Randomised studies in general practice: how to integrate the electronic patient record

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ABSTRACT

The ‘randomised database study’ strategy was first proposed in 1997, with the aim of combining the generalisability of observational database studies based on electronic patient records (EPRs) with the validity of randomised clinical trials (RCTs). The key feature was to randomly assign treatments and to use routine care data, as available in the observational database, for patient identification and follow-up. To our knowledge, however, the idea of the randomised database study has not been implemented yet.

The conduct of a randomised study in an observational database requires adjustments to methods of medical information processing in the general practice. We developed a software system that facilitates the conduct of an RCT with observational databases based on EPRs. It identifies eligible subjects and presents them one by one to the physician once their EPR is accessed. The general practitioner can then start an interactive recruitment process; after completion, the computer randomises the patients. Follow-up is documented by normal routine care in the EPR.

Although the randomised database study has many methodological advantages, it has never been tested. Our software system is meant as a tool to implement and facilitate evaluation of the randomised database approach.

Keywords: electronic patient record (EPR), observational study, pragmatic, randomised clinical trial
Introduction

The randomised controlled trial (RCT) is considered the gold standard in clinical research. The main objective of an RCT is to evaluate whether an intervention is efficacious.1 This evaluation is usually performed by randomisation, blinding, intensive patient monitoring, and strict management according to Good Clinical Practice (GCP) guidelines and protocols. Although these conditions facilitate the measurements of treatment effects, they limit generalisation of the results to other populations and settings.

Observational studies usually have a greater generalisability because they cover treatment patterns in normal care.2 However, the absence of randomisation in the treatment allocation often hampers sound comparison between treatments. Hence, observational studies are considered unsuitable for the evaluation of effectiveness of treatments.3,4

General practitioners (GPs) are faced with the problem of applying evidence from studies that are conducted in strictly controlled settings to patients in normal care.5,6 Ideally, for them, evidence of treatment effectiveness should be obtained in routine care, in pragmatic randomised trials with patients normally seen by GPs.7 Although RCTs in general practice may have better applicability to the primary care setting, there are many difficulties in conducting them.8–10 Frequently reported problems are lack of time, recruitment of investigators and patients, obtaining informed consent, randomisation and data collection. However, most of the randomised studies in general practice use conventional methods for patient selection, recruitment and data collection.

A new approach that could facilitate RCTs in general practice is the randomised database study that was proposed by Sarcristan and colleagues in 1997.11 This approach is based on good experience with observational databases based on electronic patient records (EPRs) in the conduct of observational outcomes studies. An observational database in this context contains data on regular patient care, which is collected for other purposes than research. Sarcristan argues that inclusion of a randomisation module in the EPR would allow assessment of drug effectiveness in a large population.12 The EPR would further function as a source for patient selection, and data collection during a naturalistic follow-up, as in observational studies. Although researchers recognised the advantages of randomised database studies, to our knowledge none have been implemented.

The conduct of a randomised database study requires adjustments or additions to routine methods of processing medical information with the EPR system. The objective of this paper is to describe additions to the method of information processing with an EPR system that facilitate the conduct of a randomised database study.

Method

The proposed adjustments in data processing methods are meant to facilitate the conduct of a randomised study within the normal care process; they are made possible by installation of additional software in the EPR system. The RCT procedures and the proposed additions to the EPR system are described in Table 1.

Setting

The setting of this study is an ongoing longitudinal general practice research database, the Integrated Primary Care Information database (IPCI). This database is also used in observational studies.

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database is described in more detail elsewhere, and has
been used extensively for observational epidemiologic
and drug outcomes studies. In brief, the IPCI re-
search database contains ELIAS EPRs of over 500,000
patients from 150 physicians throughout The Nether-
lands. (ELIAS is a Dutch primary care EPR system.)
The database comprises patient demographic inform-
ation (date of birth, sex, anonymous patient identi-
fication, insurance, date of registration and transferring
out, date of death), medical notes, diagnoses (both as
codes and as free text), prescriptions and indications
for therapy, physical findings, referrals, hospitalisations
and laboratory values. The method we describe
allows for a randomised study in the setting of the IPCI
database.

Patient selection
The first process in the conduct of an RCT is the
identification and selection of potential patients (see
Table 1). The physicians or investigators usually do
not systematically search for eligible patients, and
recruitment may be organised by asking consecutively
presenting patients. Patients included are generally
not compared with non-included eligible patients
(since these are not identified), therefore little can be
said about the generalisability of the data.

In our approach, the EPR database is used to select
potential patients. With tailored software, the re-
searchers may build queries to select eligible patients
in the individual EPR systems. This method standard-
ises the selection procedure across research sites. An
additional advantage is that all eligible subjects in the
complete source population are identified and marked.
Availability of demographic and medical information
on all eligible subjects in the database allows for
detailed comparison of included and non-included
patients and a better estimate of external validity.

Patient recruitment
The second process in a randomised study is patient
recruitment. GCP guidelines require a signed informed
consent if a patient is randomised to treatment, even if
these treatments are already licensed for marketing.
Physicians often fail to recruit a sufficient sample due
to waning enthusiasm and the time needed to com-
plete the recruitment process. Providing information
and asking for participation is probably one of the
major hurdles in recruitment, and little can be
done to reduce the recruitment time. Due to lack of
time and disruption of normal care, physicians per-
ceive it as difficult to ask their patients to participate
and to address all their questions during a normal
consultation.

