MEDUCATE trial: effectiveness of an intensive EDUCATional intervention for IT-mediated MEDication management in the outpatient clinic – study protocol for a cluster randomized controlled trial

F. van Stiphout1*, J.E.F. Zwart-van Rijkom2,3, J.E.C.M. Aarts4,5, H. Koffijberg6, E. Klarenbeek-deJonge7, M. Krulder7, K.C.B. Roes8, A.C.G. Egberts2,3 and E.W.M.T. ter Braak1

Abstract

Background: Using information technology for medication management is an opportunity to help physicians to improve the quality of their documentation and communication and ultimately to improve patient care and patient safety. Physician education is necessary to take full advantage of information technology systems. In this trial, we seek to determine the effectiveness of an intensive educational intervention compared with the standard approach in improving information technology–mediated medication management and in reducing potential adverse drug events in the outpatient clinic.

Methods/Design: We are conducting a multicenter, cluster randomized controlled trial. The participants are specialists and residents working in the outpatient clinic of internal medicine, cardiology, pulmonology, geriatrics, gastroenterology and rheumatology. The intensive educational intervention is composed of a small-group session and e-learning. The primary outcome is discrepancies between registered medication (by physicians) and actually used medication (by patients). The key secondary outcomes are potential adverse events caused by missed drug–drug interactions. The primary and key secondary endpoints are being assessed shortly after the educational intervention is completed. Sample size will be calculated to ensure sufficient power. A sample size of 40 physicians per group and 20 patients per physician will ensure a power of >90 %, which means we will need a total of 80 physicians and 1,600 patients.

Discussion: We performed an exploratory trial wherein we tested the recruitment process, e-learning, time schedule, and methods for data collection, data management and data analysis. Accordingly, we refined the processes and content: the recruitment strategy was intensified, extra measures were taken to facilitate smooth conductance of the e-learning and parts were made optional. First versions of the procedures for data collection were determined. Data entry and analysis was further standardized by using the G-standard database in the telephone questionnaire.

Trial registration: ISRCTN registry: ISRCTN50890124. Registered 10 June 2013.

Keywords: Continuing medical education, CPOE, Information technology, Meaningful use, Medication management, Physicians

* Correspondence: f.vanstiphout@umcutrecht.nl
1Department of Internal Medicine and Centre for Research and Development of Education, University Medical Centre Utrecht, the Netherlands, Hijnans van den Berggebouw kamer 4.21, Huispostnummer HB 4.05, Postbus 85500, 3508, GA Utrecht, The Netherlands
Full list of author information is available at the end of the article
Background

Treating patients with medication is one of the core activities of physicians in the outpatient clinics of internal medicine and related specialties. Unfortunately, adverse drug events (ADEs) frequently occur in this setting [1, 2]. Patients are often treated simultaneously for more than one medical condition, by more than one physician, with more than one drug and use various pharmacies to obtain prescribed and non-prescribed medications. This may result in scattering of information about the patient’s previous and actual medication use and allergies. One of the causes of ADEs is a discrepancy between what the physician thinks the patient is taking and what the patient is actually taking at home [3]. To prevent these discrepancies and resulting medical consequences, medication should be appropriately managed by physicians in the outpatient setting. This includes appropriate documentation of the medication, appropriate communication to other health care providers and engaging patients in management of their own medication [4, 5].

Using information technology (IT) for medication management is an opportunity to support physicians to improve the quality of their documentation and communication and ultimately to reduce ADEs. IT for medication management refers to the combination of computerized physician order entry (CPOE) and clinical decision support systems.

To stimulate the improvement of quality of care by use of IT, “meaningful use” criteria are used in the United States. With respect to CPOE, these criteria include maintaining an active medication and allergy list for each patient and providing all patients with a copy of their medication information [4]. In the Netherlands, a guideline, “handover of medication information between care settings”, has come into force [6]. This guideline advises physicians to be aware of which medications the patient is taking and to provide patients with a printed overview of their current medications, recent changes and the reasons therefor.

Education of users (that is, physicians) is necessary to improve medication management and to take full advantage of IT systems. In addition, inappropriate use of IT may lead to new kinds of errors [6].

The objective of the present study is to determine the effectiveness of an intensive educational intervention compared with the usual approach in improving IT-mediated medication management and in reducing ADEs in the outpatient clinic. This objective pertains to the cluster (physician) level.

