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CLINICAL PHARMACY RESEARCH REPORT

Cost-consequence analysis evaluating multifaceted clinical pharmacist intervention targeting patient transitions of care from hospital to primary care

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Aims: Drug-related problems are a common complication in the transition from hospital to primary care and are associated with morbidity and increased health care costs. In this study, we evaluated the cost and consequences of a comprehensive pharmaceutical intervention compared with usual care, comprised of a medication review and patient interview before discharge and follow-up for polypharmacy patients.

Methods: This economic evaluation was embedded within a randomized clinical trial. Patients were randomized to either the basic intervention group (n = 493) which received a medication review, the extended intervention group (n = 476) which received a medication review, discharge interview, and follow-up, or the control group (n = 498) which received standard care. Total health care costs were estimated over a period of 180 days at individual patient level from a health sector perspective.

Results: The mean cost per patient was lower in the intervention groups (basic, €16 748; extended, €15 631) compared with the control group (€17 288), although these differences did not reach statistical significance. The costs of additional time used on medication reviews, patient interviews, and follow-ups (€88) were outweighed by a decrease in costs of readmissions. The results of the clinical study favored the extended intervention group on clinical outcomes, with statistical significance on a composite of readmissions or emergency department visits within 180 days after inclusion (hazard ratio 0.77, 95% confidence interval 0.64-0.93).

Conclusions: This comprehensive pharmaceutical intervention was not costly and positive effects were seen in the clinical outcomes, thereby reaching a decrease in total cost per patient on average. The results thus indicate that the intervention is cost-effective and that the positive net effects can justify costs of the intervention.

KEYWORDS

clinical pharmacists, cost analysis, economics, pharmaceutical, pharmacy service, hospital, polypharmacy

1 | INTRODUCTION

Polypharmacy patients are at risk of drug-related problems when transferred from hospital wards to primary care. The probability of inappropriate medication and adverse events increases with the number of prescriptions per patient,[1,2] and each year, 69 000 to 162 000 incidents of drug-related hospital admissions occur in Denmark.[3] Pharmacist-led medication reviews have been suggested as a solution to some of these problems.[4] Costs and effects of clinical pharmacy services, including medication reviews, have been investigated in primary studies and literature reviews.[4–9] A randomized controlled trial from Ireland comprised of a structured pharmacist review of medications supported by computerized clinical decision support software demonstrated a reduction in adverse drug reactions, and was indicative of cost-effectiveness.[5] A different result was found in a Swedish randomized controlled trial which reported that a composite in-hospital clinical pharmacist service (with medication review, drug treatment discussion with the patient at discharge, and medication report) was not cost-effective because of non-significant effects in the EuroQol five-dimensional questionnaire results (EQ-5D: an instrument for the measurement and valuation of health[10]) and an increase in costs.[6] A review of different types of medication reviews found that robust health economic studies in the area are rare, but that the value of the service is generally accepted by health professionals despite the lack of evidence on costs and clinical effects.[7] Three reviews assessed clinical pharmacy interventions, including medication reviews in hospitals, and found that economic evaluations of such interventions suffer from methodological limitations.[4,8,9] Some "good quality" studies revealed reductions in costs and in number of drug-related readmissions that compared clinical pharmacy interventions to usual care, but not all. The authors concluded a need for clinical and cost effectiveness evidence to justify existence of, or extension of, routine clinical pharmacy.[9] These somewhat diverse results in the literature point toward a need for more evidence and health economic evaluations, with a broad perspective on costs and outcome measures.

Recently, we reported on the effects of a multifaceted pharmacist's intervention comprised of a structured patient-centered pharmaceutical medication review, a pharmaceutical discharge interview with the patient concerning medicine status, and follow-up with the patient and primary sector after discharge.[11] The study was carried out in a publicly financed cross-sector setting, and several clinical outcomes were used to assess whether to implement the service. Along with the clinical trial, a health economic evaluation was also carried out. The objective of the economic evaluation was to estimate the cost and consequences of a multifaceted clinical pharmacist intervention, and the difference in average costs per patient across the three patient groups (control, basic intervention, and extended intervention) in the trial. The overall aim of this study was to assess the cost and consequences of each intervention arm for comparison with usual care.

