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Cost-effectiveness of a medication review intervention for general practitioners and their multimorbid older patients with polypharmacy

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ABSTRACT

Older adults with multiple chronic conditions and polypharmacy are at an increased risk of having adverse health outcomes, affecting quality of life and generating costs. Primary care has to be effective to guarantee excellent treatment to these patients, who are among the most vulnerable. This project aimed to assess the cost-effectiveness of a tool aimed at improving general practitioners' (GPs) performance, namely a medication review intervention centered around an electronic clinical decision support system (eCDSS). We performed a pre-planned within-trial cost-effectiveness analysis of the OPTICA trial, a cluster randomized controlled trial in Swiss primary care practices aimed at optimizing medication appropriateness and reducing prescribing omissions. Trial participants were older adults aged ≥65 years with ≥3 chronic conditions and ≥5 medications. The 160 participants in the intervention group received a medication review intervention centered around an eCDSS provided by their GP and followed by shared decision-making with their GP. The 163 participants in the control group had a medication discussion in line with usual care with their GP. Patients were followed-up for 12 months. Considering the clustered structure of the data at GP practice level, we applied Generalized Structural Equation Models (GSEMs) on a multiple imputed sample to estimate intervention effects on costs and quality-adjusted life years (QALYs). The intervention strategy was dominant with cost-savings of CHF 1′857 (95 % confidence interval (CI): CHF -3′620 to −93, p-value <0.039, with CHF 1≅USD 1.11 as of November 2023) and a gain of 0.026 incremental QALYs (95 % CI: 0.013 to 0.040, p-value <0.001) per study participant. In robustness analyses, directions of effects were fully consistent, albeit some effect estimates non-significant. Subgroup analyses suggested stronger effects in men and older adults aged 65–74 years or aged ≥85 years. The medication review intervention led to cost savings and an improvement in quality of life, potentially resulting from an accumulation of multiple small positive intervention effects, such as fewer hospitalizations and nursing visits at home.

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1. Introduction

Our study focuses on assessing an intervention aimed at improving the effectiveness of primary care. Given the increasing workload-related and financial pressure on healthcare systems globally, it is important to ensure that primary care services, which are at the forefront of patient care, are able to meet increasing demands for healthcare services. Literature has widely explored the technical efficiency of hospitals and, albeit less, of primary care settings, mainly by adopting frontier analysis approaches to determine the optimal output allocation in terms of physicians, number of beds, et cetera [1–7]. Less evidence has been produced on the effectiveness of primary care systems.

In our study we do not refer to technical efficiency, but we rather ask how to primary care could be made more effective by introducing the adoption of an innovative intervention that leverages new technologies. In particular, we assess the cost-effectiveness of a medication review intervention based on an electronic clinical decision support system (eCDSS). By assessing the efficiency of this eCDSS through a cost-effectiveness analysis, this work contributes to how we can deal with a healthcare system-wide decision problem that occurs frequently. Thanks to medication review interventions, more efficient prescribing might help prevent adverse events by ensuring that medications are used more appropriately [8].

1.1. Inappropriate medication use in older adults

In the context of aging societies, the number of older adults with several chronic conditions, commonly defined as multimorbidity [9], is globally increasing. Due to their complex healthcare needs, multimorbid patients often have polypharmacy, which means that they are regularly using $\geq$5 medications [10]. Patients with polypharmacy are at an increased risk of inappropriate prescribing, which encompasses prescribing omissions as well as the prescribing of "no longer necessary", "never necessary", and "indicated but not beneficial" medications [11]. This means that they may be exposed to unnecessary and avoidable medication-related risks.

1.2. Consequences of inappropriate medication use

Adverse events are one of the key problems of healthcare delivery [12]. Inappropriate polypharmacy in older adults has been associated with various negative health outcomes, such as medication-related adverse events, falls, and functional decline in activities of daily living [13–16]. Medication-related adverse events are highly common and have both immediate as well as long-term effects on patients and healthcare systems [17]. Older adults are at a higher risk of medication-related adverse events, which in turn can have health, social and economic consequences [18,19]. Besides the money spent on inappropriate prescriptions, these adverse health outcomes lead to increased healthcare costs [18,20–23]. For instance, long-term prescriptions of benzodiazepines and non-steroidal anti-inflammatory medications were found to be associated with significantly increased costs and reduced quality-adjusted life years (QALYs) [24].

1.3. Rationale for conducting medication review interventions

Medication review interventions can have various socioeconomic implications. First, they can lead to cost savings for both individuals and healthcare systems, by saving costs of potentially inappropriate treatments and related adverse events (e.g., hospital admissions and emergency treatments). This implies that interventions aimed at reducing inappropriate polypharmacy may be a promising way forward to reduce healthcare costs with no deterioration or even an improvement in patient health outcomes. A study from the US showed that around 10 % of medication costs were spent on potentially inappropriate medications [23]. A systematic review demonstrated that the use of potentially inappropriate medications can increase the cost of treatment by around 2000 USD per patient per year [21].

Second, medication review interventions can not only reduce the number of potentially inappropriate medications and help improve clinical outcomes such as cognition [25,26], but also other patient-relevant outcomes, such as a reduced symptom burden, and improved quality of life [27]. For example, older adults who can manage their health effectively with the right medications are more likely to maintain their functional independence, fall less often, and be less frail [28,29]. This leads to additional socioeconomic implications, as it reduces the need for long-term care services and helps older individuals stay engaged in the workforce or community activities, and, as a consequence, this also reduces indirect costs.