Methods/Design

The Standard Protocol Items: Recommendations for Intervventional Trials (SPIRIT) 2013 guidelines were used to write the study protocol [7] We are conducting a two-arm cluster randomized superiority trial, with a 1:1 allocation ratio in two academic hospitals. Physicians are the unit of allocation. The intervention is targeted on the cluster (physician) level.

Physicians are randomly allocated either to the control group, who have already received the “usual approach”, or the intervention group, who also have already received the usual approach and now will receive an additional intensive educational intervention. Randomization will be done by using a computerized system with randomly permuted blocks. A small block size of six clusters per block will be chosen because the clusters are recruited and randomized sequentially. Randomization will be stratified by hospital to balance the influence of the geographic areas, work environments and IT systems of the two hospitals [8].

A cluster randomization design was adopted because the intervention is at the level of the physician and there is a risk of contamination at the level of the physician. Physicians trained in a new technique will find it difficult to revert to an old technique at the toss of a coin. Allowing physicians to deliver similar care to similar patients ensures that the trial is following typical clinical practice more closely [8].

Setting

The study will be conducted in outpatient settings of internal medicine departments and related specialties at two academic hospitals in the Netherlands: University Medical Center Utrecht (UMCU) and Erasmus University Medical Center Rotterdam (EMC). The study is focused on internal medicine physicians because pharmacotherapy is their core treatment option.

CPOE systems are available in the two participating hospitals. UMCU uses the ChipSoft hospital information system (ChipSoft BV, Amsterdam, the Netherlands), in which the CPOE is fully integrated into the electronic health record. EMC uses a CPOE system called iSoft Mediator (Computer Sciences Corp (CSC), Groningen, the Netherlands), which is partly integrated into the electronic health record. Both CPOE systems meet the basic requirements of CPOE systems, which are ability to store a current medication list and allergies and basic decision support (drug–drug interaction, dose, duplicate order, contraindications) [9].

The ethical review boards of both academic hospitals reviewed the protocol and declared that this research does not fall under the Dutch legislation for research on human subjects, because of its limited burden on participating patients. The ethical review board of the Dutch organization of medical education approved the protocol and telephone questionnaire with respect to scientific content and accuracy.
Participants: eligibility, recruitment, informed consent and time line

**Inclusion criteria for physicians**
- Specialists and residents of internal medicine (including general internal medicine, nephrology, endocrinology, infectious diseases, oncology, hematology, vascular medicine, inherited and metabolic diseases, and acute internal medicine), cardiology, pulmonology, geriatrics, gastroenterology and rheumatology
- Physicians with consultations in the outpatient clinic for at least 4 hours per week

**Exclusion criterion for physicians**
- Physicians who were involved in the development of the intensified educational intervention being investigated

**Inclusion criteria for patients**
- Patients older than 18 years of age
- Patients visiting the outpatient clinic consulting a physician who is participating in the study

**Exclusion criteria for patients**
- Patients who are unable to understand and speak Dutch or English
- Patients who have insufficient understanding of their medications to answer questions about their medicine, or patients who do not have a caregiver who can answer the questions

Physicians are recruited by giving a talk about the study in a meeting with eligible physicians. During the talk, physicians are given the information letter, and they are asked to participate in the study. They are asked to sign a consent form if they decide to participate. Physicians in the intervention and control groups will receive the same information letter and informed consent form. Physicians in our study are not fully informed about the measurements of the (patient-related) outcomes, because this information could influence the behavior of participants in the control group. This approach was subject to the approval provided by the ethical review board.

Consecutive patients who visit a participating physician for an outpatient consultation during the enrollment period are asked in a telephone questionnaire to give information about their medication use, and they are asked to give permission for access to their medical records.

There will be two ways of asking patients to participate: by a research assistant present in the waiting room or by medical assistants. To avoid physicians‘ changing their behavior because they know patients are included, the inclusion process is as non-intrusive as possible.

When patients immediately agree to participate, they sign the informed consent right away. Patients who consider participation will be called in the week ahead. If they agree to participate, they are asked to return the informed consent by mail.

In our study, the physician represents the cluster. The intervention is targeted on the physician who cares for individual patients. This holds that patients are not able to avoid a treatment of a physician who received or did not receive the intervention. However, they are able to choose whether to participate in the telephone questionnaire and whether to give us permission for access to their medical record.