2 | METHODS

This economic evaluation followed the international standards for conducting and reporting health economic evaluations of health improvement interventions by the Consolidated Health Economic Evaluation Reporting Standards.[12] The study was designed as a randomized controlled intervention, and the study protocol was approved by the Danish Data Protection Agency. The national committee on Health Research Ethics found that the study did not need ethical approval according to Danish law. Patients admitted to the emergency department at four hospitals in Denmark (Odense University Hospital, Odense and Svendborg; Holbæk Hospital, Holbæk and Regional Hospital Viborg, Viborg) were randomized into the following three groups: the control group (usual care during and after the hospital stay), the basic intervention group (pharmaceutical medication review), and the extended intervention group (pharmaceutical medication review, pharmaceutical discharge interview with the patient concerning medicine status, and follow-up including primary sector after discharge).

2.1 | The intervention

A full account of the intervention is described in the clinical paper.[11] In brief, patients assigned to the control group received usual care during the hospital stay (n = 498), and hence no clinical pharmaceutical effort. The basic intervention group (n = 493) had a medication review during admission carried out by a clinical pharmacist, and suggestions for changes were registered in the patient chart and communicated to the physician in charge if possible. The extended intervention group (n = 476) received a similar medication review plus a printed version of the medication list and a 30-minute discharge interview with the clinical pharmacist, along with a summary of medication changes. Further, patients in the extended intervention group received a follow-up interview 3 to 5 days after discharge to evaluate the discharge interview. In addition to this, a summary note with information on changes in dose, new medicines, and drug discontinuations was sent to the general practitioner (GP) and, if relevant, the nursing home. The GP, caregiver, and primary care pharmacy were contacted by phone if changes were necessary to act upon (eg, deletion of old prescriptions) approximately three work days after discharge. Finally, they conducted a follow-up interview 180 days post discharge.[11]

Patients were included if the following inclusion criteria were met: above 18 years of age, had polypharmacy (defined as five or more prescribed drugs on a daily basis), spoke and understood Danish, were referred for emergency admission, and had the ability to give informed consent or relatives to do so. Patients were excluded if they participated in other clinical pharmaceutical trials, suffered from severe dementia, or were terminally ill. Block randomization was carried out (blocks of four and six) using the sequentially numbered opaque sealed envelope technique. The randomization to intervention arm groups was initially blinded for both patients and health professionals, but revealed after the medication review. The study took place at hospitals in the Danish health care sector, which is a tax funded system with universal health care coverage. As the project aimed at reducing medication errors during and after the transition from hospital to primary sector, it may affect the resources used both in hospitals and at the GP and therefore the costs of contacts to GPs were included in the analysis.

2.2 | Study perspective

This study evaluated the intervention from a broad health sector perspective, which included direct costs for the hospital, primary care, and medical costs. Our evaluation shows how patients' use of resources is changed across health sectors from the point of inclusion until 6 months after.

2.3 | Health outcomes

In the clinical trial, health outcomes were measured by comprising data on events from national registers.[11] The outcomes from the clinical study were readmissions, defined as an admission within 30 and 180 days after the index admission, a composite of readmissions and emergency department visits. Secondary outcomes were all-cause mortality, drug-related mortality, and drug-related readmissions within 30 and 180 days. The type of economic evaluation was cost-consequences where clinical outcomes are listed along with the costs.[13]

2.4 | Resource use and costs

Direct health care costs were considered (ie, costs related to the intervention [medication review time, preparation, coordination between sectors, and follow-ups]) and to the use of health care (hospital admissions, emergency contacts, outpatient visits, and general practitioner contacts). Costs of medication include prescription medication only. Data on costs of the intervention were obtained from records of working hours completed by the clinical staff. Data on use of health care were collected on an individual basis from the National Patient Register for hospital contacts and the National Health Service Register for GP services. Registry data was collected from the years 2013 to 2015. Estimates of prices on use of inpatient and outpatient hospital care were determined individually for each patient from the National Patient Register[14] and based on Diagnosis Related Groups (DRG) from the Danish reimbursement system. Prices of the intervention were estimated for each individual by multiplying average salaries for the implicated professions with recorded time use. Costs were reported in Euros. All health care costs were discounted at appropriate rates to reflect 2016 prices, and were derived from national registers.

