Medication review in patients using automated drug dispensing systems reduces drug related problems

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Effects of Medication Review on Drug-Related Problems in Patients Using Automated Drug-Dispensing Systems

A Pragmatic Randomized Controlled Study

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Abstract

Background: There are concerns that automated drug dispensing may increase inappropriate drug use. Automated dispensing could lead to perpetual repeating of drug therapies without the necessary re-evaluation.

Objective: The aim of this study was to examine the effect of a pharmacist-led medication review on drug-related problems (DRPs) in older patients receiving their drugs via automated dispensing.

Methods: This was a pragmatic randomized controlled study conducted in primary care. Patients were recruited from six Dutch community pharmacies. They were eligible if they lived at home, were aged ≥65 years, and used five or more different drugs, of which at least one had to be dispensed via an automated system. Patients were randomly allocated to receive a medication review at the start of the study (intervention group) or after 6 months (waiting-list group). Each patient was independently reviewed by two pharmacist reviewers. The results of these medication reviews were sent to the community pharmacist to be discussed with the patient's general practitioner (GP). The primary outcome measure was the number of DRPs leading to a recommendation for drug change. Secondary outcomes were the total number of drug changes and the number of drug changes related to a recommendation. In order to analyse drug changes, medication records were collected 6 months after the medication review or index date in the waiting-list group. Potential DRPs were classified using the DOCUMENT classification.

Results: There were no baseline differences between the 63 patients in the intervention group and the 55 patients in the waiting-list group with respect to age, sex, number of drugs per patient and type of drug prescribed. The mean number of DRPs per patient at baseline in the intervention group and waiting

list combined was 8.5, with no difference between the groups. At baseline, the mean number of DRPs leading to a recommendation for drug change was 4.5 per patient and did not differ between the two groups. After 6 months, the number of DRPs leading to a recommendation for drug change decreased by 29% in the intervention group versus 5% in the waiting-list group ($p < 0.01$). Recommendations for cessation of a drug were more frequently accepted than recommendations to add a new drug (82% vs 44%, $p = 0.01$).

Conclusions: This study shows that patients using automated drug dispensing have a high number of DRPs. Medication review decreases the number of DRPs among these patients. We recommend that all patients with automatic drug dispensing should have a thorough medication review by pharmacists and prescribers.

Background

At least 5% of hospital admissions are directly related to adverse drug reactions (ADRs).[1-4] Higher rates have been reported among elderly patients, who are likely to be receiving multiple medications for long-term illnesses.[1] In most studies, these ADRs were not only side effects but also drug-related problems (DRPs) such as prescribing errors, poor adherence and insufficient monitoring.[4] A recent study in the Netherlands suggested that almost half of these medication-related hospitalizations could be avoided.[2,5] That study also identified a relationship between drug-related hospital admissions and decreased cognition and poor medication adherence.[2,5]

Dosing aids may help patients adhere to their therapeutic regimens. Automated drug dispensing is a sophisticated dosing aid that provides patients with robot-dispensed unit doses. All drugs intended for one dosing moment are gathered in disposable bags and labelled with patient data, drug contents, and the date and time for intake.[6]

Automated drug dispensing is more likely to be offered to patients with a high probability of inappropriate drug use but cannot be considered a panacea for all such patients.[7,8] Firstly, for practical reasons not all dosage forms (e.g. powders, inhalers, ointments) can be dispensed using the distribution robot.[6,9] Secondly, automated drug dispensing may not solve inappropriate drug use, and may even aggravate it. Automated dispensing could lead to perpetual repeating of prescribed therapies without the necessary re-evaluation. It is therefore suggested that automatic dispensing should be combined with regular patient counselling and medication review.[8] In Finland, a medication review performed by the pharmacist is required before a patient can be enrolled in an automated dispensing programme.[10]

Community pharmacists in the Netherlands have limited experience with medication review. Therefore, we decided to support community pharmacists with an expert panel of pharmacist reviewers with experience in identifying DRPs in a pharmaceutical care plan.

The aim of the present study was to examine the effect of a community pharmacist-led medication review of DRPs in older patients receiving their drugs via automated dispensing.

