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Title	Cost-effectiveness analysis of a physician-implemented medication screening tool in older hospitalised patients in Ireland
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Publication date	2018-07-13
Original Citation	O'Brien, G.L., O'Mahony, D., Gillespie, P., Mulcahy, M., Walshe, V., O'Connor, M. N., O'Sullivan, D., Gallagher, J. and Byrne, S. (2018) 'Cost-effectiveness analysis of a physician-implemented medication screening tool in older hospitalised patients in Ireland', Drugs and Aging, 35, 751 (12pp). doi: 10.1007/s40266-018-0564-0
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1007/s40266-018-0564-0
Rights	© 2018, Springer International Publishing AG. This is a post-peer-review, pre-copyedit version of an article published in Drugs and Aging. The final authenticated version is available online at: https://doi.org/10.1007/s40266-018-0564-0
Download date	2026-11-06 04:34:14
Item downloaded from	https://hdl.handle.net/10468/6602

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Cost Effectiveness Analysis of a Physician-Implemented Medication Screening Tool in Older Hospitalised Patients in Ireland

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Running head: Cost Effectiveness of Physician-Implemented Medication Review

Three key points:

(1) A physician-implemented medication screening intervention based on the STOPP/START criteria demonstrated positive outcomes in terms of reduction of adverse drug reactions in older hospitalised patients.

(2) The physician-implemented intervention is not likely to be cost-effective compared with usual care, unless the healthcare provider is willing to pay a large amount of money to prevent an adverse drug reaction.

(3) Pharmacist and/or computerised clinical decision support systems employed to carry out such medication reviews may be a more cost-effective approach than acquiring a physician.

Word count (excluding the title page, summary, references, tables, and figures): 5771

Number of tables: 3

Abstract

Background: A recent randomised controlled trial (RCT) conducted in an Irish University teaching hospital that evaluated a physician-implemented medication screening tool, demonstrated positive outcomes in terms of reduction of incident adverse drug reactions (ADRs).

Objective: The present study objective was to evaluate the cost-effectiveness of physicians applying this screening tool to older hospitalised patients compared with usual hospital care in the context of the earlier RCT.

Method: Cost-effectiveness analysis alongside conventional outcome analysis in a cluster RCT. Patients in the intervention arm (n= 360) received a multifactorial intervention consisting of medicines reconciliation, communication with patients' senior medical team and generation of a pharmaceutical care plan in addition to usual medical and pharmaceutical care. Control arm patients (n= 372) received usual medical and pharmaceutical care only. Incremental cost-effectiveness was examined in terms of costs to the healthcare system and an outcome measure of ADRs during inpatient hospital stay. Uncertainty in the analysis was explored using a cost-effectiveness acceptability curve (CEAC).

Results: On average, the intervention arm was more costly but was also more effective. Compared with usual care (control), the intervention was associated with a non-statistically significant increase of €877 (95% CI −€1,807, €3,561) in mean healthcare cost, and a statistically significant decrease of −0.164 (95% CI −0.257, −0.070) in the mean number of ADR events per patient. The associated incremental cost-effectiveness ratio (ICER) per ADR averted was €5,358. The probability of the intervention being cost-effective at threshold values of €0, €5,000 and €10,000 was 0.236, 0.455 and 0.680 respectively.

Conclusion: Based on the evidence presented, this physician-led intervention is not likely to be cost-effective compared with usual hospital care. More economic analyses of structured medication reviews by other healthcare professionals and by computerised clinical decision support software (CDSS) need to be explored to inform future healthcare policy decisions in this field.

1 Introduction

Within the 35 member countries of the Organisation for Economic Co-operation and Development (OECD), people born today have an average life expectancy of 80.6 years [1]. Given this 10-year increase in life expectancy from just 45 years ago, the greatly expanded older person population is one of the most resource-consuming patient groups interfacing with healthcare systems in all OECD countries [2]. This cohort is often exposed to inappropriate prescribing and polypharmacy [3, 4] which can frequently lead to adverse drug reactions (ADRs) [5, 6]. The increasing incidence of ADRs within the older population is a growing health problem [7]. It is estimated that approximately 2000 bed days are due to an ADR at any one time and where the total costs are likely to exceed £171 million annually for ADRs occurring during admission in the UK [8]. This cost rises to approximately £1 billion when all ADRs are taken into account [9]. Initiatives which enhance medication management in the older people can ameliorate patient outcomes and attenuate unnecessary expenditure [10, 11]. Given that an estimated 57% of all ADRs are considered avoidable, it makes sense to invest in interventions to prevent ADRs, particularly in older people who are at highest risk [12].

Structured and unstructured medication reviews in the hospital environment can be an effective means to optimise pharmacotherapy. However, there can be variability in the ways these reviews are implemented. [13]. They are generally carried out on an *ad hoc* basis and can differ depending on which healthcare professional performs the review [14]. The published literature has numerous examples of randomised controlled trials (RCTs) testing different interventions that have the common overarching aim of improving prescribing in the older adult [15-17]. One trial in particular demonstrated a statistically significant reduction in serious ADRs [18]. However there are only two published clinical trials that have used potentially inappropriate medication (PIM) or potential prescribing omission (PPO) criteria as a structured medication review intervention for the purpose of ADR prevention in high-risk hospitalised older adults [19, 20].