2.5 | Choice of model and assumptions

Cost-consequence models analyze costs and consequences separately so that interpretations can be made on each outcome in comparison to the cost of the intervention. Intervention costs were estimated by multiplying an hourly wage by the time used by the pharmacist on the intervention. Our estimate did not include overhead or training of personnel. According to the Danish DRG reimbursement system for hospitals, outpatient visits to hospitals are priced such that regardless of the number of visits in 1 day, the fee reflects the most expensive of the visits. GPs in Denmark are paid a capitation fee per citizen enrolled in the practice per year, which constitutes around 50% of total yearly pay, and another fee for services at each consultation. The prices in our data reflected the latter. The cost of medication was estimated as the price a pharmacy receives when distributing the drug, which is a summary of the price paid by the patient plus the reimbursement by the public health insurance.

The clinical study found some variations in outcomes across sex and age, and it identified that the risk of drug-related admission increases with age.[3] Because age might be a source of variability, the sensitivity of the main results was analyzed[13] by dividing the population into finer subgroups by gender, age (over and under 65 years of age), and intervention cost variability. For the latter, it was examined whether the total costs changed considerably when varying the hourly wage rate of the pharmacists providing the intervention. This was done by increasing the wage rate by 36.0%, which reflects the rate at effective work time provided by 1250 hours instead of the base case of full-time minus holidays given by 1720 hours.

2.6 | Analytic methods

The statistical analysis of data was based on the intention to treat analysis. All data were analyzed with statistical software R (©The R foundation, version 3.3.1: R Foundation for Statistical Computing, Vienna, Austria). The control and intervention groups were compared using descriptive statistics and tested by t tests for continuous variables and chi-squared tests for categorical variables. Data on use of resources and costs that are following a non-normal distribution were tested with Mann-Whitney U rank sum tests. The derivation of clinical outcomes was accounted for in the clinical study.[11] Statistical significance was defined at a 5% significance level. Results were presented by means (confidence interval [CI]) for all variables included in the cost analysis.

3 | RESULTS

Overall, 1499 patients were randomized and a total of 1467 patients were included in the analysis of costs. There were no noteworthy differences between the randomization groups in the baseline

TABLE 1 Baseline characteristics of patients enrolled in the randomized controlled trial

	Usual care group, *n* = 498	Basic intervention group, *n* = 493	Extended intervention group, *n* = 476	*P* value
Gender, male (%)	220 (44.2)	245 (49.7)	214 (45.0)	0.171
Age, median (IQR)	73 [65, 80]	72 [63, 80]	71 [63, 79]	0.25
Number of admissions 1 year prior to inclusion, median (IQR)	2 [1, 3]	2 [1, 3]	2 [1, 3]	0.946
Number of days in hospital at the inclusion admission, median (IQR)	4 [2, 8]	3 [1, 7]	3 [2, 8]	0.433

Abbreviation: IQR, interquartile range.

TABLE 2 Unit cost per item included in the analysis, €

Cost component, mean (range)	Unit cost	Description	Source
Pharmacist hour	€ 46	Average hourly wage rate of a pharmacist at a public hospital	Mini HTA-scheme[a]
Hospital doctor hour	€ 63	Average hourly wage rate of a public hospital doctor	Mini HTA-scheme[a]
Caretaking nurse hour	€ 31	Average hourly wage rate of a caretaking nurse at a public hospital	Mini HTA-scheme[a]
Admission service	€ 3848 (18.56-131.800)	Average cost of a hospital service or procedure at admission for patients included in the study	Danish health data authorities[b]
Emergency department visit	€ 103 (102.7-103)	Average cost of an emergency department visit (not including operations or major procedures) for patients included in the study	Danish health data authorities[b]
GP services	€ 11.5 (3.6-262.2)	Average cost of a GP service for patients included in the study	The general practitioners association table of fees[c]
Medication costs	€ 22.8 (1.95-4066.11)	Average cost per medication for patients included in the study	Danish health data authorities[d]

