness in the WARG multicentre study.

Methods

WARG is a cohort study with prospective data collection. It is coordinated from the department of clinical pharmacology at Karolinska Institutet at Karolinska University Hospital Huddinge, with participation of a large number of clinical hospital units and primary health care centres from all over Sweden. The collaborating centres recruit patients requiring *de novo* treatment with warfarin, a blood sample is collected and clinical background data are entered into a data bank. The blood samples are stored in a bio-bank that is linked with information about haemorrhage incidence and will be used to identify and quantify genetic risk factors predisposing to bleeding complications during warfarin medication (Figure 1). In order to correctly understand the complex interactions between genetic and nongenetic predictors of pharmacological response, detailed clinical information is also continuously entered into the database (Table 1). The study has been approved by the ethics committees in all parts of the country where the study is performed and patients are included only after giving written informed consent to study participation, genetic analyses, and entering of their clinical data into a web-based database.

To facilitate data collection and to evaluate the potential of new techniques in clinical research, we chose an Internet-based protocol for the study. The system specifications were developed by the steering group in collaboration with representatives from participating centres and the program development enterprise. The coding was done in HTML (hypertext markup language)

Figure 1

In the warfarin genetics (WARG) study, patients are registered online from participating centres all over Sweden. Blood samples are sent by mail to the coordinating centre and clinical data are continuously entered using the web-based protocol

by a contracted software company specialized in medical Internet solutions (MedSciNet AB, Stockholm, Sweden). The system is physically located on a central web server and is accessed by the collaborating centres via the Internet, using the web browser Internet Explorer as interface.

The trial protocol's entrance is a study homepage (<http://www.druggene.org>), containing public access general information about the study, newspaper quotes, etc. From this homepage, collaborating centres can log into the actual study protocol, using individually assigned user-names and passwords obtained from the coordinating centre. Following log-in, all data transfer is encrypted to protect from unauthorized access. As an extra precaution, each patient's data can only be accessed from the coordinating centre and from the clinic where he/she is treated.

The study protocol

The study protocol was designed for three main purposes:

- 1 Registration of new patients in the study
- 2 Continuous entry of clinical data and bleeding complications
- 3 Feed-back and communication between centres

Registration of a new patient includes entry of baseline data including target INR (international normalized ratio), known risk factors for thrombosis or haemorrhage and concurrent medication. To rationalize and standardize the data entered, extensive use of checkboxes and multiple-choice menus is employed (Figure 2). Automated instantaneous validation of the data is ascertained by checking for contradictory data or missing mandatory data. In addition to the on-line registration, every patient signs a written informed consent form, available for printout in the study protocol.

Table 1

Examples of clinical data collected in the warfarin genetics (WARG) study

Age
Sex
Indication for warfarin therapy
Target INR (international normalized ratio)
Concomitant medication, including herbal drugs
Risk factors for haemorrhage or thrombosis
INR measurements
Warfarin doses
Bleeding complications

Figure 2
Screenshot showing one of the data input forms of WARG

During the course of anticoagulation, clinical data about the treatment are continuously entered into the system. Since this is a frequently repeated task, great care has been made to reduce time-consumption, while maintaining high data quality. Examples of time-saving measures are optimized page lay-out fitting all fields into one page, one-button renewal of last dosage, automatic calculation of dose per week, table interface for input of aggregated data from multiple visits and the use of check-boxes where applicable. To avoid accidental omission of information, active confirmation is required when no bleeding complication or alteration of concomitant medication has taken place. To assist the participants in fulfilling scheduled follow-up, automatic notifications are made when blood-samples are missing, patients are missing from follow-up or scheduled end-of-treatment dates have been overlooked.

When a serious bleeding complication occurs, necessary information is entered by the participant using an

electronic form within the protocol system. For classification of severity, the World Health Organization definitions are used. According to these, serious adverse drug reactions are those that are lethal or life threatening, require inpatient hospitalization or prolongation of hospitalization and those that result in persistent or significant disability. Apart from being stored in the central study database, information about the adverse drug reaction can be automatically sent by E-mail to the Regional Centre of adverse drug reactions which is part of the national pharmacovigilance program.