To ensure a representative sample of patients per physician, no more than five patients per day per physician will be asked to participate. To minimize the chance of interim changes in their medications, patients will be called as soon as possible, with a maximum lapse of 2 weeks after the index visit at the outpatient clinic.

Participant flow is illustrated in Fig. 1. The measurements for the primary and key secondary outcomes will take place in groups of physicians to allow for flexible planning. After completion of the educational intervention, consecutive patients of these physicians will be invited to participate in the study. The enrollment period is also flexible because of the variations in numbers of patients a particular physician sees in the outpatient clinic.

Electronic assessment of knowledge and skills will be carried out in three groups to allow for approximately equal time between randomization and assessment. The intervention group will be assessed at a time point approximately 6 months after completing the educational intervention. The control group will be assessed at a time point approximately 6 months after the median number of months whereafter the intervention was completed after randomization by physicians in the intervention group, with the control assessment time point being the median number of months between randomization and completion of education by intervention group plus 6 months).

**Blinding**
Physicians are randomly allocated right after inclusion by the investigator, following the assignment generated by the computer system. As the assignment for the next allocation is provided at the moment of randomization, allocation is sufficiently concealed. Of course, the intervention itself is not blinded to the participating physicians.

Patients are blinded to the intervention status of their physicians. Physicians are not fully informed about the nature of the patient-related outcome measures. Researchers
who mediate the group sessions are aware of the intervention status of the physicians. Research assistants are aware of the intervention status of physicians, but they are not knowledgeable about the content of the educational intervention. The researcher who is analyzing the data does not collect the data. Data analysis will be undertaken blinded to study arm allocation; that is, the control and intervention will be identified only as “A” and “B” until analysis is complete.

**Intervention**

*Usual approach as control*

In the context of this study, the usual approach is the instruction that is currently given when IT for medication management is made available to physicians. Usually, classroom instruction consisting of a lecture demonstrating the main features of the system is offered, and limited opportunities for practical exercises exist. In this study, the usual approach was not standardized between hospitals and physicians.

**Usual approach plus intensive educational intervention**

In addition to the usual instruction, physicians in the intervention arm will receive an intensive educational intervention consisting of a small-group session and e-learning. Physicians will attend a small-group session with discussions on the advantages and disadvantages of IT-mediated medication management to establish mutual agreements between professionals about how the medication management task is properly performed. There will be also opportunities to share experiences, ask questions and discuss cases. There will be approximately eight physicians in the group session, which will last approximately 1 hour.
In the e-learning, physicians will be informed about
the expected benefits and limits of IT to adequately cali-
brate their trust in IT and form an appropriate attitude
toward IT. A social norm will be set for effective and
safe IT-mediated management by role modeling of ex-
erts on video. The training is built up from easy to dif-
cult cases to promote self-efficacy. Physicians are given
step-by-step procedural instructions and information to
support problem solving. The training will be tailored
because it is self-directed. Physicians may choose their
starting level, to practice a case again, to practice a spe-
cific self-chosen part of a task again or to go on to the
next level of difficulty. This part of the intervention will
be individually delivered as e-learning modules devel-
oped according to the four-component instructional de-
sign (4C/ID) model [10]. The 4C/ID model allows for
research-based design of educational interventions. The
e-learning is generic, but specific procedures in CPOE
are tailored to the actual local CPOE system in use [11].

To stimulate adherence to the intensive educational
intervention, physicians in the intervention group receive
several reminders. Earning continuing medical education
credits when both the small-group session and the e-
learning modules are finished further stimulates adherence.

Outcomes
Primary outcome: medication discrepancies
Differences between the two study arms are analyzed
using as the primary outcome the proportion of medica-
tion discrepancies per physician. Medication discrepan-
cies are defined as discrepancies between medications regis-
tered by physicians in CPOE and medications actually
used by patients, obtained by the telephone questionnaire.
Each discrepancy is counted; that is, any patient can con-
tribute multiple discrepancies.

The following events are taken into account:

- Omission in registration of the current medication: A
drug is taken by the patient but is not registered in
the list of medications in CPOE
- Addition in the registration of the current
medication: A drug is not used by the patient but is
registered in CPOE.