Both of these RCTs have employed the widely used STOPP/START (Screening Tool of Older Persons' Prescriptions / Screening Tool to Alert doctors to Right Treatment) criteria (version 1) [21]. The fundamental aim of the STOPP criteria is to minimise medication-related adversity by highlighting and avoiding PIMs. The complementary aim of the START criteria is to minimise preventable therapeutic failures by highlighting PPOs and encouraging appropriate prescriptions if they are absent for no justified clinical reason [22]. One of these cluster RCTs applied a structured pharmacist review of medication (SPRM) which was supported by a computerised clinical decision support system (CDSS). It resulted in significant reductions of ADRs [20] and proved cost-effective [23].

The other cluster RCT involved a single time-point intervention in which patients had their medications screened according to the STOPP/START criteria by a physician. Instances in which STOPP and START "rules" had been contravened were highlighted to the attending medical team with advice to adjust the patients' prescriptions accordingly. This once-off application of STOPP/START criteria alongside usual pharmaceutical care resulted in a significant reduction in incident ADRs compared to similar older patients receiving usual pharmaceutical care only [19]. However, before adopting any medication optimisation technology, appraisal of its economic and budgetary impact is important. Notwithstanding the significant ADR attenuation that arose from the application of the STOPP/START criteria [19], an economic evaluation of this intervention has not yet been undertaken. The aim of this study was to conduct a cost-effectiveness analysis of the physician-implemented structured medication review based on its application in a RCT in an older population that aimed to reduce incident hospital-acquired ADRs. This is the first economic evaluation of a physician-led intervention that is based on the application of the STOPP/START criteria.

2 Methods

2.1 The Prevention of ADRs in Older Hospitalised Patients RCT

Full details of the particular RCT methods are published elsewhere [19, 24]. In brief, the single-blinded RCT was conducted in an 810-bed University teaching hospital in the south of Ireland over a 13-month period between May 2011 and May 2012. This trial was cluster-randomised with consultants from each speciality represented in each trial arm. Patients were randomised into either intervention or control groups based on the consultant with primary responsibility for their care during their hospital stay. The intervention arm consisted of 360 patients. The control arm included 372 patients. All in this study received usual medical and pharmacist inpatient care, which consisted of full medication reconciliation, surveillance of prescription order sheets

(independent of medical prescribers) with specific written advice attached to the prescription order sheets. The baseline characteristics and trial-related outcomes of the study population are presented (see **Table 1**). No significant differences existed between the groups in terms of age, functional status, cognitive function or number of medications at entry to the study [19]. Although there was a statistically significant sex imbalance between the groups, it is unlikely that this had a significant influence on the primary outcome results [19, 25].

Table 1 Baseline characteristics and trial-related outcomes of study population in the RCT

Variable	**Measure**	**Intervention (n = 360)**	**Control (n = 372)**	***P*-value**
Age	Median (IQR)	80 (73-85)	78 (72-84)	0.100
Male	n (%)	130 (36.1%)	187 (50.3%)	0.001
Female	n (%)	230 (63.9%)	185 (49.7%)	0.001
Nursing home residents	n (%)	51 (14.1%)	36 (9.6%)	0.080
Total number of daily drugs	n	3,147	3,212	0.520
Distribution of drugs	Median (IQR)	9 (6-11)	8 (6-11)	0.710
Length of hospital stay	Median (IQR)	8 (4 – 14)	8 (4 – 14)	0.961
Hospital mortality rate	n (%)	11 (3.1%)	9 (2.4%)	0.535

Key: IQR – Interquartile range, NS – Non-significant (Type 1 error rate of 0.05 used)

A research physician applied the STOPP/START intervention to patients' medication lists within 48 hours of admission. The intervention consisted of three elements. The first of these involved the research physician applying the STOPP/START criteria once only in each intervention group participant on the basis of the diagnoses documented in their case records and the list of prescribed drugs and doses at the time of study enrolment. The second element involved the research physician discussing the presence of any STOPP/START-defined PIMs and/or PPOs with a senior member of the patient's attending team (i.e. senior residents or in most cases, consultants). Thirdly, within 24 hours of applying STOPP/ START criteria, the research physician placed a printed report in the participant's case record, reinforcing the oral recommendations based on the specific criteria that applied in each case. The final decision regarding acceptance or rejection of STOPP and START criteria recommendations lay with the participant's attending senior medical staff. All patients aged ≥ 65 years admitted under the care of the medical or surgical services through the emergency department were considered eligible for inclusion. However, exclusion criteria were: (i) aged < 65 years, (ii) admission directly to psychiatric services, intensive care unit, palliative care unit, specialist geriatric or clinical pharmacology services, (iii) anticipated length of stay (LOS) <48 hours, (iv) elective admission, (v) terminal illness, (vi) refusal to participate.