We developed an interactive software module with
a reminder and data pre-processing function to facili-
tate the recruitment process. As soon as the EPR of a
selected patient is opened, the physician is informed
about the eligibility of the patient and given the option
to start the recruitment procedure. The software also
enables researchers to monitor inclusion and the
reasons for exclusion.

Randomisation
In conventional multi-centre clinical trials, random-
isation usually occurs at one co-ordinating centre.
However, while centralised randomisation is often
used, decentralised remote access, via web or tele-
phone, is increasingly employed.

With the EPR software, randomisation is conduc-
ted automatically in the EPR system after recruitment
is finalised. The incorporated randomisation scheme
should be unpredictable in order to avoid anticipation
of treatment assignment by the GP, especially if the
trial is not blinded.

Data collection and patient
assessment
Data collection in standard RCTs is often done by
means of paper-based case report forms and stand-
ardised questionnaires. Errors and incompleteness are
monitored and corrected as far as possible by a clinical
research organisation. Even though this method en-
sures complete and accurate data, it is labour-intensive.

Since all the important clinical findings and baseline
characteristics are usually documented in the EPR,
it can be used as the primary information source for
baseline information and clinical outcome assess-
ment.

Case study
We implemented a randomised database study to
compare gastrointestinal tolerability of diclofenac
and celecoxib in patients diagnosed with osteoarthritis.
Project-specific software was built and implemented
in the EPR systems of the participating GPs. The local
EPR databases were used to select patients older than
18 years of age who were diagnosed with osteoar-
thritis. Patient selection was based on historical data in
coded and free text format. Researchers reduced false
positive hits by manually validating selections based
on free text information. The software was installed in the EPR system of 42 GPs and it selected 7127 possible candidates. These patients were the source population from which the study population later emerged.

An electronic reminder was placed in the EPRs of the selected patients to enable immediate recognition by the GP when the patient visited. If a patient diagnosed with osteoarthritis required a non-steroidal anti-inflammatory drug treatment during that regular visit, the GP could start the interactive recruitment procedure facilitated by the installed software module. The GP could verify the inclusion and exclusion criteria (for example, contraindication to the treatment under study) and the software documented the inclusion or reason for exclusion in the EPR system. As a result, we could quantify the number of patients who refused to participate, those excluded because of exclusion criteria, and the number of patients ‘missed’ by the GPs.

Immediately after written informed consent was obtained, the patient was allocated to diclofenac or to celecoxib by the randomisation software. The data recorded with the EPR during the naturalistic course of the treatment were sent to the central observational database (IPCI). This database was used to assess outcomes, as done in other observational studies.

Discussion

In this paper, we proposed a method of using the EPR in the conduct of an RCT and described software designed for the practical implementation of a randomised database study. The major advantages of this method are, firstly, the potential reduction in resources needed to conduct a study, and secondly, the availability of detailed information about external validity, since medical and demographic information of both included and non-included patients is available.

Although the idea is attractive, the randomised database study is not without limitations or prerequisites. The successful implementation depends on the possibilities of interfering with the existing EPR system and the method of processing medical information during normal clinical practice.

In order to minimise disruption of normal consultation routines, we inserted an electronic reminder system to alert the GPs about eligible patients, but subsequent steps had to be initiated by the GP. Although this gives some freedom to the GP, it might also lead to non-inclusion and therefore selection bias. Because we had demographic and medical information on the entire source population, however, it is now possible to estimate the magnitude of such selection bias.

By national regulation, both the GPs’ and the patients’ identities are confidential in observational databases that are used for medical research. However, for the randomised database study, named informed consent is required. The requirement to keep the level of privacy in line with national regulations increases the complexity of communication between the researchers, the research database organisation and the physicians. We used an extra identification number on top of the anonymous IPCI number to avoid the possibility of the patient name being directly linked to the existing database number, which would otherwise lead to the possibility of unauthorised access to non-anonymised medical information in subsequent studies.

The randomised database study approach is a clinical trial under the terms of the GCP guidelines. As a result, the principles of the GCP need to be followed; this could potentially reduce the possible resource savings. For example, if a patient is found to be eligible during a consultation, extra time is necessary to explain the study and obtain informed consent. However, the need for this extra time cannot readily be anticipated and scheduled, which could create problems during busy consultation sessions.

With the randomised database study, it is difficult to adhere to the GCP requirements regarding documentation, since the EPR rather than a case report form is the primary data collection tool. GCP requires that source information cannot be altered. An EPR can be changed retrospectively, which could go unnoticed if time stamping does not occur accurately. Therefore, the EPR may not be considered as a source document and a time-stamped printed version of the medical record in the database should be used instead.

Investigator recruitment is a major obstacle in the conduct of RCTs in general practice. GPs recognise the need to improve evidence-based medicine in primary care, but their lack of participation in clinical trials is also evident. GPs report the lack of support staff for research as being a major barrier to participation in RCTs. However, use of a clinical research nurse requires a change in the study strategy. It would not be cost-efficient to recruit patients only when they present themselves at normal visits. Preferably, they should be called in actively. Although the proposed software might facilitate the conduct of a randomised study in general practice, it cannot remove all obstacles, and participation will always increase the workload. Sufficient patient recruitment may therefore remain a problem even with the proposed methods.

Conclusions

In summary, this paper describes our approach to actually implementing a randomised database study.
With adjustments and additions to the methods of information processing with the EPR, the selection, recruitment, randomisation and data collection processes of an RCT can be integrated into the normal care process. Our case study proved that it is possible. However, now that it is possible to facilitate the ‘randomised database study’, it should be evaluated on its validity and performance.

REFERENCES


CONFLICTS OF INTEREST

None.

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