Discrepancies in dosing (dose per intake and number
of intakes per unit of time) are not taken into account.

The proportion of discrepancies is then calculated using
(1) the number of discrepancies (omissions and additions)
as the numerator and (2) the sum of the number of dis-
crepancies and the number of medications a patient is tak-
ing and the number of medications registered in CPOE
minus the overlap as the denominator. Thus, no medica-
tion is counted twice in the denominator.

The proportion of discrepancies will also be deter-
mined and analyzed, restricted to high-risk medications
specifically. The high-alert medication list of the Insti-
tute for Safe Medication Practices will be used to indi-
cate high-risk medications [12].

The data collected by means of the telephone ques-
tionnaire are considered the gold standard for the pa-
ient’s use of medication and past ADEs. The telephone
questionnaire is derived from the structured medica-
tion history [5], the telephone questionnaire used by
Gandhi et al. [1] and Consumer Quality Index ques-
tions tailored for individual patient experiences in
health care [13]. A prior version of the telephone ques-
tionnaire was validated against the medication history
obtained during home visits. Improvements were made
accordingly.

Data collectors are medical students or medical doc-
tors in the phase just before or after their graduation or
should be experienced research nurses. Data collectors
are trained in two ways. First, there is a standard oper-
ating procedure (SOP) describing how exactly the ques-
tionnaire should be carried out and what to do in
various circumstances (for example, when a caregiver
answers the questions). Second, data collectors work
their first day together with an experienced data col-
lector and have opportunities to practice and receive
feedback.

The telephone questionnaire will be made available at
the trial website only after completion of data collection
to ensure blinding of participating physicians for the
outcome measures involved [14]. Data managers extract
the following data from the CPOE systems: medication
on the index date and registered ADEs.

Key secondary outcome: missed drug–drug interactions
with potential for causing harm
The key secondary outcome is any difference between
the two study arms in the proportion of patients per physi-
cian with at least one missed drug–drug (DD) interaction
with potential for causing an ADE (PADEs) per physician.
Whether there is a DD interaction with potential for an
ADE is assessed by following the Dutch clinical guidelines
for management of DD interactions using the G-standard
database. The G-standard is the Dutch drug database,
which is used by all Dutch parties in health care, including
physicians, pharmacists, manufacturers, health insurers
and the government. The G-standard supports the dif-
f erent processes in health care, such as, among others,
decision support on DD interactions. Also, information
is given about the (published) effect of the interaction.
The G-standard categorizes the effects of the interac-
tions into six levels of severity ranging from A (minor)
to F (potentially lethal) [15].
Other secondary outcome measures

Discrepancies in adverse drug events Differences between the two study arms in the proportion of patients with at least one missed ADEs per physician are defined as discrepancies between the registration of ADEs in CPOE versus the information regarding ADEs obtained from the patient via the telephone questionnaire. We take into account the ADEs with moderate or severe potential consequences. The European Medicines Agency guideline will be used to assess the severity of the ADE [16].

Use of computerized physician order entry Physicians’ use of CPOE will be registered with log files of the CPOE systems to assess whether physicians meet the official meaningful use criteria [4]. Also, additional criteria were formulated to assess meaningful use. The following aspects will be assessed:

- The number of lines inserted in CPOE per week (numerator) divided by the number of patients scheduled for outpatient consultation per week (denominator)
- The number of allergies inserted in CPOE per week (numerator) divided by the number of patients scheduled for outpatient consultation per week (denominator)
- The number of complete ADE registrations (medication, symptoms, severity) inserted in CPOE per week (numerator) divided by the number of ADEs inserted in CPOE per week (denominator)
- The number of prescriptions with unspecified doses in CPOE (numerator) divided by the number of lines inserted in CPOE per week (denominator)

(In the numerator, we will exclude medication obliged to be prescribed this way, because doses are adjusted to frequent measurements, such as insulin and vitamin K antagonists.)

CPOE use will be logged 2 months before the intervention, during the intervention and until 6 months after the intervention. These data will give an indication whether the intervention remains effective over a longer period of time (that is, retention of learning).

