In-hospital medication reviews reduce unidentified drug-related problems

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Introduction

Although drug treatment is an important cornerstone in the prevention, relief or cure of diseases or symptoms, it can also be a cause of illness and death. A drug-related problem (DRP) is defined as "*an event or circumstance that actually or potentially interferes with desired health outcomes*" [1]. DRPs, including adverse drug reactions, can result in admission to hospital [2-6], increase the length of stay at the hospital [7-9], increase the cost of the hospital stay [8-9] and increase mortality rate [9]. A considerable proportion of these hospitalisations are preventable [4, 10]. Thus, it is important to identify and resolve DRPs. Clinical pharmacy is a health speciality, aiming to provide the best treatment alternative for the individual patient, maximising the clinical effect and minimising the risk of treatment-induced adverse events [11]. The clinical pharmacy process involves identifying potential and actual DRPs, resolving actual DRPs and preventing potential DRPs. Previous studies have demonstrated that clinical pharmacy services for in-patients reduce the number of drug-related problems [12], the length of stay [13-16], costs [13, 16-17], adverse drug reactions [18], rates of readmission [14-15] and rates of drug-related readmission [19].

The main purpose of this study was to examine the impact on the number of unidentified DRPs of a new model of care, in which a clinical pharmacist would conduct structured medication reviews and the multiprofessional team would collate systematic medication care plans. The study was also intended to classify and describe the types of DRPs identified during the intervention period and their impact on the patients' medication therapy, and to assess the satisfaction of the health care practitioners with the new model of care.

Methods

Ethical considerations

This study was approved by the ethics committee of Lund University, LU 589-01. Written consent to participate in the study was signed by each patient or next of kin. The study was also performed in accordance with Swedish ethical legislation and the Declaration of Helsinki.

Study setting and design

Elderly patients admitted to an internal medicine ward at the University Hospital of Skåne, Lund, Sweden, were included in the study after giving informed consent. Patients were recruited to the study by the admitting nurse of the ward at the time of admission. The study was designed as a prospective two-period study with retrospective evaluation (**Figure 1**). Control patients were recruited from November 2001 to May 2002, while intervention patients were recruited from January 2004 to April 2004. Control patients received conventional care, provided by physicians, nurses, care providers and paramedics. The conventional care included a computerised physician order entry system with integrated drug safety alerts concerning C/D-interactions (C interactions are those involving a drug combination that could require dose adjustment, D interactions are those involving a drug combination that ought to be avoided) and interchangeable drugs (generic and analogous substitution according to a regional interchangeable list). The intervention was a new model of care which was implemented four months before the recruitment of intervention patients began. Included patients were ≥ 65 years of age on the day of admission and used at least three medicines on a daily basis. Patients were excluded if they stayed on the ward for fewer than five weekdays or if they had been included in the same study before during the control or intervention periods.

The intervention

At admission, the nurses assessed the symptoms of the intervention patients using the LIMM (Lund Integrated Medicine Management) symptom-scoring form. This form assessed the following ten symptoms: dizziness, general fatigue, memory deficiency, sleeping difficulties, dry mouth, nausea, constipation, micturition difficulties, pain and cough, and was used to screen patients for possible adverse drug reactions.

Four times a week, before morning rounds, a clinical pharmacist conducted structured medication reviews using the LIMM form and monitored all available relevant information on the patients, using the medication lists in the patient records, health record notes, laboratory test results and other results (e.g. blood pressure, heart rate, oxygen saturation). The clinical pharmacist used the LIMM medication review form to identify DRPs according to specific categories of risk, and formulated suggestions for changes to medication treatment. During rounds, the patients' drug treatment was discussed by multiprofessional teams, consisting of physicians, nurses, care providers, the clinical pharmacist and paramedics. The physician served as the team leader and coordinator. The LIMM symptom-scoring form, the identified DRPs and other clinical opinions served as a base for any decision to change the drug treatment. Patients were followed up twice weekly to enable identification of new drug-related problems and to monitor previously identified problems.

A systematic medication care plan was then established, based on the multiprofessional discussion. Changes in drug therapy were prioritised and documented in the LIMM medication care plan form for each patient. The reason and the goal for each change was also documented, together with information on what was to be assessed, and how, when and by whom it was to be assessed. This care plan was continuously followed up at rounds.

The health care practitioners' satisfaction

The health care practitioners' (physicians and nurses) satisfaction with the intervention was assessed shortly after the inclusion of the last patient, using a questionnaire which assessed the following aspects: the intervention in general, the working methods, the usefulness for the patient and the usefulness of the clinical pharmacist. Answers were obtained using six-point ordinal scales, from 1 (not useful) to 6 (very useful).