Methods

Study Design

This was a pragmatic randomized controlled study. Patients were enrolled between October 2007 and February 2008.

Patients

Patients were recruited from six Dutch community pharmacies. Pharmacists were a conve-

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nience sample. They were invited to participate based on information from the provider of automated drug dispensing systems that these pharmacists had a sufficient number of home-dwelling patients using automated drug dispensing systems. Each community pharmacist invited two general practitioners (GPs) to participate in the study.

Patients were eligible if they used five or more medicines, were aged ≥65 years and lived at home. At least one of their medicines had to be dispensed via an automated system. In the Netherlands, patients are recruited for automatic dispensing mostly by referral from a GP when he/she suspects inappropriate drug use (e.g. complicated medication regimens, decreased cognition, [suspected] non-adherence or severe psychiatric problems).

Patients with automatic dispensing systems were informed about the medication review service by their pharmacist. Patients could decline participation. Because the pharmacists and GPs were introducing a new service, it was not feasible to review all the patients at the same time. Therefore, selected patients were randomized into two groups per pharmacy using computer-generated random numbers. Patients were allocated to an intervention group, which received a medication review at the start of the study, or to a 6-month waiting-list group.

Ethics and Patient Confidentiality

As the study did not involve a major invasion of the participant's autonomy and no standard care was withheld, no formal ethical approval was needed. Patients received written information about the study and were able to decline participation. In order to protect the patient's privacy, all medical data were anonymized by the community pharmacist using a randomly assigned unique number for each patient.

Intervention

For each patient, data from both the community pharmacy and the GP were collected by the community pharmacist and included drug dispensing records, information on co-morbidity and/or drug intolerance, relevant patient notes, and laboratory data (e.g. blood pressure, glycosylated haemoglobin and creatinine clearance). No face-to-face interviews with patients were conducted by the community pharmacists.

The data for each patient were independently reviewed by two independent pharmacists from a pool of five pharmacist reviewers (AF, HB, HK, JKD and MB). The pharmacist reviewers used in this study had several years of experience of medication review as well as in-depth knowledge of national clinical guidelines.

The reviewers used both implicit and explicit criteria to identify potential DRPs. Explicit criteria consisted of a list of clinical rules based on Dutch treatment and prescription guidelines. Examples of clinical rules were "Lack of appropriate treatment for secondary prevention for CHD [coronary heart disease] (antiplatelet, lipid-lowering, β-blocker [β-adrenoceptor antagonist], ACE-inhibitor)", "Lack of appropriate treatment for patients with diabetes mellitus and LDL [low-density lipoprotein] cholesterol >2.5 mmol/L (lipid lowering therapy)" or "No available monitoring data for blood pressure, lipids, glucose, BMI [body mass index] or data >1 year old in patients for whom these measurements are indicated in treatment guidelines".[11] Implicit criteria for identifying DRPs were based on a structural assessment by Cipolle[12] according to a rational order of indication, effectiveness, safety and compliance. The two reviewers reached consensus in a case conference. If no consensus was achieved, a third reviewer was consulted until consensus was reached. The results of these medication reviews were sent to the community pharmacist to be discussed in a case conference with the patient's GP within 4 weeks.

The waiting-list group patients underwent their medication review at time (t) = 6 months, i.e. 6 months after the intervention group. As a consequence, the waiting-list group was reviewed retrospectively by pharmacist reviewers using the data available at time (t) = 0. Before discussing the pharmaceutical care plan for the waiting-list group with the GP, the community pharmacist checked whether any medication changes had taken place between t = 0 and t = 6. We assumed that

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any medication change at t = 6 in the waiting-list group was a result of usual care. The follow-up of recommendations for the waiting-list group was not included in this study.