2.2 Economic Evaluation

The economic evaluation consisted of a trial-based analysis conducted alongside the cluster RCT. The perspective of the Irish public healthcare provider, the Health Service Executive (HSE), was adopted with respect to trial-related costs and outcomes. Evidence on resource use and patient health outcomes were collected by the research physician during the course of the trial and a retrospective review of patient medical records was carried out. The time horizon for ADR evaluation was confined to patient discharge or 10-day follow-up, whichever was sooner; this was informed by average LOS for an elderly patient in the Irish hospital system at the time [26]. The average LOS for patients aged 65 – 74 years is 7.9 days and is 10.4 days for patients aged 75

– 84 years. The study was not designed to measure the medium/long term impact of this intervention and discounting of costs or outcomes was not required due to the limited follow-up period. Moreover, missing/censored data were not an issue in this evaluation, as follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period. Statistical analysis was conducted on an intention to treat (ITT) basis, and in accordance with guidelines for conducting economic evaluations alongside cluster RCTs [27], which require that both the correlation and clustering of the cost and effect data be explicitly considered.

2.3 Cost Analysis

Multiple cost components were included in the analysis and are described (see **Table 2**). Costs are expressed in Euros (€) using 2012 prices (unless otherwise stated). The primary component was the cost of employing the research physician, who then held the post of specialist registrar (i.e. senior resident) physician in geriatric medicine, to implement the required intervention steps. The mid-point of the HSE specialist registrar physician pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland [28, 29]. Salary was adjusted for employers' insurance cost, pension payments and general overheads. Based on experience-based opinion from the primary research team and estimates from the literature [30], it was assumed for the analysis that 40 minutes was an appropriate duration to assign for the trained research physician to apply the intervention.

The second component consisted of the associated follow-up time for senior members of patients' attending teams to discuss and decide upon the suggested STOPP/START recommendations. Based on experience-based opinion from the primary research team, it was assumed for the analysis that this took seven minutes. The mid-point on the HSE consultant physician pay scale was used in the cost analysis. The third major component was the cost of hospital inpatient stay; this cost was obtained from aggregated national data [31]. In general, micro-costing estimates for patients are preferable. However, in the context of this piece of research, the 24-hour national Irish hospital stay average cost per patient was more pragmatic to use despite patients being admitted with a diverse range of primary indications. The fourth component consisted of the specialist registrar's training in the use of STOPP/START criteria. Interactive training courses given by the creators of the STOPP/START criteria generally last for approximately four hours and were costed accordingly.

All resource use was valued using a vector of unit cost data presented in 2012 Euro (€) prices and summed to calculate a total cost variable for the statistical analysis given that the trial was completed in 2012. However, at the time of manuscript preparation (December 2017), the contemporaneously available healthcare costs (CAHC) in the Irish context were re-applied to the intervention steps. These costs are expressed in 2015 Euros (€) prices (unless otherwise stated). See Electronic Supplementary Material Table S1 (**ESM Table S1**). Statistical analysis was re-run with the CAHC and original trial effectiveness data (see **ESM2**). This supplementary analysis was undertaken as a point of interest to examine the stability of medical inflation in Ireland during the post financial crisis period.

Table 2 Costs associated with care of patients in intervention arm in 2012

Cost Component	**Unit Cost(€)**	**Description**	**Reference**
Training of research physician in intervention criteria (once-off)	0.56	Circa 240 minutes of training required costing approximately €200.00	Experience-based opinion from primary research team
Research physician applying the intervention	2.50	Median time of three minutes to apply intervention [30]	HSE salary scales [29]
Research physician informing specialist consultant of intervention findings and answering related questions	5.83	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales [29]
Specialist consultant being made aware and possibly implementing intervention findings	16.33	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales [29]
Research physician compiling printed report of intervention findings	25.00	Approximated time of 30 minutes (Experience-based opinion from original research team)	HSE salary scales [29]
Hospitalisation costs	820.00	24-hour national Irish hospital stay average cost per patient	Healthcare Pricing Office [31]

Key: HSE – Health Service Executive

2.4 Effectiveness Analysis

The primary outcome measure of this cluster RCT was the difference in the proportion of participants in the two arms experiencing one or more ADRs during index hospitalisation. ADRs were identified by the research physician and a blinded second researcher. A comprehensive description of ADR identification and outcomes is provided elsewhere [19].

2.5 Cost-Effectiveness Analysis

In an economic evaluation, one health technology (treatment/intervention) is considered more cost-effective than its comparator if it meets one of the following criteria [32];

a) Less costly and more effective;

b) More costly but more effective, with an incremental cost-effectiveness ratio (ICER) which is considered acceptable by decision-makers;

c) Less costly and less effective, but the additional cost per unit of effect of its comparator is not considered worth paying by decision-makers.

In the context of the current study, we conduct a cost effectiveness analysis to identify which of the three conditions applies here. Notably, the ICER represents the additional cost per unit effect, which in this case, is the additional cost of preventing an additional non-trivial ADR in secondary care. This raises the concern of what healthcare policymakers and decision-makers in Ireland would be willing to pay to prevent an ADR. While threshold values exist for some generic measures such as quality-adjusted life years (QALYs), no such value per ADR prevented currently exists. In this analysis, we present our results in the context of a number of hypothetical thresholds, as previously proposed in the literature [23]. Recent work that compares methods for estimating direct costs of ADRs may inform a threshold value for ADR prevention in the future [33].