Evaluation and classification of DRPs

DPRs identified during the prospective intervention

In order to improve detection of DRPs, a checklist including eight categories of risk was compiled by a clinical pharmacist and a geriatrician. The eight categories of risk were: 1) interchangeable drugs (generic and analogous substitution according to a regional interchangeable list); 2) C/D interactions (C interactions are those involving a drug combination that could require dose adjustment, D interactions are those involving a drug combination that ought to be avoided); 3) less appropriate drug therapy[20]; 4) drug or dose of drug not adjusted according to renal function or inability to calculate creatinine clearance; 5) drugs that required therapeutic drug monitoring (TDM); 6) problems with handling the drugs (for example swallowing, crushing); 7) problems with allergy or similar; and 8) other problems. These eight categories of risk were used in both the retrospective evaluation process and during the prospective intervention period.

The DRPs identified by the clinical pharmacist during the intervention period were initially classified as actual or potential DRPs. The DRP was classified as actual if an event was present (or if the patient's health was currently affected) and potential if the event was not present but there was a risk of future events. The DRPs were then further classified into nine subcategories, comprising the seven categories used by Cipolle, Strand and Morley [21]: *need for additional therapy, unnecessary drug therapy, wrong drug, dosage too low, adverse drug*

reaction, dosage too high and *non-compliance*, with the addition of two further categories: *transferring error* and *sub-optimal monitoring of drug treatment*.

DPRs identified during the retrospective evaluation

Shortly after the inclusion of the last patient, in May 2004, all patient records were printed out, randomly assigned identification numbers, and blinded regarding dates and patient identities. This was done for both intervention and control patients. During March 2006 and June 2008, a clinical pharmacist identified DRPs and drug changes from the blinded records, using the eight-point risk checklist described above. The identified DRPs and drug changes were computed into an Access program, developed by one of the authors. Two pairs of evaluators (each comprising a clinical pharmacist and a geriatrician or a GP with special interests in geriatrics) then independently evaluated and classified the DRPs and drug changes from the blinded patient records of five consecutive patients as having been identified or unidentified during the hospital stay.

The DRPs were classified as identified if changes related to the DRPs were made or if comments in the records indicated that the DRPs had been identified. The DRPs were then further classified according to type and clinical significance. The type of DRP was classified according to the nine-category modified version of Cipolle, Strand and Morley [21] outlined above, with the addition of two further choices: *drug treatment indicated* (no DRP present) and *impossible to judge*. The clinical significance of the DRPs was classified according to Hatoum [22] into five groups: *no significance, somewhat significant, significant, very significant* and *extremely significant*. New DRPs identified by the evaluators during the review were added and classified.

If the DRPs where not classified identically by the two pairs of evaluators, a clinical pharmacist (not earlier involved in the classification) decided which evaluation to choose. The records were then un-blinded and the DRPs classified as unidentified for intervention patients

were re-classified as identified if they had been identified on the LIMM medication review form during the intervention.

Statistical analysis

The study was designed to have 80% power to detect a mean difference of two unidentified DRPs between intervention and control patients; sample-size calculations showed that 70 patients were required per study group at a two-tailed significance level of 0.05.

The incidence of DRPs per patient was presented as the total number of DRPs (M-DRPs), including instances where one medication was associated with several different DRPs, and as the number of medications associated with DRPs (P-DRPs), irrespective of the number of DRPs each medication was associated with [23].

An unpaired student's t-test was used to compare the groups with respect to continuous patient characteristics variables and Fisher's exact test was used for ordinal variables. The Wilcoxon rank sum test was used to compare the groups with respect to the number of unidentified problems, and the type and clinical significance of the M-DRPs. Descriptive statistics were used for intervention patients to describe the results of the systematic symptom scale, the types of P-DRP, and the outcomes of the M-DRPs. A significance level of $p < 0.00122$ was used, according to the Dunn-Sidák correction, for each of 42 comparisons performed in this study, giving a total significance level of $p < 0.05$.

Descriptive statistics were performed using Excel 2003 (Microsoft Corporation). Statistical analyses were completed in the R language and environment for statistical computing (www.r-project.org).