Data Classification

Drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification. Potential DRPs were classified using the DOCUMENT classification system[13] with modifications as described. Information concerning the DRPs consisted of the type and subtype of problem (see Appendix S1, Supplemental Digital Content 1, which shows the DOCUMENT classification system, http://links.adisonline.com/DAZ/A12).[14,15] The original DOCUMENT system was developed in accordance with the major requirements for a DRP classification system.[15,16] In addition to the original DOCUMENT classification system, we added five DRP subtypes. Within the DRP type 'Drug selection', DRP subtypes 'Lack of indication or unclear indication', 'Lack of effectiveness' and 'Contra-indication/intolerance' were added. Within the DRP type 'Toxicity or adverse reaction', DRP subtypes 'Risk of adverse effects' and 'Possible drug treatment in response to adverse effect' were added. See Appendix S2, Supplemental Digital Content, for a summary of these modifications.

All coding and classification was undertaken by one investigator (HK) and a student investigator (DT). Each investigator coded all data independently. When there were differences in coding, the investigators reached consensus in a case conference with a third investigator (either AF or MB).

Outcome Measures

After 6 months (t = 6), medication records were collected in order to analyse the drug changes. The outcomes could only be assessed for patients with complete medication records from t = 0 until t = 6. The primary outcome measure was the reduction in the number of DRPs leading to a recommendation for drug change. Secondary outcome measures were the total number of drug changes and the number of drug changes related to a recommendation.

Drug changes refer to prescription drugs and were defined as a cessation of a drug, a dose change, an addition of a drug, a replacement of a drug, a change in dose frequency/schedule or a drug formulation change. A drug change could be related to a recommendation from the treatment review, but could also be related to the process of usual care (not related to a recommendation). The total number of drug changes is the sum of drug changes related to a recommendation and drug changes not related to a recommendation. A qualitative process evaluation was performed by means of a questionnaire completed by the participating community pharmacists. The aim of this questionnaire was to reveal the opinion of the community pharmacists about the medication review process.

Sample Size Calculation

Based on a literature review we assumed that our intervention would result in an additional mean reduction of 1.5 DRPs (related to a drug-change modification) per patient in the intervention group. With a 95% confidence interval, power of 0.8 and a standard deviation of 2.5 for the number of medication-related problems per patient, we needed 45 patients in both study groups. Expecting a drop-out rate of 25%, we aimed at including 60 patients in both groups.

Statistical Analysis

All data were analysed using database (Microsoft Access®, 2003; Microsoft Corporation, Redmond, WA, USA) and statistical software (SPSS version 17.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for basic characteristics. Independent sample t-tests were applied for sex, age, number of prescription drugs and number of DRPs to test the difference between groups. Pearson chi-squared (χ^2) tests were used for each categorical variable. A paired t-test was used to test for differences in DRPs per patient between t = 0 and t = 6. A p-value <0.05 was considered statistically significant.

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Results

Six pharmacies recruited 125 patients aged ≥65 years. Seven patients were excluded after randomization but before the actual start of the medication review (t = 0) [figure 1]. Reasons for exclusion were death (2/125), admission to hospital (1/125), admission to nursing home (1/125), start of automated dispensing after t = 0 (2/125) and no medication data (1/125). At baseline (t = 0), 63 patients remained in the intervention group and 55 patients remained in the waiting-list group.

At baseline, there were no differences in age, sex and numbers of prescribed drugs in both groups (table I). Furthermore, there were no significant differences in the types of drugs prescribed. Antithrombotic agents were the most commonly prescribed drugs in both groups. In the intervention group, a mean of 8.6 potential DRPs per patient were found compared with 8.4 in the waiting-list group (p = 0.8). In both groups, DRPs were most often classified as either 'Monitoring' or 'Drug selection' (table I).

Between t = 0 and t = 6, eight patients in the intervention group were lost to follow-up: two had died, four had moved away and two patients were admitted to a nursing home. Two patients in the waiting-list group died between t = 0 and t = 6. At t = 6, 55 patients in the intervention group and 53 in the waiting-list group had complete medication records (figure 1).

Patients in the intervention group (n = 55) had a mean of 4.5 potential DRPs with a recommendation for drug change versus 4.4 in the waiting-list group (n = 53). At t = 6, mean DRPs per patient had decreased by 29% in the intervention group versus 5% in the waiting-list group (p < 0.01) [table II].