Statistical techniques were adopted to account for the effect of both clustering and correlation of cost and effect data collected alongside cluster RCTs [34]. The incremental analysis was undertaken using multilevel regression models for both the cost and effect data. Both models were estimated to control for treatment arm, age, sex, number of medications at admission and consultant (cluster group). The regression for total cost variable was estimated using a multilevel mixed-effects linear regression model and the regression for the ADR event variable was estimated using a mixed-effects logistic regression model. The estimated treatment arm effects represent the incremental costs and incremental effects for the intervention relative to the control. The 95% confidence intervals report the statistical significance of these co-efficients based on standard errors estimated using the '*mixed'* command in STATA® version 13 (IBM SPSS Statistics 22; IBM Corporation, Armonk, NY, USA).

Uncertainty in the analysis was addressed by estimating confidence intervals and a cost-effectiveness acceptability curve (CEAC), which links the probability of a treatment being cost-effective to a range of potential threshold values (λ) that the healthcare system may be willing to pay for an additional unit of effect [35]. Commonly, non-parametric bootstrapping can be conducted on the difference in mean costs and mean ADRs to generate ICER replicates with which to construct a CEAC [36]. However, the CEAC in this analysis was estimated parametrically using the net benefit regression framework following the method proposed by Hoch *et al.* [37]. The CEAC explicitly presents the uncertainty relating to the threshold value coupled with the statistical variability inherent in trial data.

Finally, a series of scenario analyses was performed which varied the time required by all healthcare professionals to complete the intervention by +/- 50%. The incremental cost-effectiveness analysis was re-run using CAHC and the original trial effectiveness data (see **ESM Table S2**). The aim was to assess the cost-effectiveness of this intervention if it was to be implemented in usual clinical care by hospitals today. Analysis was performed using STATA® version 13 and Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

2.6 Guidelines and Ethical Considerations

This manuscript followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting health economic evaluations [38] (see **ESM Table S3**) with joint reference to the published good research practices for cost-effectiveness analysis alongside clinical trials, i.e. the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices: Randomized Clinical Trials-Cost-Effectiveness Analysis (ISPOR RCT-CEA) report [39]. The original clinical cluster randomised trial conformed to Consolidated Standards of Reporting Trials (CONSORT) guidelines [40]. The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol and the trial was registered with the United States National Institutes of Health (NCT01467050-

http://clinicaltrials.gov/show/NCT01467050). Written consent was sought and obtained from all participating patients, prior to enrolment in the original cluster RCT study.

3 Results

The physician-led STOPP/START intervention resulted in a marked absolute risk and relative risk reduction for incident ADRs i.e. 11.4% and 47.7% respectively [19]. However, this was accompanied by an increased cost relative to usual medical and pharmaceutical care (see **Table 3**). The mean (standard deviation (SD)) cost of caring for an intervention patient during a single admission was €12,102 (€13,490). In the control group, the mean (SD) cost of care was €11,160 (€12,506). Median costs were higher for the intervention group (€7,430) compared to the control group (€7,380). Following application of a multi-level mixed effects model in STATA® version 13 and accounting for baseline differences across both arms, the adjusted incremental difference in cost of €877 was statistically non-significant.

In contrast, the effectiveness measures favoured the intervention strategy and were statistically significant. The odds ratio for a patient experiencing an ADR was 0.391 when comparing the intervention (STOPP/START) group to the control (usual hospital care) group. This related to an adjusted difference in the mean number of ADRs of −0.164. Although the physician-implemented STOPP/START intervention was more costly, it too was more effective than usual clinical care. The calculated ICER was €5,358 for the prevention of an ADR. However, as with all attempts to calculate the cost-effectiveness of an intervention, there is a degree of uncertainty surrounding the ICER. Even if the healthcare payer was willing to pay the €5,358 for the prevention of an ADR, the probability of the intervention being cost-effective was 50%. There was a 92.6% probability that the intervention would be cost-effective if the healthcare payer was willing to pay €20,000 for the prevention of an ADR (see **Table 3**). When the cost-effectiveness analysis was rerun using CAHC and the original trial effectiveness data, the ICER underwent a slight increase to €5,469 (see **ESM Table S2**). Scenario analyses demonstrated that if healthcare professional times associated with the intervention were altered by +/- 50%, this had a minimal effect on the original ICER estimate (see **ESM Table S4**). This was also true of the scenario analyses that used CAHC and original trial effectiveness data (see **ESM Table S5**).

The overall cost of applying the STOPP/START intervention to a group of 360 patients was estimated to be approximately €18,000 or €50 per patient. The majority of the intervention costs were associated with the expense of the research physician's time conducting the intervention (~€33 per patient). Length of hospital stay was responsible for the majority of the cost associated with management in both arms of the cluster RCT.