To inspire study collaborators, selected data from the study database are graphically presented within the protocol system with comparisons between the participants' own clinic and the entire study population. Variables presented this way are, for example, number of included patients, indications for warfarin treatment and distribution of INR values. There is also a discussion forum, accessible to participants.

As an aid to using the protocol, a comprehensive on-line user's manual is included in the system, supplemented with a more detailed printed manual. In addition, instant telephone support is offered during office-hours. This support is given by a full-time employed research nurse, who also monitors the database and aids in the recruitment of new participating centres.

There is a specialized monitoring interface available only to the study coordinators. This interface offers direct access to the interconnected WARG databases, filter functions and possibilities to manually change data if necessary. Furthermore, it offers extended statistics on incoming data and system usage.

During the course of the study an alternative web-based solution has been developed, available to selected study centres. Approximately 40% of the specialized anticoagulation clinics in Sweden use a computerized anticoagulation medical record system from one specific software company. The high prevalence made this system an attractive candidate for a tailored data transfer system for automated data extraction. Such a system has now been developed in collaboration with the software programmers of the medical record system and the WARG study group. In the medical record system, an export function has been added where clinical data regarding patients identified as study participants are regularly exported to a central server. From this server, the data are automatically imported into the WARG database employing a newly developed import interface. In the centres using this technology, the extra work associated with study participation is thus reduced to obtaining patient's consent, drawing the blood sample and marking a study participation field in the medical record. Since the data are aggregated in the original WARG database, the monitoring procedures are virtually unaffected by the new mode of data acquisition.

Study data

Data regarding the first 207 patients finishing their warfarin treatment are presented below. This small sample is not sufficient to answer the questions addressed in the WARG study, but it serves as an example of the patient population characteristics and the range of interim analyses available.

Results

Since the WARG study was launched in March 2002, 39 centres have joined the project. Thirty-four percent of these were visited by WARG representatives prior to enrolment, while the remainder were contacted only by phone, mail and E-mail. Although most participants are

familiar with computerized medical record systems, computer knowledge is not required to join the study. Since no formal education in using the system is offered, initial problems in its handling were apprehended. To facilitate training in a safe environment, a mirror version of the protocol with fake patients had been prepared. However, most participants have chosen to use the real protocol from the start. As an extra precaution, most centres have included their first patient with phone guidance from the monitoring nurse. Following that, the average number of questions requiring telephone support has been less than one per month and the support has generally been able to solve these problems instantaneously.

In a few centres, fire-wall software has initially blocked communication with the central server. In all cases, it has been possible to solve this problem in collaboration with the local computer security departments.

A continuous dialogue with the study participants has resulted in major improvements of the system and the centralized design has facilitated instantaneous distribution of the changes to all centres involved. Thanks to such fine-tuning of the protocol, data regarding an INR measurement with dose adjustment can now be entered in less than 1 min.

The alternative data transfer system has been in use since September 2003, with a functionality that has promoted the recruitment of several new participating centres.

At present, 909 patients have been included, contributing to a total follow-up time of 511 patient years. Sixty-nine percent of the patients were included using the original on-line study protocol, but since the medical record data extraction system was launched it has become the main route of patient inclusion. In 219 patients originally included via the on-line protocol, data collection has subsequently been re-routed to the new system. This switch revealed a good similarity between data collected on-line and corresponding data extracted from the medical record system. However, the medical record data contained additional information about 145 concomitant drugs not registered on-line. This discrepancy was most pronounced for drug therapies commenced after inclusion.

Severe bleeding episodes have been reported in 13 patients, equivalent to 2.5 events per 100 patient-years. To validate the reporting of severe haemorrhages, the study database has been linked and matched with national registries of causes of death and of reasons for hospitalization. These registries do not yet contain any compiled data from 2003 or 2004 and only one severe haemorrhage was reported in WARG before

Table 2

Characteristics of the patients who have completed their anticoagulant treatment

Total number of patients	207
Sex, male/female	119 (57%)/88 (43%)
Median age at inclusion (years)	60 (23–87)
Median duration of warfarin treatment (months)	4 (0.6–13)
Indication for anticoagulation	DVT: 100 (48%) AF: 50 (24%) PE: 34 (16%)
Median number of INR measurements	16.5 (5–44)
Median fraction of treatment period within therapeutic interval	66% (12–98%)

Percent values in parentheses refer to fractions of patient population, intervals to value ranges. DVT, deep venous thrombosis; AF, atrial fibrillation; PE, pulmonary embolism.