Results

Patient characteristics

A total of 201 patients (96 intervention and 105 control patients) were initially included in the study. During the control period, 34 patients were excluded: 27 because of short hospitalisation times and seven who declined to participate. During the intervention period, 26 patients were excluded, all because of short hospitalisation times. A total of 141 patients (70 intervention and 71 control patients) was thus included in the analysis. The mean age of the total population was 81.6 years (SD 7.0) and 64 % of the total population were females (**Table 1**).

Categories of risk

During the hospital stay, the control group used a higher number of less appropriate medicines than the intervention group (69.0% vs 41.4%; **Table 2**).

The unidentified DRPs: numbers, types and clinical significance

Altogether, the evaluators classified 2744 possible M-DRPs and drug changes. Of these, 498 M-DRPs (18 %) were not identically classified; 352 (13% of the total) differed regarding the classification identified/unidentified and 440 (16% of the total) differed regarding the classification type of M-DRP.

The numbers of unidentified M-DRPs and P-DRPs were significantly lower in the intervention group (76 M-DRPs and 74 P-DRPs using the LIMM medication review form plus the records; 299 and 268 using just the records) than in the control group (733 M-DRPs and 594 P-DRPs; all $p < 0.001$; **Table 3**).

All sub-categories of M-DRPs that were frequent in the control group were significantly reduced in the intervention group (**Table 4**). Similarly, the DRPs were less clinically significant in the intervention group (**Table 5**).

Intervention patients: LIMM symptom-scoring form, types of DRPs and actions taken

The LIMM symptom-scoring form was completed for all intervention patients. The most frequently reported symptoms were general fatigue, dry mouth and cough (**Table 6**).
During the intervention period, a total of 690 M-DRPs were identified (mean 9.9 M-DRPs, median 9 M-DRPs per patient), 393 (57 %) were classified as actual DRPs and 297 (43 %) were classified as potential DRPs. The three most common types of M-DRP identified were: *wrong drug, unnecessary drug therapy* and *adverse drug reaction* (**Table 7**).
From the 690 identified M-DRPs, a total of 450 (65 %) suggestions for changes in drug therapy were discussed with the physician. Of those discussed with the responsible physician, 329 suggestions (73 %) were implemented in accordance with the pharmacist's advice (directly accepted), while 31 suggestions (6.9 %) were not implemented (rejected). After discussion with the physicians or further review of the patients' records, 90 M-DRPs (20 %) were further resolved. This means that 93 % of the suggestions were accepted, and changes in drug therapy were made by the physician. Types of action taken for attempting to resolve or prevent the M-DRPs are shown in **Table 8**.

The health care practitioners' satisfaction

A total of 21 of the 22 participating physicians and 14 of the 15 participating nurses completed and returned the questionnaire. All health care practitioners were very satisfied with the model of care during the intervention (**Table 9**).

Discussion

Patients receiving the new model of care, i.e. a clinical pharmacist conducting medication reviews and the multiprofessional team collating systematic medication care plans, benefited from a reduction in unidentified DRPs. In Swedish in-patient settings, there is a growing trend for physicians, nurses, care providers and sometimes paramedics to work together in teams

(as seen in our study for the control group). Our findings showed that increasing the focus of the multiprofessional team, including a clinical pharmacist, on the medications and DRPs effectively resulted in more DRPs being identified. To our knowledge, no other comparative studies examining the effects of medication review using a systematic team-based approach on the number of unidentified DRPs, the types of DRP and the clinical significance of DRPs in in-patients have been carried out. Lipton *et al* [12] found that drug reviews reduced the percentage of patients with DRPs; 83% of intervention patients and 92% of control patients had DRPs. Our study also showed that all the sub-categories of M-DRPs that were frequent in the control group were significantly reduced in the intervention group. This was also found for the clinical significance of the DRPs.

In order to resolve DRPs, it is essential to identify them. In our study, an average of 9.8 (median 9) M-DRPs were identified per patient in the intervention group. This was more than three times higher than the number of identified DRPs in other studies conducted in medical wards: Blix *et al.* [24] reported 2.6 DRPs and 2.1 clinical DRPs per patient and Mannheimer *et al.* [25] reported 2.2 clinical DRPs per patient. This difference could have occurred for several reasons: the patient population in our study used more drugs or may have had a higher disease burden, or the LIMM medication review form used by the pharmacist in our study may have detected more DRPs by missing fewer unidentified DRPs.