Table 3 Incremental cost-effectiveness analysis using 2012 data

	Intervention group (n = 360)	Control group (n = 372)
Cost analysis		
Total healthcare cost (€)		
Mean (SD)	12,102 (13,490)	11,160 (12,506)
Effectiveness analysis		
Participants experiencing ≥ 1 ADRs [n (%)]	42 (11.67)	78 (20.97)
ADRs experienced per patient [n (%)]		
0	318 (88.33)	294 (79.03)
1	39 (10.83)	67 (18.01)
2	3 (0.83)	11 (2.96)
ADRs per patient [mean (SD)]	0.125 (0.356)	0.239 (0.492)
Incremental cost-effectiveness analysis	Intervention vs Control	
Incremental cost		
Difference in mean healthcare cost (€) [a,b]	877 (95% CI −1807, 3561)	
Incremental effect		
Difference in odds ratio for ADR events [a,c]	0.391 (95% CI 0.233, 0.657)	
Difference in mean ADR events [a,c]	−0.164 (95% CI −0.257, −0.070)	
ICER per ADR averted (€)	5,358	
Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective [d]	
0	0.236	
500	0.255	
1,000	0.275	
5,000	0.455	
10,000	0.680	
20,000	0.926	

Key: SD = standard deviation; ADR = adverse drug reaction; CI = confidence interval; ICER = incremental cost-effectiveness ratio

[a] Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between arms

[b] Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

[c] Regression for ADR event estimated using mixed effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

[d] Probabilities for cost-effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value

4 Discussion

It is unlikely that the physician-led STOPP/START intervention is cost-effective. For instance, at a willingness-to-pay threshold of €10,000 per ADR averted; the probability of the intervention being cost-effective is only 68%. The probability of the intervention being cost-effective increases to 92.6% if a significantly higher threshold of €20,000 is applied. The willingness-to-pay thresholds used in this analysis were arbitrary but when one considers that the mean cost associated with a single ADR event in secondary care has been estimated at €2,250 [41], the threshold values presented in **Table 3** are a reasonable measure of what could be considered value for money. This cited mean cost of a single ADR also suggests that it is unlikely decision-makers would be willing to pay the quoted threshold values because a high probability of cost-effectiveness is only reached at high threshold values.. Similar increases in the cost of care could be imputed from this study, as patients who experienced an ADR had their median LOS increased by three days [19].

The principal barrier to the application of this intervention by a trained physician at a wider level is physician working hours' capacity. The senior resident research physician screened no more than four new patients each day for trial enrolment during the cluster RCT. It should be noted that the research physician was not employed on a full-time basis to apply the intervention to patients. If all older hospitalised patients were to receive this level of pharmaceutical care, increased staff numbers would likely be required. However, given the results from the analysis, it could be argued that the role of the specialist physician is to conduct all relevant medical duties in the secondary care environment. Although there are some published data in the primary care setting literature [42], we could find no reputable references dealing with economic analyses of physician-led medication-related interventions in the secondary care setting literature. Thus, it is difficult to align the results of this analysis with similar studies. One similar trial involving a research pharmacist conducting a similar medication review-based intervention supported by computerised CDSS proved to be cost-effective relative to routine hospital care [23]. A recent systematic review investigating the effectiveness and cost-effectiveness of interventions aimed at preventing medication error (medicines reconciliation) at hospital admission demonstrated that the majority of these interventions are pharmacist-led, not physician-led [43] and that the pharmacist-led interventions are generally considered more cost-effective than the respective study comparator [44]. In addition, two ongoing European multi-centre randomised clinical trials i.e. SENATOR and OPERAM [45, 46] implement the STOPP/START criteria using a computerised CDSS. A recent systematic review concluded that computerised interventions are associated with a significant reduction in potentially inappropriate prescribing (PIP) in older hospitalised patients [47]. Computerised interventions in this field appear to reduce cost [48] and be cost-effective [49]. It is also envisaged that the application of STOPP/START criteria in the SENATOR and OPERAM trials may prove less labour-intensive and more cost-effective than its application in the trial analysed in this study. Given all of this evidence, it is likely that the more clinically effective and cost-effective medication screening interventions in older hospitalised patients in the future will comprise of pharmacist-led and/or computerised CDSS interventions.

A study conducted in Canada assessed the cost-effectiveness of self-managed versus physician-managed oral anticoagulant therapy over a 5-year period using a Bayesian Markov model [50]. Self-management resulted in fewer adverse drug events than physician management with the average discounted incremental cost of self-management relative to physician management calculated to be $989 per patient with incremental QALYs of 0.07 gained [50]. Although this study did not assess medication screening in the elderly *per se*, it is yet another example of where a physician-implemented medication intervention was not found to be cost-effective. Conversely, the literature once again appears to favour medication screening programmes involving or

implemented by pharmacists. This point is supported by two recently published studies demonstrating cost-effectiveness of pharmacist-driven medication reviews towards optimisation in older patients [15, 51].