Data derived from the telephone questionnaire supports the analysis of the physicians’ adherence to the Dutch guidelines regarding handover of medication information between care settings by calculating the difference between study arms in the following terms:

- Proportion of patients who were actively asked for their use of medication during the consultation
- Proportion of patients who were given a printed medication overview at the end of the consultation

Knowledge and skills

With an assessment after the intervention period, physicians’ knowledge and skills regarding IT-mediated medication management will be measured. To ensure content validity of the assessment, a test matrix is used to guarantee an even distribution of training content in the questions. The checklist for constructing written test questions for basic and clinical sciences will be used to ensure high-quality questions [17]. An expert team of an educator, pharmacist, clinical pharmacologist and internist will be asked to review the questions and propose improvements. The distinctiveness of the assessment will be determined by asking an expert and a naive end user to pretest the assessment. Improvements will be made according to the findings.

Patient-related outcomes

Patient-related outcomes will be analyzed on the basis of the data derived from the telephone questionnaire by calculating the difference between study arms in terms of

- Patients’ satisfaction with their care regarding their medications
- Patients’ sense of responsibility to self-manage their medications

Sample size calculation

For the sample size considerations, the following assumptions are made. Per specialist and per period, the same number of patients are followed. The primary outcome is the percentage of discrepancies between medication records and patient information. The design is a cluster (physician) randomized trial with proportions as outcomes. The comparison between groups should be able to detect a difference of at least 10 % (from 70 % to 80 % and from 80 % to 90 %), and testing is done at a significance level of 5 % (two-sided) for each contrast. The intraclass correlation coefficient is assumed to be 0.1, following the method of Schnipper et al. [18]. To ensure sufficient power, a sample per group of 40 physicians and 20 patients will ensure a power of >90 % for a total of 80 physicians and 1,600 patients. If (substantially) more physicians can be recruited, this may lead us to recruit fewer patients while maintaining power.

Statistical methods

Descriptive statistics

We will use baseline characteristics of hospitals, physicians and patients according to covariates known from the literature or anticipated covariates, including, among others, physician's age, sex, years of experience in prescribing and computer literacy, as well as patient’s number of medications [18–21].
Comparisons between study arms

The primary analyses will be focused on comparing the two study arms with regard to the proportions of discrepancies and resulting PADEs. The unit of analysis is the cluster (physicians). The analysis will follow the intent-to-treat principle, including all physicians in the analysis as randomized. However, physicians who do not contribute any patients (and hence contribute no observations) will be excluded from the analysis. No imputation of resulting missing values will be done.

The primary outcome per patient is the proportion of discrepancies, as defined above. A full regression model appropriate to the structure of the data could be applied. However, the proportions as defined most likely cannot be modeled as binomial quantities, but a continuous approximation may be sufficiently adequate if the average proportion per cluster (physician) is analyzed. This analysis is somewhat less efficient than a full model (if that can be correctly specified), but cluster effects are appropriately included in the error term. Hence, this linear model will be used to analyze the data (potentially appropriately transformed if model evaluation so indicates).

The population-averaged model with inclusion of the covariate can be written algebraically as follows:

\[ Y_{ijh} = \alpha_i + x_{ij} + z_h + e_{ijh}, \]

where \( i \) is the intervention arm, \( j \) is the cluster (physicians), \( h \) is the Hospital, \( Y_{ijh} \) indicates the value of the average outcome for the \( i \)th treatment arm from the \( j \)th physician of hospital \( h \), \( \alpha \) is the constant, \( \beta \) is the effect size of the intervention, \( x_{ij} \) indicates the intervention arm (value 1 = intervention arm, value 0 = control arm), \( z_h \) indicates the categorical covariate (\( h \)th hospital), and \( e_{ijh} \) is the residual for \( j \)th physician in treatment arm \( i \) and hospital \( h \).

The analysis of secondary endpoints is exploratory and will follow the same analytical approach used for the primary endpoint. Because of the exploratory nature of the analysis, no type I error correction for multiplicity will be done.

Data management

The data are collected by telephone and entered at the core coordinating center (UMCU) in Research Online 2 (RO2). RO2 is an electronic data capture system that will be used for data collection. Integrity is enforced when data entry takes place in the web-based case report forms by means of checks on value ranges, logical checks (for example, the interview date cannot be later than the actual date of interview), skip rules preventing unnecessary data collection and coded answering options. To ensure analogy between data entry in RO2 and CPOE, the G-standard database is implemented in RO2.