Between t = 0 and t = 6, the mean number of drug changes per patient was significantly higher among patients in the intervention group compared with patients in the waiting-list group (2.2 vs 1.0, p = 0.02). Of these drug changes, 62% (1.3/2.2) in the intervention group were related to a recommendation versus 20% (0.2/1.0) in the waiting-list group (p = 0.003) [table III]. Recommendations for cessation of a drug were more frequently adopted than recommendations to add a new drug (82% vs 44%, p = 0.01).

Interviews with the pharmacists revealed problems in the implementation of discussion points raised at case conferences between pharmacists and GPs. This included difficulties in making appointments as well as differences in the receptiveness of GPs to adapt the medication regimen in order to solve DRPs. See table S1, Supplemental Digital Content, which shows the participating community pharmacists' opinions about the medication review process.

Discussion

This study shows the relevance of medication review in elderly patients receiving drugs via automated dispensing. These patients had a high mean number of DRPs (8.5 per patient). We

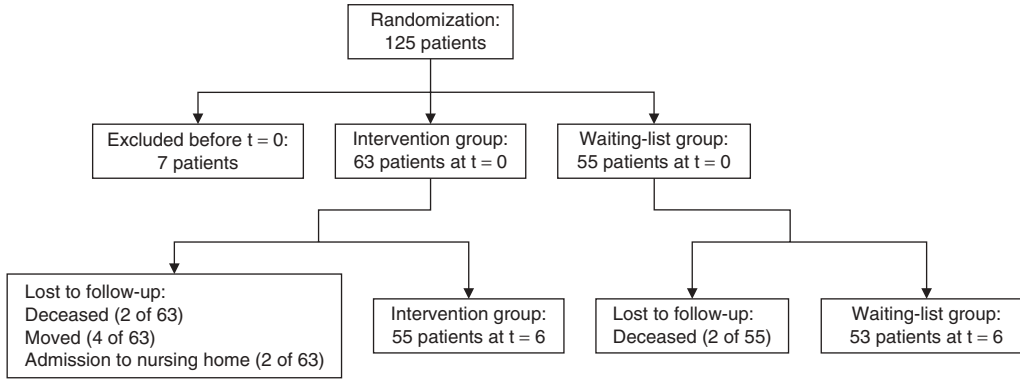

Fig. 1. Study flow chart. **t = 0** signifies baseline (0 months); **t = 6** signifies 6 months.

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Table I. Baseline sociodemographic and drug-related characteristics of patients in the intervention and waiting-list groups

Characteristic	Intervention group (n = 63)	Waiting-list group (n = 55)	p-Value
Female [n (%)]	48 (76)	33 (60)	0.1
Age [y, mean ± SD]	78.7 ± 6.8	80.0 ± 7.2	0.3
Number of prescription drugs per patient [mean ± SD]	10.3 ± 3.1	9.8 ± 3.6	0.4
Number of drugs by automated dispensing per patient [mean ± SD]	6.7 ± 2.2	7.2 ± 2.6	0.3
All prescribed drug groups (ATC) at t = 0 [n (%)]			
Antithrombotic agents (B01A)	46 (73)	42 (76)	0.7
β-Blocking agents (C07A)	35 (56)	38 (69)	0.1
Agents acting on the renin-angiotensin system (C09)	36 (56)	31 (56)	0.9
Lipid-modifying agents (C10A)	29 (46)	30 (55)	0.4
Benzodiazepine derivatives (N05BA, N05CD)	33 (52)	23 (42)	0.3
High-ceiling diuretics (C03C)	28 (44)	28 (51)	0.5
Drugs for peptic ulcer and GORD (A02B)	29 (46)	27 (49)	0.8
Drugs used in diabetes (A10)	30 (48)	24 (44)	0.7
Drugs for obstructive airway diseases (R03)	20 (32)	14 (26)	0.5
Low-ceiling diuretics (C03A, C03B, C03E)	17 (27)	16 (29)	0.8
Number of DRPs (total) [mean per patient ± SD]	**539 [8.6 ± 2.8]**	**455 [8.4 ± 2.8]**	**0.8**
D(rug selection)	140	129	0.4
O(ver or underdose prescribed)	78	48	0.1
C(ompliance)	5	2	0.6
U(ntreated indications)	86	72	0.9
M(onitoring)	181	145	0.6
T(oxicity or adverse reaction)	49	59	0.1