Abbreviations: GP, general practitioner; HTA, Health Technology Assessment.
[a] See http://www.ouh.dk/wm122682.
[b] See http://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2016.
[c] See https://www.laeger.dk/PLO-honorarer-og-takster.
[d] See http://esundhed.dk/sundheds%C3%B8konomi/medicinpriser/Sider/medpris001.aspx.

characteristics as described in Table 1. The hospital length of stay, when patients were included in the study, was 1.0 day higher on average in the control group, although not reaching statistical significance (P = 0.433). As seen in Table 2, the cost per work hour for a clinical pharmacist was € 46.0; a GP service in our sample was € 11.5 on average, and a unit of prescribed medication was € 22.8 on average. Hospital admissions had the highest unit price at € 3848 on average.

3.1 | Incremental costs and outcomes

In Table 3, use of resources is reported by median (and mean) along with P-values testing for statistically significant differences between: (a) usual care and basic intervention, P-value (0,1), and (b) usual care and extended intervention, P-value (0,2). Time for the pharmacist and other personnel groups was provided in the upper part of Table 3 and was comprised of time used for the different elements in the intervention. The basic intervention required 26 minutes of intervention on average whereas the extended intervention required nearly 2 hours, which is in accordance with the intervention design. The average use of in-hospital services after discharge were lower in the extended intervention group compared with the usual care group, and the difference in number of average admissions per patient was statistically significant (P < 0.001). The average use of GP services and medicine consumption after discharge was lower in the extended intervention group as well, though not reaching statistical significance (P = 0.8711), (P = 0.1509). The average costs were estimated and reported as mean cost per patient in the groups and SD in Table 4. The costs of the basic intervention and extended intervention were € 20 and € 88, respectively. The average hospital costs comprised by resource use in Table 3 was highest in the usual care group at € 16 802, and lower in the basic and extended intervention groups, correspondingly, but this difference did not reach statistical significance (P = 0.074). Neither did the difference in costs of GP services, where the intervention groups showed a slightly higher average than the control group (P(0,1) = 0.1652; P(0,2) = 0.9746). Costs of drug-related admissions were statistically significantly higher in the basic intervention and extended intervention groups compared with usual care (P(0,1) = 0.031; P(0,2) = 0.007). Medication costs were € 250 on average in the usual care group, which was higher than the basic intervention group at € 225 and the extended intervention group at € 226. Overall costs were the lowest in the extended intervention, where the total costs difference between usual care and the extended intervention reached € 1657 on average. Clinical outcomes are provided in Table 5 and comprise results of the clinical study measures. The primary outcome was number of patients experiencing either admission or emergency department visit within 180 days after inclusion. The number was lower in the extended intervention group and statistically significant (Hazard Ratio [HR] 0.77, CI 0.64-0.93). The extended intervention group also had statistically significant effects on number of patients who experienced readmissions within 30 days (HR 0.62, CI 0.46-0.84) and readmissions within 180 days (HR 0.75, CI 0.62-0.90). The extended intervention appears to decrease drug-related admissions also, but the effects are statistically insignificant (HR 0.80, CI 0.59-1.08).

3.2 | Supplementary analysis

Total costs on average for specified subgroups are given in Table 6. Costs are lower on average for the extended intervention group, specifically in the subgroup analyses of men with statistical significance (P (0,2) = 0.02). Lower costs were also noted in men under 65 years, women overall, and women above 65 years, but these differences were not statistically significant. The impacts on total costs from varying the pharmacists' wage rate up by 36% (from €46 to €63 per hour) were € 16 732 (base case € 16 725) in the basic intervention group and € 15 662 (base case € 15 631) in the extended intervention group. The results followed the primary analysis and the impact on the overall result was minor as total costs for the extended intervention increased 0.2% compared with the base case.