The acceptance rate of advice concerning DRPs was also high in this study: 93.1 %, comprising a 73.0 % direct acceptance rate and 20.1% solution of DRPs after discussion with the physicians or further review of the patients' records. This is comparable with the results of Barber *et al.* [26] (96.3 % acceptance), Blix *et al.* [23] (91.8 %), Lee and McPherson [27] (84 %), and Bosma *et al.* [28] (82.4 %), but is higher than those of Mannheimer *et al.* [25] (63 %). The high acceptance rate in our study and the high satisfaction rate of the health practitioners indicates that the discussed DRPs were clinically significant. Sending written advice to the

physician, as in Mannheimers' study, seems to result in lower acceptance rates. In our study, and other studies with comparable acceptance rates, medication reviews were conducted in close liaison with the physician in charge, enabling mutual handling and understanding of the DRPs. Other factors shown to influence acceptance rates include ward type, pharmacist experience, total time spent on the ward by the pharmacist [26], patient characteristics and clinical significance of the DRPs addressed [24].

A number of different classification systems for evaluating DRPs have been used in previous studies [29], making it almost impossible to compare the types of DRP among the different studies. It is also difficult to reach a conclusion as to whether all identified DRPs, or only the clinically relevant ones, are presented, and also whether several DRPs have emerged from a single medication or not. In this study, we therefore decided to present the results both as P-DRPs (the number of medicines associated with any DRP per patient) and as M-DRPs (the total number of DRPs per patient, including instances where there were several per drug). P-DRPs have the advantage of being a more accurate measure of the extent of the drug-related problems for each patient. However, the use of P-DRPs has disadvantages when the DRPs are to be classified into sub-groups, since each medication can cause several types of DRP and this makes it almost impossible to choose which category to use. When M-DRPs are used in conjunction with P-DRPs, a more detailed picture is available and it is possible to specify sub-groups of DRPs.

Because of the team approach, we had to choose a prospective open study design, with a blinded end-point evaluation. Although this study was not randomised and did not have a true parallel control group, the prospective design should be emphasised, as many studies on DRPs have been retrospective. Another strength of the study involves the use of two pairs of blinded evaluators to independently evaluate and classify the DRPs. We also developed predefined structures (for example, tools like the LIMM medication review form and the

systematic medication care plan) and then used these tools and the continuously documented process variables to control the process. The structures (the tools and the clinical pharmacist) were available to support the processes of improving drug therapy (the intervention), which in turn resulted in a specific outcome: the reduction of unidentified DRPs. According to Donabedian [30], outcomes are only one of several measures of health care quality; structure and process measures are also necessary to achieve quality. The fact that only one ward was included in the study and only one pharmacist worked in the ward may have limited the generalisability of the results. However, during the intervention period, 22 physicians and 15 nurses worked with the new model of care. Another limitation of the study was the fact that intervention patients were recruited with 2 years lag compared with control patients. For intervention and control patients to be comparable we decided to include patients at the same season, in order to minimise seasonal variation in admission reason. Intervention patients were recruited the same season after the forms were developed and tested. Further the more, no structural changes took place at the ward during the study period. Taking these facts into consideration, we believe that the progression of the practice is minimal.

This study focused on detecting and solving DRPs during the hospital stay. Medication errors are, however, also frequent at the interface between levels of care [31-33]. In order to minimise this problem, we have also developed and evaluated separate methods for use at admission to [34] and discharge from [35-37] hospital. These studies contribute to the evidence of the usefulness of the entire in-hospital patient care process model, the LIMM model, which comprises a model of care from admission, through the hospital stay to discharge and transferral of the patient back to primary or community care. The benefit of the entire model has been demonstrated previously [38]. Further evaluation and studies are on-going.

In conclusion, a multiprofessional team, including a clinical pharmacist, used structured medication reviews and a systematic medication care plan to effectively reduce the number of unidentified DRPs experienced by elderly in-patients. This study further establishes the quality of the LIMM model for in-patient care.

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Table 1 Patient characteristics for the intervention and control groups.

	Intervention group (n=70)	Control group (n=71)	p value
Mean age (years) (SD)	81.9 (7.5)	81.3 (6.5)	0.58[a]
Sex (male) (%)	23 (33)	28 (39)	0.48[b]
Housing before admission (n)			
Home without homecare	36	35	0.78[b]
Home with homecare	28	27	
Nursing home	6	9	
Mean number of days (SD)			
In the hospital	15.8 (8.5)	21.6 (21.6)	0.03[a]
In the ward	14.5 (7.7)	20.6 (21.2)	0.04[a]
Mean number of drugs (SD)			
At admission			
Continuous use	7.7 (3.4)	7.9 (3.8)	0.79[a]
As required	1.5 (1.6)	1.2 (1.3)	0.16[a]
At discharge			
Continuous use	8.8 (3.6)	9.4 (3.8)	0.32[a]
As required	1.7 (1.7)	1.4 (1.4)	0.33[a]
During the hospital stay			
Initiated	3.4 (2.5)	3.6 (2.5)	0.59[a]
Stopped	2.3 (2.0)	1.7 (1.9)	0.09[a]
Initiated and stopped	2.9 (2.7)	3.6 (5.0)	0.28[a]

[a] Student t-test

[b] Fishers exact test

Table 2 Categories of risk for drug-related problems identified during the hospital stay in the intervention and control groups. Results are presented as number of patients (%) with at least one risk factor within each category of risk.