ATC = Anatomical Therapeutic Chemical classification; **DRPs** = drug-related problems; **GORD** = gastro-oesophageal reflux disease; **t = 0** signifies baseline (0 months).

identified only one study with a comparable high mean number of DRPs (7.8 per patient);[17] most studies identified a mean of less than five DRPs per patient in home-dwelling ambulant populations.[15,18-20]

Medication review increased the number of drug changes and decreased the mean number of potential DRPs per patient by 29%. This raises the question of whether drug therapy is appropriately monitored in these elderly patients. In the Netherlands, prescriptions for such patients are often repeated based on medication lists, without critical re-evaluation.[6] This is confirmed by the finding that medication review by study pharmacists revealed a mean of 4.5 potential DRPs with a recommendation for a drug change per patient.

The most commonly suggested recommendation was cessation of a particular drug. Similar findings on the type of recommendations have been reported previously.[19,21]

In the present study, 29% of the recommendations led to an actual change in drug therapy. Although this seems a rather low percentage, it is comparable with the results of earlier studies in the Netherlands in which 28–30% of the recommendations suggested by community pharmacists were implemented after case conferences.[18,19] Studies in other countries have revealed a somewhat higher implementation rate (55–58%).[20,22,23] Under more controlled conditions (in hospital or using experienced clinical pharmacists), 75–78% of suggested actions were implemented.[17,21] The low proportion of recommendations that resulted in drug changes is presumably a reflection of the acceptance rate by GPs. This could partly be explained by the process of medication review in the present study. The reviews were conducted by pharmacist reviewers at a distance and the GP was not involved in an early stage of the medication review process. Furthermore, there is a structural lack of shared expectations of collaboration

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between community pharmacists and GPs, and a lack of routine face-to-face interactions.[24] Stricter structuring of the cooperative relationship between GPs and pharmacists will result in more opportunities for pharmacists in terms of their advisory and interventional roles.[25-27] GPs also seem to be more reluctant to change a medication regimen in patients with a more complex medical profile, as was the case with patients in the present study.[19] Moreover, recommendations are based on general treatment guidelines that GPs might not always find appropriate for the elderly population (e.g. initiating HMG-CoA reductase inhibitor [statin] therapy might not be considered relevant in a patient with a relatively short life expectancy). There are no evidence-based standards for the treatment of patients with multiple pathologies, leaving the GP to treat the individual patient to the best of his/her knowledge and judgement.[28] Research into the underlying reasons for low acceptance of recommendations is therefore necessary.

In the present study, we found no indication that patients showed any resistance toward changes in medication. Future studies should investigate whether this assumption is valid and whether face-to-face interviews with patients using automated dispensing might identify additional DRPs.

The number of drop-outs was higher in the intervention group (n = 8) than in the control group (n = 2). Although medication review could

Table II. Drug-related problems (DRPs) with a recommendation for drug change for patients in the intervention and waiting-list groups at t = 0 and t = 6

DRP type and subtype	Intervention group (n = 55)		Waiting-list group (n = 53)	
	t = 0	t = 6	t = 0	t = 6
D(rug selection)	**92**	**64**	**87**	**84**
duplication	5	3	9	9
drug interaction	6	4	7	7
wrong dosage form	3	2	5	5
lack of indication or unclear indication[a]	39	28	39	38
lack of effectiveness[a]	31	21	26	24
contraindication/intolerance[a]	8	6	1	1
O(ver or underdose prescribed)	**57**	**39**	**40**	**37**
dosage too high	30	24	18	16
dosage too low	12	5	14	14
inappropriate dose frequency/schedule	15	10	8	7
C(ompliance)	**3**	**2**	**0**	**0**
taking too little	0	0	0	0
taking too much	3	2	0	0
U(ntreated indications)	**60**	**42**	**61**	**59**
condition not adequately treated	47	37	45	43
preventive therapy required	13	5	16	16
M(onitoring)	**1**	**1**	**2**	**1**
laboratory monitoring required	0	0	0	0
non-laboratory monitoring required	1	1	2	1
T(oxicity or adverse reaction)	**36**	**27**	**41**	**40**
toxicity evident	0	0	0	0
risk of adverse effects[a]	30	23	32	31
possible drug treatment in response to adverse effect[a]	6	4	9	9
Total (mean per patient)	**249 (4.5)**	**175 (3.2)**	**231 (4.4)**	**221 (4.2)**

a Modifications made to the original DOCUMENT system for the current study.

t = 0 signifies baseline (0 months); **t = 6** signifies 6 months.