TABLE 3 Resource utilization, average per patient

	Usual care group, *n* = 498	Basic intervention group, *n* = 493	Extended intervention group, *n* = 476	*P* value (0,1)[a]	*P* value (0,2)[a]
Resource use for the intervention, mean					
Medications review during hospitalization					
Pharmacist hours	0	0.43	0.46		
Hospital doctor hours	0	<1 min	<1 min		
Caring personnel hours	0	<1 min	<1 min		
Compliance-improving initiatives during admission					
Pharmacist hours	0	0	0.03		
Interview at discharge					
Pharmacist hours	0	0	0.56		
Follow-up (3-5 days)					
Pharmacist hours	0	0	0.51		
Care personnel hours	0	0	<1 min		
Follow-up <6 months (after inclusion)					
Pharmacist hours	0	0	0.04		
Follow-up (at 6 months)					
Pharmacist hours	0	0	0.31		
Hospital resource use, mean (CI)					
Number of admissions	1.94 (1.82;2.05)	1.90 (1.79;2.02)	1.68 (1.58;1.78)	0.5951	0.0007[c]
Number of readmissions[b]	0.35 (0.28;0.42)	0.33 (0.25;0.40)	0.23 (0.17;0.29)	0.5006	0.0139[c]
Number of in hospital days	11.61 (10.24;12.97)	11.11 (9.87;12.35)	9.62 (8.45;10.79)	0.424	0.0352[c]
Number of acute visits	0.30 (0.22;0.38)	0.26 (0.20;0.32)	0.23 (0.17;0.29)	0.8484	0.3499
Number of drug-related admissions	0.27 (0.21;0.32)	0.29 (0.23;0.36)	0.23 (0.18;0.29)	0.8878	0.111
GP resource use, mean (CI)					
Number of services at GP	22.0 (20.65;23.36)	23.80 (22.31;25.30)	22.27 (20.89;23.65)	0.1694	0.8711
Medicines consumption, mean (CI)					
Number of prescribed medications	25.62 (23.83;27.41)	25.37 (23.72;27.01)	24.43 (22.67;26.20)	0.9027	0.1509

Abbreviations: CI, confidence interval; GP, general practitioner.
[a] *P*(0,1) tests H0: usual care differ from basic intervention, *P*(0,2) tests H0: usual care differ from extended intervention.
[b] Admissions less than 30 days after discharge from hospital.
[c] $P \leq 0.05$.

4 | DISCUSSION

In this cost consequence analysis of a comprehensive pharmacist intervention, the results favored the extended intervention group as the total costs were lower on average. In the base case analysis, total costs differed by € 540 between usual care and basic intervention and € 1657 between basic intervention and extended intervention on average, largely driven by difference in the costs related to admissions to the hospital. The differences in total costs were not statistically significant. In addition, the intervention demonstrated a clinical effect on admissions and acute visits within 180 days and on readmissions within 30 days.

It was observed that a higher number of patients opted out of the extended intervention group, withdrawing consent and thereby also withdrawing from the intention to treat analysis. This was attributed to the burden of participating, as some patients did not have the

TABLE 4 Estimated average cost per patient (€), mean (CI)

	Usual care group, *n* = 498	Basic intervention group, *n* = 493	Extended intervention group, *n* = 476	*P* value (0,1)[a]	*P* value (0,2)[a]
Intervention costs	0	19.98 (18.98;20.99)	88.04 (84.44;91.63)		
Hospital costs-hereof	16 802 (15 296.98;18 307.40)	16 240 (14 727.83;17 752.37)	15 072 (13 562.34;16 580.70)	0.5451	0.0744
drug-related admission costs	1171 (882.29;1459.09)	1560 (1090.63;2029.4)	1348 (970.27;1726.28)	0.0311[b]	0.0074[b]
GP	245 (229.00;260.03)	269 (251.01;286.66)	256 (237.54;274.05)	0.1652	0.9746
Medication costs	250 (200.25;299.66)	225 (200.26;250.17)	226 (198.76;254.21)	0.1511	0.9746
Total costs	17 288 (15 780.48;18 794.97)	16 748 (15 232.79;18 263.82)	15 631 (14 120.26;17 141.86)	0.6036	0.1083

Abbreviations: CI, confidence interval; GP, general practitioner.
[a] *P*(0,1) tests H0: usual care differ from basic intervention, *P*(0,2) tests H0: usual care differ from extended intervention. Test by nonparametric Mann-Whitney U rank sum test.
[b] $P \leq 0.05$.