Notwithstanding the research physician's absence during medical rounds, the 83.4% acceptance rate of STOPP/START recommendations by attending doctors is noteworthy [19]. However, in a very similar analysis where the research pharmacist was absent during medical rounds, a lower acceptance rate of 38.5% by attending doctors was notable [52]. As the present analysis argues that pharmacist-led medication screening interventions are an effective and a cost-effective solution, the low rate of acceptance of pharmacist prescribing recommendations by attending physicians needs to be further investigated. In relation to pharmacist medication reviews, a robust method for economic evaluation of such medication assessments has been elucidated [53]. Ideally, the evaluation should be conducted with a 1-year follow-up period from a healthcare service provider viewpoint. Health-related quality of life (HRQoL) is contended as the preferred effectiveness measure utilised, allowing correlation with confirmed societal values. The ultimate and most comprehensive appraisal would be a cost-benefit evaluation over a 5-year period from a societal perspective. Thus, if the standard practice model of medication reviews is to be pharmacist-led, the economic evaluation aspect of such reviews should be conducted using the proposed methods.

The cluster randomisation of the RCT that this evaluation is based upon resulted in a statistically significant sex imbalance between the control and intervention groups (significantly fewer women in the control group (49.7%) than in the intervention group (63.9%)). Although sex imbalance in any RCT is not desirable, there is no evidence to indicate that sex had a significant influence on the prevalence rates of PIMs, PPOs, or incident ADRs in the trial. The literature has shown that females experience higher rates of PIMs and ADRs relative to males [54-56]. Given the higher proportion of women in the intervention group, one would have expected higher rates of ADRs in this arm yet the results demonstrated the contrary. Therefore, it is unlikely that the sex imbalance between groups had a significant influence on primary outcome results. There were no other significant demographic differences between the two treatment arms. As stated, demographic analysis is presented in the original RCT paper [19].

It has been established that conducting economic evaluations based on data from RCTs is a suitable methodology [57]. This approach has two main advantages i.e. (i) internal validity is maintained due to the comprehensive nature of data collection during the trial and (ii) there is a modest marginal cost associated with collecting required data from a trial which is predominantly clinically orientated [57]. While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in the Republic of Ireland [28], it was not a realistic outcome measure for this analysis. The population under consideration had multiple co-morbidities and often an initially poor health status [19]. Therefore, HRQoL was not appropriate in this case [58]. Appropriate methods were used to investigate the cost-effectiveness analysis of the trial data. Multi-level mixed effect models were chosen as they are an acceptable means for estimating the incremental net benefits for a clinical trial of this nature. Clustered data can potentially lead to biased results [59]. Normal statistical analyses are generally inappropriate, however the methods employed for our analysis surmounted this issue [34]. These techniques account for both the clustering and correlation of cost and effect data.

4.1 Limitations

There are several limitations to this economic evaluation, principally pertaining to extrapolation of the findings to routine clinical practice. Training costs and time estimates were not recorded at time of event and were retrospectively informed by the primary research team. It is likely that some costs associated with this intervention may have been overestimated or underestimated. For example, the seven minute time period allocated for discussion of STOPP/START recommendations could vary considerably depending on the number of recommendations generated and the subjective prescribing assessment thought processes of the attending consultant. In addition, the 30-minute time period allocated to compiling the research physician's printed report could be replaced by a five minute handwritten summary of recommendations into patients' medical records. However, the scenario analysis demonstrated that if healthcare professional time associated with intervention implementation was altered by 50% in both directions, this had a minimal effect on the original ICER estimate (see **ESM Table S4**). Furthermore, a time and motion study, which gathers data on healthcare professional time required to complete the intervention, would have reduced uncertainty surrounding this input. As healthcare professionals become more familiar with the application of the STOPP/START criteria, they will be able to apply them more effectively and arrive at decisions at a faster rate.

ADRs are often compared to icebergs [60]; those that are visible and identified, and those that are below the water's surface where neither patient nor intervening clinician recognise that they are drug effects, and thus unquantifiable. Therefore, it is possible that the amount of ADRs identified in both arms of the trial is not the true value. Depending on the type and severity of ADR, the cost, patient LOS, and overall impact on healthcare utilisation can vary dramatically [41, 61]. This level of detail was not reflected in our evaluation. Therefore, it is potentially dangerous to dismiss the intervention as not being cost-effective because the outcome at the time was not measureable or identifiable. There are also those that may be causing no symptoms or signs at the time but represent a real risk in the future. Ideally, a longer duration of follow-up for ADR evaluation would have been more preferable as it possibly could have allowed for further identification of ADRs.

Moreover, this evaluation is based on the work of one research physician in a single centre. Aspects of the intervention that would be variable between sites include the clinical experience of the research physician involved and the extent of the uptake of STOPP/START criteria recommendations by the receiving medical team. The attending physician is solely responsible for deciding whether the application of the STOPP/START criteria is clinically important or not. This is a subjective choice, irrespective of formal training. There are other examples of medication optimisation due to the application of the STOPP/START screening tool [22]. This single study site increased the possibility of crossover learning between healthcare colleagues within the secondary care environment. However, if healthcare decision-makers are insistent about supporting and promoting physician-led medication screening interventions, this evaluation should be carried out on a larger scale involving multiple hospital sites as in the SENATOR and OPERAM trials [45, 46].