	Intervention group (n=70)	Control group (n=71)
Changes of interchangeable drugs[a]	56 (80.0)	48 (67.6)
C/D interactions[b]	50 (71.4)	53 (74.7)
Less appropriate drug therapy[c]	29 (41.4)	49 (69.0)
Anti-cholinergic drugs	6 (8.8)	14 (19.7)
Long-acting benzodiazepines	13 (18.6)	30 (42.3)
Polypharmacy	14 (12.0)	11 (15.5)
Not possible to calculate creatinine clearance	7 (10.0)	45 (63.4)
Drugs that require therapeutic monitoring	36 (51.4)	42 (59.2)
Digoxin	26 (37.1)	25 (35.2)
Warfarin	17 (24.3)	15 (21.1)
Theofyllin	2 (2.9)	9 (12.7)
Problems with swallowing	8 (11.4)	6 (8.5)
Problems with allergy or similar	14 (20.0 %)	12 (16.9 %)

[a] Generic and therapeutic substitution according to regional interchangeable list

[b] C interactions: drug combination that could require dose adjustment; D interactions: drug combination that ought to be avoided.

[c] As specified by the National Board of Health and Welfare, Sweden. [Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi, SoS, 2003]

Table 3 The total number of unidentified drug-related problems (M-DRPs) and the number of medications associated with DRPs (P-DRPs) in the intervention and control groups. Results are presented as the number of DRPs within each group and as the median (1st - 3rd quartile).

	Intervention group		Control group	p value[c] Intervention (drug review and record information) vs Control	p value[c] Intervention (record information) vs Control	p value[c] Intervention (drug review and record information) vs Intervention (record information)
	Drug review and record information[a]	Record information[b]				
M-DRPs	76 1 (0-2)	299 4 (2-6)	733 9 (6-13.5)	< 0.001	< 0.001	< 0.001
P-DRPs	74 1 (0-2)	268 3 (2-5)	594 8 (5-10)	< 0.001	< 0.001	< 0.001

[a] Information regarding unidentified DRPs identified in the patient records and in the LIMM medication review form.

[b] Information regarding unidentified DRPs identified in the patient records only.

[c] Wilcoxon rank sum test

Table 4 Types of unidentified drug-related problems (M-DRPs) in the intervention and control groups. Results are presented as number of M-DRPs in each category.

	Intervention group		Control group	p value[c] Intervention (drug review and record information) vs Control
	Drug review and record information[a]	Record information[b]		
Need for additional drug therapy	10	27	58	< 0.001
Unnecessary drug therapy	32	113	171	< 0.001
Wrong drug	9	69	241	< 0.001
Dosage too low	3	17	44	< 0.001
Adverse drug reaction	15	33	75	< 0.001
Dosage too high	2	23	79	< 0.001
Compliance	0	0	0	not significant
Transferring error	1	8	24	< 0.001
Sub-optimal monitoring of drug treatment	4	9	41	< 0.001

[a] Information regarding unidentified DRPs identified in the patient records and in the LIMM medication review form.

[b] Information regarding unidentified DRPs identified in the patient records only.

[c] Wilcoxon rank sum test

Table 5 Clinical significance of unidentified drug-related problems (M-DRPs) in the intervention and control groups. Results are presented as number of M-DRPs in each category.

	Intervention group		Control group	p value[c] Intervention (drug review and record information) vs Control	p value[c] Intervention (record information) vs Control	p value[c] Intervention (drug review and record information) vs Intervention (record information)
	Drug review and record information[a]	Record information[b]				
No significance *(not specifically related or meaningful to the patient)*	18	76	197	< 0.001	< 0.001	< 0.001
Somewhat significant *(neutral in effect)*	33	104	215	< 0.001	< 0.001	< 0.001
Significant (*requiring care to a more acceptable and appropriate level)*	22	99	234	< 0.001	< 0.001	< 0.001
Very significant (*involving a potential or existing major organ dysfunction)*	3	20	85	< 0.001	< 0.001	0.009
Extremely significant (*life and death situation)*	0	0	2	0.16	0.16	NA

[a] Information regarding unidentified DRPs identified in the patient records and in the LIMM medication review form.