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Table III. Type of drug change per patient between t = 0 and t = 6 in the intervention and waiting-list groups

Type of drug change	Intervention group (n = 55)[a]	Waiting-list group (n = 53)[a]
Cessation of drug	32/39 (82)	5/9 (44)
Dose change	16/30 (53)	2/13 (15)
Addition of drug	15/34 (44)	2/23 (9)
Replacement of drug	9/15 (60)	1/6 (17)
Dose frequency/schedule change	1/1 (100)	0/0 (0)
Drug formulation change	1/1 (100)	0/0 (0)
Total	**74/120 (62)**	**10/51 (20)**

a Number related to a recommendation (%).

t = 0 signifies baseline (0 months); **t = 6** signifies 6 months.

lead to identification of clinical problems that result in admission to hospital or a nursing home, in this study, we have no reason to assume that medication review actually resulted in such admissions in the intervention group. It is more likely that the differences were due to chance.

The medication review process as presented in this study is probably not a suitable method for daily clinical practice. Half of the community pharmacists stated that the pharmacist reviewers had a lack of information. Almost all of them said they preferred to conduct medication reviews themselves in the future. However, the question arises as to whether community pharmacists have sufficient expertise to perform such reviews. A practical solution could be for community pharmacists, who start the medication review, to participate in a course in which feedback on reviews from expert reviewers (and portfolio building) plays an essential role.

There are some potential limitations associated with this study. First, we used intermediate primary outcomes (i.e. the change in the number of potential DRPs and drug changes). There is no guarantee that reducing DRPs will have a positive impact on all clinical outcomes (e.g. hospitalizations and quality of life).[29-31] However, a correlation between the presence of DRPs and the control of cardiovascular risk factors, quality of life and healthcare costs has recently been established.[32] In our study, the reduction in the number of DRP subtype 'Risk of adverse effects' was due to the cessation of (mostly) CNS drugs. This might be correlated with a reduction in falls, because medication review in care homes has been associated with a reduction in the number of falls.[23] In the latter study, almost one-third of the medicines that were ceased were CNS drugs, which are a well established cause of falls.[23] It is also important to note that only drug changes could be measured; the follow-up of recommendations with solutions other than drug changes (e.g. instructions to patients or additional monitoring) was not documented.

Secondly, the medical information for each patient (e.g. indications and laboratory data) was limited because we used only readily available data. A full clinical medication review, including complete medical records and a patient interview, might have revealed additional DRPs.[33]

Thirdly, each medication review was conducted by two reviewers from a pool of five well trained pharmacist reviewers. This raises the question of whether less experienced reviewers would have identified identical DRPs. On the other hand, the use of experienced reviewers probably led to more complete and standardized medication reviews.

Finally, patients in both groups were treated by the same pharmacists and GPs. Recommendations in the intervention group could have led to some contamination in the waiting-list group. However, because there were very few changes in the waiting-list group, we believe that any such contamination would have been relatively small.

Conclusions

This study indicates that the quality of pharmacotherapy for patients with automated drug

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dispensing can be improved. We recommend that all patients with automatic drug dispensing should undergo a thorough medication review by pharmacists and prescribers.

Future research should focus on the impact of a clinical medication review in patients with automatic drug dispensing. Patient interviews can reveal user-related problems with automatic drug dispensing, and may also serve to check the use of drugs for self-administration.

The optimal frequency for performing medication reviews and follow-up will probably differ between individual patients. Future studies may help provide recommendations on the timing and frequency of medication reviews for patients with automatic drug dispensing.

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All authors declare that they have no conflict of interests that are directly relevant to the content of this study.

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