As stated, the trial was conducted in 2011/2012 and cost-effectiveness was calculated using 2012 healthcare costs. When the analysis was re-run using CAHC and original trial effectiveness data, the cost of the intervention was marginally lower (see **ESM Table S1**); however, there was a slight ICER increase which is attributed to the increased 24-hour national Irish hospital stay average cost per patient (see **ESM Table S2**). It is unlikely that healthcare policy decision-makers would execute the rollout of this intervention today as it has become less cost-effective recently. However a budget impact analysis would have to completed alongside the cost-effectiveness analysis to assess if policymakers were serious about its adoption [62]. In addition, the results of economic analyses based on RCTs must be interpreted with caution especially if there are limitations or flaws inherent in trial design. However, the RCT that formed the basis of the present cost-effectiveness analysis achieved 80% power to detect a statistically significant difference in ADR incidence between the groups at the 95% confidence level [19]. It would have been interesting to calculate the incremental net benefit statistic to derive the same conclusion on cost-effectiveness like that of the ICER. This was not possible since a willingness-to-pay threshold for ADRs has not yet been elucidated.

This is the first study to evaluate the economic impact of a physician-led medication review intervention based upon the STOPP/START criteria. Since their development in 2008 [21], STOPP/ START criteria have become an extensively used method of identifying and improving instances of potentially inappropriate prescribing [52, 63]. This analysis provides further information about the adoption of STOPP/START guidelines as a fundamental part of any healthcare review conducted by a healthcare professional in an older population. The present analysis has implemented recommendations from the CHEERS statement to ensure that this manuscript presents a transparent high quality evaluation.

5 Conclusion

Based on the information extracted from the cluster RCT, the physician-implemented medication screening tool based on the STOPP/START criteria is unlikely to be considered cost-effective. The healthcare payer would have to pay €20,000 to attain a 92.6% probability that this intervention, which prevents ADRs, is cost-effective. However, as the authors are unaware of decisions previously made based on the cost per ADR prevented, there is uncertainty regarding the cost-effectiveness status of the intervention from a policy perspective. Moreover, while the difference in incremental effects on an individual basis did demonstrate statistical significance, the difference in overall incremental costs did not. To date, the literature appears to be sparse with regard to physician-implemented medication review interventions in secondary care in contrast with the multiplicity of studies describing pharmacist-led programs which appear to be clinically effective and budget positive [44]. At a minimum, this evaluation further adds to the growing body of evidence that a structured form of medication review and reconciliation incorporating STOPP/START criteria is superior to usual clinical practice. The present data suggests that a pharmacist with/without CDSS designed for STOPP/START criteria employed to

carry out such medication reviews may be a more cost-effective approach than a medication review by a specialist physician.

Compliance with Ethical Standards

Funding

This research project was funded by the Health Research Board of Ireland (Grant HRA_HSR/2010/14) and the Irish Research Council (GOIPG/2016/635). The funders had no part in the design of the analysis; the collection, analysis, and interpretation of the data; the writing of the report; or the decision to submit the article for publication.

Conflicts of Interest

Stephen Byrne and Denis O'Mahony have part ownership in a patent "A Prescription Decision Support System" (based on STOPP/START prescribing rules); the patent was registered with the European Patent Office (Munich); Patent No. 11757950.8–1952. Stephen Byrne and Denis O'Mahony are also involved with two European Commission–funded grants that involve clinical trials in which there is computerized deployment of the STOPP/START criteria as part of an intervention designed to optimize pharmacotherapy in older adults. The first EC grant is called "Development and clinical trials of a new Software Engine for the Assessment & Optimization of drug and non-drug Therapy in Older peRsons [SENATOR]," grant agreement 305930, awarded under the Seventh Framework Programme (FP7). The trial is registered with the United States National Institutes of Health (NCT02097654 - http://clinicaltrials.gov/show/NCT02097654). Denis O'Mahony is coordinator of the SENATOR project. The second EC-funded project is called "OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly." OPERAM is funded under the Horizon 2020 programme (PHC 17–2014). The OPERAM trial is based on another software intervention called "Screening Tool to Reduce Inappropriate Prescribing", which uses STOPP/START rules to assess the pharmacotherapy of older people. The trial is registered with the United States National Institutes of Health (NCT02986425 - http://clinicaltrials.gov/show/NCT02986425). Gary O'Brien, Paddy Gillespie, Mark Mulcahy, Valerie Walshe, Marie O'Connor, David O'Sullivan and James Gallagher declare that they have no conflicts of interest relevant to the content of this article.

Ethical Approval

The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol and the trial was registered with the United States National Institutes of Health (NCT01467050 - http://clinicaltrials.gov/show/NCT01467050).

Informed Consent

Written consent was sought and obtained from all participating patients prior to enrolment in the study.

Author Contributions

Gary O'Brien, Stephen Byrne, Denis O'Mahony, Paddy Gillespie, James Gallagher, Valerie Walshe and Mark Mulcahy wrote the manuscript; Gary O'Brien, Paddy Gillespie and James Gallagher analysed the data; Stephen Byrne and Denis O'Mahony designed the original research trial; Marie O'Connor and David O'Sullivan recruited trial participants and gathered original trial data.