RO2 data traffic over the Internet is encrypted using secured data communication protocols. Dedicated databases and web servers are hosted in data centers that meet the highest available standards for security (XS4ALL data center, Diemen, the Netherlands: https://www.xs4all.nl/).

Access to and exporting of the RO2 data are limited to data management staff of the Julius Center of UMCU, who are not involved in the conduct of the trial. The patients’ data are coded, and the linking codes are stored in separate password-protected locations. The data will be prepared for analysis and stored on a secure server within the IT facilities at UMCU. Access to the specific folders on this server containing the research data is kept to a minimum and granted only to researchers who are specified by the principal investigator. Data will be locked at the end of the study and securely stored for 15 years. Only after the principal investigator has granted permission the data will be allowed to be unlocked.

Files with patient-related data will be sent from one academic center to the core coordinating center. These files will be sent using FileSender (SURFnet: https://filesender.surfnet.nl/), a specially secured way to send data with passwords. Files are zipped and encrypted before sending.

Discussion

We performed an exploratory trial wherein we tested the following:

1. Recruitment process
2. Technical smoothness of the e-learning
3. Physicians’ reactions to the e-learning
4. Potential room for improvement regarding the primary outcome
5. Appropriateness of the time schedule
6. Data collection methods
7. Data management
8. Categorization of medication and interaction discrepancies

We refined the processes and content according to our findings as follows:

1. We intensified the recruitment strategy.
2. We gave special warnings for certain systems hindering the smoothness of e-learning and introduced the possibility of carrying out the first module together with the research physician.
3. Physicians were mostly positive, but they found the e-learning too long. Therefore, we made some of the content of the e-learning optional.
4. It turned out that there was enough potential room for improvement, because only 37 % of the medication records in the exploratory trial were
complete. After finishing the e-learning, most physicians reported their intent to change their behavior regarding IT-mediated medication management or had already changed their behavior.

5. Physicians needed more time to finish the e-learning.

6. First versions of the SOPs for data collection were determined.

7. Data entry was further standardized by using the G-standard database in the telephone questionnaire.

8. Improvements in categorization were made, mostly with the automation of the categorization process.

Trial status

Trial recruitment was completed on 1 January 2015.

Abbreviations

ADE: Adverse drug event; 4C/ID: Four-component instructional design; CPOE: Computerized physician order entry; DD: Drug–drug EMC, Erasmus Medical Center: Rotterdam, the Netherlands; IT: Information technology; MRC: Medical Research Council; PADE: Potential adverse drug event; RO2: Research Online 2; SOP: Standard operating procedure; UMCU: University Medical Center Utrecht, Utrecht, the Netherlands.

Competing interests

The Netherlands Organization for Health Research and Development (ZonMw) is funding the personnel costs of EWMtB, who is the Principal Investigator of the trials as well as of the research assistants who recruit patients and collect data from the patients. The design, management, analysis, interpretation and reporting of the study are entirely independent of the funder. The authors declare that they have no other competing interests.

Authors’ contributions

EWMtB is the Principal Investigator of the trial. FvS is the Research Physician of the trial. EWMtB and FvS conceived of the study, initiated the study design and are grant holders. HK, JEFzVR, JECMA and ACGE supported the elaboration of the study design. KCBR provided statistical expertise in cluster randomized trial design and contributed to the plan of the analysis of the discrepancies and potential adverse drug effects. EK-dJ and MK assessed the randomization, maintenance of trial IT system (Research Online) and data entry, data verification. The other authors contributed to the quality of the telephone questionnaire and conducted the exploratory trial, respectively.

Acknowledgements

This research is supported by grant 171103005 awarded by the Netherlands Organization for Health Research and Development (ZonMw). Committees: Principal Investigator (EWMtB) and Research Physician (FvS); design and conduct of MEDUCATE, preparation of protocol and revisions, preparation of the telephone questionnaire for patients, organizing steering committee meetings, study planning, describe standard operating procedures, budget administration, publication of study reports, data verification, organization of recruitment and training of physicians and patients.

Steering committee (all authors)

Agreement of final protocol, reviewing progress of the study and, if necessary, agreeing on changes to the protocol to facilitate the smooth running of the study.

Data manager: randomization, maintenance of trial IT system (Research Online) and data entry, data verification.