2003. This case was confirmed in the registry match and no additional cases were revealed. Additional matches will be performed continuously as the registries are updated.

Twenty-six patients have left the study prior to warfarin withdrawal, corresponding to a dropout rate of 2.8%. Of these, five were excluded because of previous warfarin treatment while four patients withdrew their consent. Twelve patients were lost to follow-up due to change of medical care-giver (after a mean observation time of 6 months). In the remaining five patients observation ceased when the centre including them left WARG because of staff turnover.

By November 2003, 207 of the included patients had finished the warfarin treatment. Their characteristics are presented in Table 2. When a sufficient number of complications has been reported, the main aims of the study will be addressed using automated algorithms for patient matching, data extraction and statistical calculations.

Discussion

The WARG study is an authentic example of the usability of Internet-based protocols, both as stand-alone software solutions and as integrated parts of existing medical record systems. With an intuitive user interface, a comprehensive users' manual and a full-time telephone support in the working hours, it has been possible to completely eliminate the need for expensive on-site education of the study participants. A dropout rate of less than three percent proves the system's applicability in long-term use.

The validity of the sampled data was confirmed by the linking and matching of WARG study data with national registries of causes of death and of reasons for hospitalization. Although there was a perfect concordance for the years 2001 and 2002 this is of small predictive value since only one severe haemorrhage occurred during this period. Future registry matches for periods with a larger patient population at risk will be of great importance in determining the validity of data collected using the WARG study protocols. Overlapping data in patients switching between the two data acquisition techniques offered additional information about the data validity. Although there was a good over-all concordance between the two methods, the data automatically extracted from medical records contained better information about concomitant medication. This finding indicates that such data extraction in some cases might not only be time-saving but may also increase the accuracy of study data.

Internet-based protocols may facilitate trials in several ways by reducing administrative costs, improving standardization, and potentially increasing enrolment success rates. Their main advantage lies in making data entry and transfer safer and more efficient. Consequently, they are particularly valuable in studies involving large numbers of patients and trial centres dispersed over large geographical areas. The instantaneous pooling of data makes it possible to monitor the study in real-time. This greatly improves the odds of detecting and solving potential problems at an early stage. The centralized data storage also guarantees perfect concordance between different centres regarding protocols, forms and study data. Moreover, the website provides administrative support to study centres and periodic updates on trial progress to the medical community at large. By careful planning, the aggregating database can be formatted in a fashion suited for interim and final statistical analyses without further rearrangement of the data. The electronic protocol can also be equipped with functions for randomization, automatic stratification and selected feedback to study participants. The initial cost of the software development may be substantial but it is virtually independent of study size. The cost-effectiveness of an Internet based solution would therefore be most pronounced in large studies, where savings due to increased effectiveness could counterbalance the cost. One way of saving money and start-up time could be to develop generic Internet study protocols, where program code could be reused with only minor adaptations to the individual projects.

Future areas of development will be self-reporting patient based systems on the web where the patient himself can report symptoms, development, etc. These systems can be combined with comprehensive informed consent, educational and other support resources. Further comparative studies on efficiency and overall cost effectiveness of Internet based data management and strategies are required.

Internet studies are potentially problematic from a safety point of view. To maintain full data integrity, access should be restricted using, for example, passwords, smart-cards and encrypted data transfer. Technical problems causing loss of access to the Internet or the protocol server could cause problems, especially if real-time data entry is essential for the study. These difficulties can be prevented by installing a protocol program locally on the computers in the study centres, using intermittent data transfer to the study server. However, this is a trade-off with flexibility since updating the software becomes a more complex task. With these limitations adequately addressed, Internet based study protocols are potent research tools, with a great potential in clinical research.

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