Acknowledgements

The authors would like to thank the patients and practitioners who participated in the trial study.

Journal of Economic Literature (JEL) Classification

This article is classified as I19 according to the JEL system.

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Electronic Supplementary Material (ESM)

Electronic Supplementary Table S1

Costs associated with care of patients in intervention arm in 2015 (CAHC)

Cost Component	Unit Cost (€)	Description	Reference
Training of research physician in intervention criteria (once off)	0.56	circa 240 minutes of training required costing approximately €200.00	Experience-based opinion from primary research team

Research physician applying the intervention	2.50	Median time of three minutes to apply intervention [30]	HSE salary scales [64]
Research physician informing specialist consultant of intervention findings and answering related questions	5.83	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales [64]
Specialist consultant being made aware and possibly implementing intervention findings	15.17	Approximated time of seven minutes (Experience-based opinion from original research team)	HSE salary scales [64]
Research physician compiling printed report of intervention findings	25.00	Approximated time of 30 minutes (Experience-based opinion from original research team)	HSE salary scales [64]
Hospitalisation Costs	839.00	24-hour national Irish hospital stay average cost per patient	Healthcare Pricing Office [65]

Key: HSE – Health Service Executive

Electronic Supplementary Table S2

Incremental cost-effectiveness analysis using CAHC and original trial effectiveness data

	Intervention group (n = 360)	Control group (n = 372)
Cost analysis		
Total cost (€)		
Mean (SD)	12,380 (13,802)	11,419 (12,795)
Effectiveness analysis		
Participants experiencing ≥ 1 ADRs [n (%)]	42 (11.67)	78 (20.97)
ADRs experienced per patient [n (%)]		
0	318 (88.33)	294 (79.03)
1	39 (10.83)	67 (18.01)

2	3 (0.83)	11 (2.96)
ADRs per patient [mean (SD)]	0.125 (0.356)	0.239 (0.492)
Incremental cost-effectiveness analysis	Intervention vs Control	
Incremental cost		
Difference in mean healthcare cost (€) [a,b]	895 (95% CI −1851, 3642)	
Incremental effect		
Difference in odds ratio for ADR events [a,c]	0.391 (95% CI 0.233, 0.657)	
Difference in mean ADR events [a,c]	−0.164 (95% CI −0.257, −0.070)	
ICER per ADR averted (€)	5,469	
Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective [d]	
0	0.236	
500	0.255	
1,000	0.274	
5,000	0.450	
10,000	0.672	
20,000	0.921	

Key: SD = standard deviation; ADR = adverse drug reaction; CI = confidence interval; ICER = incremental cost-effectiveness ratio

a) Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between arms

b) Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

c) Regression for ADR event estimated using mixed effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

d) Probabilities for cost-effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value

Electronic Supplementary Table S3

Cheers checklist

Section/item	Item No	Recommendation	Reported on Page comm. no.
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Pg 0
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pg 1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pg 2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pg 3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pg 2
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Pg 3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pg 2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Pg 3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Pg 4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Pg 5
Measurement of effectiveness	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Pg 5
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A

Section/item	Item No	Recommendation	Reported on Page comm. no.
Estimating costs and resources	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pg 4
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Pg 5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pg 6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Pg 8
Characterising uncertainty	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Pg 7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			

Section/item	Item No	Recommendation	Reported on Page comm. no.
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pg 10
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Pg 12
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Pg 12

Electronic Supplementary Table S4

Scenario analysis using 2012 data

50% increase in healthcare professional time	**Incremental Analysis -** Intervention vs Control
Incremental Cost: Total Cost (€) *Difference in Mean*	900 (95% CI −1783, 3584)
Incremental Effect: No. of ADR Events (n) *Difference in Mean*	−0.164 (95% CI −0.257, −0.070)
Incremental cost-effectiveness ratio (€)	5,500
50% decrease in healthcare professional time	**Incremental Analysis -** Intervention vs Control
Incremental Cost: Total Cost (€) *Difference in Mean*	854 (95% CI −1831, 3539)
Incremental Effect: No. of ADR Events (n) *Difference in Mean*	−0.164 (95% CI −0.257, −0.070)
Incremental cost-effectiveness ratio (€)	5,216

Key: ADR = adverse drug reaction; CI = confidence interval

Electronic Supplementary Table S5

Scenario analysis using CAHC and original trial effectiveness data

50% increase in healthcare professional time	**Incremental Analysis -** Intervention vs Control

Incremental Cost: Total Cost (€) *Difference in Mean*	918 (95% CI −1828, 3664)
Incremental Effect: No. of ADR Events (n) *Difference in Mean*	−0.164 (95% CI −0.257, −0.070)
Incremental cost-effectiveness ratio (€)	5,608
50% decrease in healthcare professional time	**Incremental Analysis -** Intervention vs Control
Incremental Cost: Total Cost (€) *Difference in Mean*	872 (95% CI −1875, 3620)
Incremental Effect: No. of ADR Events (n) *Difference in Mean*	−0.164 (95% CI −0.257, −0.070)
Incremental cost-effectiveness ratio (€)	5,330

Key: ADR = adverse drug reaction; CI = confidence interval