TABLE 5 Clinical outcomes

	Usual care group	Basic intervention group	Extended intervention group	Hazard ratio, basic intervention vs usual care group	Hazard ratio, extended intervention vs usual care group
Composite endpoint, readmission or ED visit within 180 days, *n* (%)	243 (48.8%)	233 (47.3%)	193 (40.5%)	0.94 (0.79-1.13)	0.77 (0.64-0.93)
Readmission within 180 days after inclusion, *n* (%)	243 (48.8%)	233 (47.3%)	189 (39.7%)	0.95 (0.79-1.13)	0.75 (0.62-0.90)
Readmission within 30 days after inclusion, *n* (%)	111 (22.3%)	98 (19.9%)	68 (14.3%)	0.89 (0.68-1.17)	0.62 (0.46-0.84)
ED visit, *n* (%)	21 (4.2%)	19 (3.9%)	15 (3.2%)	0.91 (0.49-1.69)	0.74 (0.38-1.44)
Died within 180 days after inclusion, *n* (%)	50 (10.0%)	42 (8.5%)	54 (11.3%)	0.84 (0.53-1.32)	1.05 (0.68-1.63)
Drug related readmission within 180 days after inclusion, *n* (%)	96 (19.3%)	95 (19.3%)	75 (15.8%)	0.99 (0.75-1.32)	0.80 (0.59-1.08)
Drug related readmission within 30 days after inclusion, *n* (%)	38 (7.6%)	34 (6.9%)	24 (5.0%)	0.90 (0.56-1.42)	0.65 (0.39-1.09)
Drug related death within 180 days after inclusion, *n* (%)	6 (1.2%)	3 (0.6%)	5 (1.1%)	0.60 (0.14-2.52)	0.83 (0.22-3.11)

Abbreviation: ED, emergency department.

physical or mental capacity to take part in the intervention. Despite this, the differences between the groups were not statistically significant at baseline, and the cost analysis was made without adjustment for personal characteristics.

The economic evaluation followed the clinical trial, and hence drew upon its internal validity from a thorough randomization, comprehensive intervention design, and existing data collection. The standard deviations following the estimated costs were fairly large, which was a manifestation of the highly skewed distribution of costs. However, the aim of the evaluation was to estimate total costs and consequences of the intervention, and because the study was powered to detect statistical significance in the clinical outcomes, it should not necessarily be expected for the differences in average cost per patient.

Compared with studies evaluating hospital costs in similar health care systems,[5,6,15] the pharmacist wage rate and hospital costs were assessed in the same way. Therefore, while the calculated costs might not reflect opportunity costs, they are comparable to other economic evaluations in the field.

Previous economic evaluations of pharmacist's interventions suffer from a lack of suitable control groups,[15] a lack of inclusion of intervention costs,[9] and an unclear perspective or insufficient description of costs.[16] These potential problems were handled in the study as the control group was chosen randomly and all pharmacists registered time used for the intervention, which was included in the cost analysis. Cost results were in line with previously published literature that yielded cost savings,[4,5,9] but opposite to the study most similar to our study.[6] This study adds to the body of literature by being larger and more intensive in the extended intervention arm.[5,6,11]

One purpose of a randomized clinical trial is to provide internal validity, but a point of attention should be drawn to whether the external validity of the study suffers from the randomized clinical trial process. In general, patients are selected on the basis of a set of criteria with the purpose of being able to show a treatment effect in as little time and in as few patients as possible, and the question is whether the randomized sample eventually represents the target population. If the sample does not represent the population, the estimated treatment effect and corresponding costs of health care can be impacted by diverging characteristics. The design and conduct of this study alleviated this potential problem by having broad inclusion criteria[11] and the pharmacists managed to include 80% of approached patients during day-time operation.