Author details

1. Department of Clinical Pharmacy, University Medical Center Utrecht, Heidelberglaan 100, 3584, CX Utrecht, The Netherlands. 2. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, PO Box 80082, 3508, TB Utrecht, The Netherlands. 3. Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands. 4. Department of Biomedical Informatics, School of Medicine and Biomedical Sciences, University at Buffalo, Roosevelt Hall, 923 Main Street, Buffalo, NY 14203, USA. 5. Department of Health Technology Assessment, Julius Center, University Medical Centre Utrecht, Utrecht, The Netherlands. 6. Faculty of Medicine, Utrecht University, Universiteitsweg 98, 3584 CG Utrecht, The Netherlands. 7. Department of Quality and Patient Safety, University Medical Centre Utrecht, Utrecht, the Netherlands.

Received: 19 November 2014 Accepted: 5 May 2015

Published online: 22 May 2015

References

1. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. N Engl J Med. 2003;348:1556–64.

2. Avery T, Barber N, Ghaele M, Franklin BD, Armstrong S, Crowe S, et al. Investigating the prevalence and causes of prescribing errors in general practice: the PRACtCe Study (PRACtCe Study). J R Coll Gen Pract. 2012. http://www.ncbi.nlm.nih.gov/pubmed/22626178. Accessed 15 May 2015.

3. Kohn LT, Corrigan JM, Donaldson MS, editors; Committee on Quality of Health Care in America. Institute of Medicine. To err is human: building a safer health system. Washington, DC, National Academy Press; 2002. 10.432/0016-6434.

4. Blumenthal D, Tavenner M. The “meaningful use” regulation for electronic health records. N Engl J Med. 2010;363:501–4.

5. Drenth-van Maanen AC, Spee J, van Hensbergen L, Jansen PA, Egberts TC, van Marum RJ. Structural history taking of medication use reveals iatrogenic harm due to discrepancies in medication histories in hospital and pharmacy records. J Am Geriatr Soc. 2011;59:1767–7.

6. Koppell R, Metlay JP, Cohen A, Alabuck B, Locallo AR, Kimmel SE, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA. 2005;293:1197–203.

7. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krlejić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:203–7.

8. Eldridge S, Kerry S. A practical guide to cluster randomised trials in health services research. Chichester, UK; John Wiley & Sons; 2012.

9. van der Sijs H, Bouamar R, van Gelder T, Aarts J, Berg M, Vulto A. Improvements in categorization were made, mostly with the automation of the categorization process.

10. van Merriënboer JJG, Kirschner PA. Ten steps to complex learning, a systematic approach to four-component instructional design. 2nd ed. New York: Taylor & Francis; 2013.

11. Grof R, Wensing M, editors. Implementatie: effectieve verbetering van de patiëntenzorg. Amsterdam: Reed Business/Elsevier Gezondheidszorg; 2006.

12. Institute for Safe Medication Practices (ISMP). ISMP list of high-alert medications in community/ambulatory care. http://www.ismp.org/commu

ny/rtools/highAlert-community.pdf. Accessed 15 May 2015.

13. BMJ Outcomes. Consumer Quality Index – measuring patient experience in the Netherlands. http://outcomes.bmj.com/index.php/journal/consumer-quality-index-measuring-patient-experience-in-the-netherlands. Accessed 15 May 2015.

14. UMC Utrecht. MEDUCATE trial. http://www.umcutrecht.nl/en/Ziektenhuis/ Meedoen-aan-wetenschappelijk-onderzoek/MEDUCATE-trial. Accessed 15 May 2015.

15. van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, et al. Clinical relevance of drug interactions: a structured as-

16. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf. Accessed 15 May 2015.

17. National Board of Medical Examiners. http://www.nbme.org/. Accessed 15 May 2015.
redesign on potential adverse drug events: a cluster-randomized trial. Arch Intern Med. 2009;169:771–80.

19. Harrison MI, Koppel R, Bar-Lev S. Unintended consequences of information technologies in health care—an interactive sociotechnical analysis. J Am Med Inform Assoc. 2007;14:542–9.

20. Linder JA, Rigotti NA, Schneider LJ, Kelley JH, Biawarsky P, Schnipper JL, et al. Clinician characteristics and use of novel electronic health record functionality in primary care. J Am Med Inform Assoc. 2011;18 Suppl 1:i87–90.

21. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med. 2008;168:1890–6.