[b] Information regarding unidentified DRPs identified in the patient records only.

[c] Wilcoxon rank sum test

Table 6 The LIMM symptom-scoring form. Results are presented as number of patients with a symptom (%); n=70.

Dizziness	30 (43)
General fatigue	58 (83)
Memory deficiency	33 (47)
Sleeping difficulties	32 (46)
Dry mouth	52 (74)
Nausea	20 (29)
Constipation	31 (44)
Micturition difficulties	23 (33)
Pain	35 (50)
Cough	40 (57)

Table 7 Types of drug-related problems (M-DRPs) identified during the intervention period. Results are presented as number of M-DRPs in each category.

Wrong drug	151
Unnecessary drug therapy	136
Adverse drug reaction	118
Dosage too high	101
Need for additional drug therapy	100
Dosage too low	53
Sub-optimal monitoring of drug treatment	22
Non-compliance	6
Transferring error	3

Table 8 Types of action taken for attempting to resolve or prevent the drug-related problems during the intervention period.

Change of drug therapy	91
Withdrawal of drug therapy	88
Initiation of drug therapy	48
Closer monitoring	43
Decreased dose	41
Increased dose	8
Change in dosage interval	6
Change of drug formulation	4

Table 9 Health care practitioner satisfaction with the model of care during the intervention. Results are presented as medians (1^{st} -3^{rd} quartiles). Answers were obtained using six-point numerical scales: from 1 (not useful) to 6 (very useful).

	Physicians n=21	Nurses n=14
General opinion about the usefulness for the patient	5 (4-5)	6 (4.5-6)
General opinion about the usefulness for the health care practitioner	5 (5-5)	5 (5-6)
The usefulness of the LIMM symptom-scoring form	3 (3-5)	4 (3-5)
The usefulness of the medication review and monitoring	5 (5-6)	6 (5-6)
The advantage of physicians receiving a better decision basis for drug changes	5 (5-6)	5 (5-6)
The usefulness of a more individualised drug treatment	5 (5-6)	6 (5-6)
The usefulness of having the DRPs, plans, and actions taken documented	4 (3-5)	6 (5-6)
The advantage of discussing drug changes during rounds	5 (5-6)	6 (5-6)
The usefulness of the clinical pharmacist as a drug expert	5 (5-5)	5 (5-6)
The usefulness of the clinical pharmacist as a discussion partner in drug queries	5 (5-5)	5 (5-6)
The usefulness of the clinical pharmacist as support for drug choice, based on studies, evidence-based medicine and recommendations	5 (4-5)	6 (5-6)
The usefulness of the clinical pharmacist for identifying drug-related problems	5 (4-6)	6 (5-6)

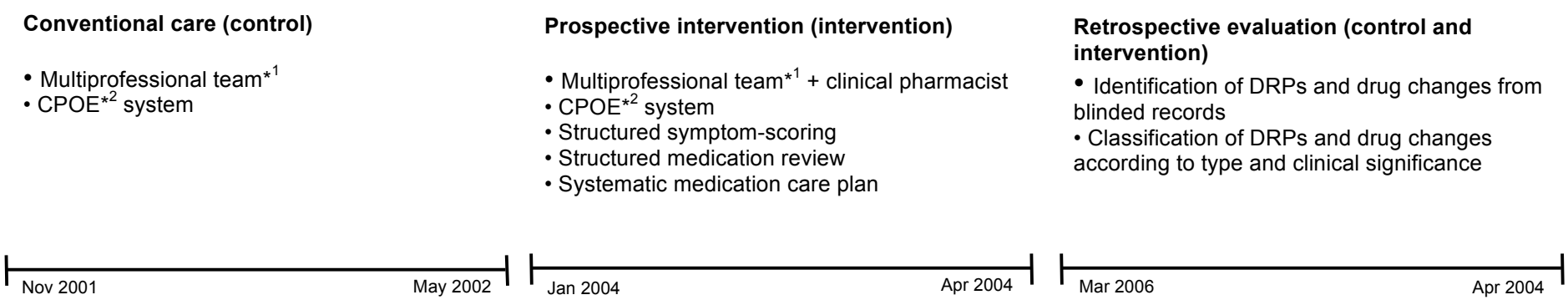

Figure 1. Study design