One limitation of our study may still be a lack of external validity, as the study design focused on internal validity. This cost analysis related to a public sector system with a comprehensive reimbursement system. Results on costs might be context specific on some parameters, which should be considered when interpreting them. The specific intervention would be applicable in other settings, but organizational aspects might influence the results. Another limitation is one of statistical insignificance in the cost results. This is hard to obtain because of the skewness in cost data, and would require an even larger sample size. A third limitation is the perspective of the health sector, which does not account for productivity loss. A proportion of the patients are under 65 as seen in Table 6, and an analysis from a societal perspective might provide a different result.

To summarize, our study provided information on estimated size of costs and outcomes to advise decision making in a public sector setting, and the combination of the analyzed costs and consequences suggested that the intervention had an effect on patients' health sector resource use. On this basis, national and local decision makers should consider implementing a medication review including follow-up for polypharmacy patients in countries with similar health care systems.

Given the differences in costs between subgroups, future studies could investigate whether patients at high risk of drug-related problems can be identified more accurately, and to what extent the intervention could be more focused. Furthermore, a study evaluating the effectiveness of the service in operation would strengthen external validity. Finally, there is room for cost-effectiveness analyses evaluating costs and health-related quality of life.

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TABLE 6 Subgroup analysis, total average costs per patient (€)

Total costs, mean (CI)	Usual care group	*n*	Basic intervention group	*n*	Extended intervention group	*n*	*P* value (0,1)[a]	*P* value (0,2)[a]
Base case	17 288 (15 780.48;18 794.97)	498	16 725 (15 232.79;18 263.82)	493	15 631 (14 120.26;17 141.86)	476	0.6036	0.1083
Men	18 674 (16 199.77;21 148.89)	220	16 898 (14 580.06;19 216.03)	245	16 545 (13 874.33;19 215.01)	214	0.1037	0.0240[b]
Men <65	16 681 (11 693.81;21 667.38)	63	15 429 (11 006.03;19 851.43)	60	12 514 (9138.86;15 890.13)	63	1	0.1734
Men ≥65	19 474 (16 615.74;22 332.98)	157	17 383 (14 647.80;20 117.25)	185	18 229 (14 726.22;21 726.05)	151	0.0478[b]	0.0817
Women	16 190 (14 327.70;18 053.13)	278	16 553 (14 588.13;18 517.85)	248	14 883 (13 201.55;16 558.51)	262	0.4921	0.8818
Women <65	12 736 (9469.88;16 002.81)	58	17 520 (13 391.58;21 648.23)	81	12 941 (9878.31;15 998.33)	67	0.0766	0.6902
Women ≥65	17 101 (14 914.98;19 287.09)	220	16 084 (13 931.12;18 236.89)	167	15 547 (13 545.66;17 548.69)	195	0.9185	0.8334

Abbreviation: CI, confidence interval.

[a] *P*(0,1) tests H0: usual care differ from basic intervention, *P*(0,2) tests H0: usual care differ from extended intervention.

[b] $P \leq 0.05$.

the participating wards, patients, physicians, nurses, general practitioners, nursing homes, and pharmacy personnel from primary care and the impartial clinical pharmacologist.

Conflict of interest

Lene Vestergaard Ravn-Nielsen reports grants from The Hospitals Pharmacies' and Amgros' Research Development Foundation, two public Regional foundations and the Actavis Foundation during the conduct of the study. Jesper Hallas has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, Leo Pharmaceuticals, Astellas and Alk-abello with grants paid to the institution where he was employed. He has personally received fees from the Danish Association of Pharmaceutical Manufacturers and from Pfizer and Menarini, unrelated to this project. Morten Rix Hansen has participated in research projects funded by Pfizer, Menarini with grants paid to the institution where he was employed. He has personally received fees from the Danish Association of Pharmaceutical Manufacturers, unrelated to this project. Marie-Louise Duckert, Mia Lolk Lund, Jolene Pilegaard Henriksen, Michelle Lyndgaard Nielsen, Christina Skovsende Eriksen, Thomas Croft Buck, Anton Pottegård, Kristian Kidholm and Maja Kjær Rasmussen have no disclosures.

Author contribution

All authors had access to the data and had a role in writing the manuscript.

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