Finally, medication review interventions can contribute to improve equity in health and healthcare distribution. The aim of this kind of interventions is indeed to ensure that everyone, regardless of their socioeconomic status, receive appropriate and effective treatments. Since the target population is mainly composed of older adults and vulnerable and often marginalized people, such interventions are potentially able to improve equity in healthcare distribution [30]. To sum up, such interventions have the potential to improve population health, increase equity in healthcare, and containing societal healthcare costs.

1.4. Evidence on medication review interventions

In recent years, innovative treatment programs to support primary care physicians have been implemented and tested [31]. Among these, several medication review interventions - ranging from educational interventions to using electronic decision support systems - have been tested in different healthcare settings, but the evidence on their clinical effectiveness remains mixed [32–34]. For instance, a systematic review showed that an isolated medication review during a short-term period had an effect on most medication-related problems, but a minimal effect on clinical outcomes and no statistically significant effect on quality of life [25]. The same uncertainty is true for the cost-effectiveness of medication review interventions, as shown by recent systematic reviews [35–37]. However, the comparability of previous studies is limited, since some of them omitted key cost components or tested substantially different interventions. A cost-effectiveness analysis of a similar intervention as the one studied in the present manuscript, but conducted in the hospital setting was based on data from the OPERAM ("*Optimizing thERapy to prevent Avoidable hospital admissions in the Multimorbid older people*") trial and also assessed a medication review intervention centered around a 'Systematic Tool to Reduce Inappropriate Prescribing'-Assistant (STRIPA) [38]. It showed a potential cost-saving of CHF 3′588[5] and gain of 0.025 QALYs per study participant [38], while the main results of the OPERAM trial were inconclusive on whether STRIPA led to a reduction in re-hospitalizations at the 12-month follow-up in inpatients [39]. Overall, there remain many uncertainties related to the cost-effectiveness of medication review interventions, particularly in primary care settings, their policy implications, as well as challenges related to the interpretability of results from different settings and countries.

The aim of this pre-specified within-trial cost-effectiveness analysis (CEA) of the OPTICA ("*Optimizing PharmacoTherapy In the multimorbid elderly in primary CAre*") trial was to evaluate potential effects of the medication review intervention on (general) health, quality of life and its economic impact [40,41]. The paper is structured as follows. First we explain the methods used in this cost-effectiveness analysis. Next we present the findings of the cost-effectiveness analysis. The paper concludes with a discussion section, which also offers some lessons learned for policymakers and healthcare providers.

[5] 1 CHF = 1.11 USD as of November 2023.

2. Methods

2.1. The OPTICA trial

The OPTICA trial was a cluster randomized controlled trial conducted in Swiss primary care settings between 2019 and 2021. The aim of the OPTICA trial was to assess whether a medication review intervention centered around an electronic clinical decision support system called STRIPA used by GPs and followed by a shared decision-making with their patient leads to an improvement in medication appropriateness in patients aged ≥65 years, with ≥3 chronic conditions, and ≥5 medications [41,42]. The STRIPA is based on the STOPP/START criteria, which are criteria for optimizing medication use in older adults, and enables a structured medication review [43,44]. The recruitment of the trial took place from January 2019 to February 2020. After their enrolment, patients were followed up by phone calls at baseline, 6, and 12 months. The trial was cluster randomized at the GP level. The control group patients received usual care. The trial took place in 43 primary care practices in the Swiss German part of Switzerland with 323 patients. Data on diagnoses, medications, lab values, and vital data were obtained from the electronic medical records of the patients through the FIRE project database for the same timepoint [45]. The details of the trial protocol, patient baseline characteristics, medication review intervention, and findings on medication appropriateness have been published previously [40–42,46]. The main results of the OPTICA trial regarding its two primary outcomes of medication appropriateness, as measured by the Medication Appropriateness Index (MAI), and the number of prescribing omissions, as measured with the Assessment of Underutilization (AOU), were inconclusive at 12 months [40,46]. However, the trial results also showed that the intervention led to the implementation of some prescribing recommendations. An average of one recommendation to stop or start a medication was reported to have been implemented per patient. The reporting of the present cost-effectiveness findings followed the CHEERS criteria [47].

2.2. Approach to cost-effectiveness analysis

Analyses followed a health economic analysis plan (HEAP) informed by the cost-effectiveness analysis of the OPERAM trial [38], which had tested a medication review intervention centered around the STRIPA in hospital settings across four European countries. The HEAP was last modified before the lock of the trial database. For deviations from the HEAP, please refer to the Supporting Material **S1**. Information on utilities, as a basis for QALYs and health services use was collected during the trial. Unit cost data were gathered from external sources. We estimated cost-effectiveness for a 12-month time period, in line with the 12-month follow-up period of the OPTICA trial. We primarily adopted a healthcare system perspective of cost assessment. Secondly, by adding the costs of informal care reportedly provided to our study participants, we approximated a societal perspective.

To estimate the incremental costs and incremental QALY (i.e. the difference of costs and QALY in the treated and controlled groups), we defined and estimated the following simultaneous equations:

$$Costs_{ij} = \beta_0 + \beta_1 Treated_{ij} + X1_{ij}\beta_2 + X2_{ij}\beta_3 + \varepsilon_{ij}$$

$$QALY_{ij} = \gamma_0 + \gamma_1 Treated_{ij} + X1_{ij}\gamma_2 + X2_{ij}\gamma_3 + \varepsilon_{ij}$$

Where $i = 1 \ldots 323$ is the individual and $j = 1 \ldots 43$ the cluster.

Both costs and QALY are regressed on the dichotomous variable *Treated* and all the potential confounders available in the data. A regression-based approach to assess intervention effects was adopted due to the clustered nature of the trial data and residual baseline imbalances [48]. We used Generalized Structural Equation Models (GSEMs), which allowed to simultaneously estimate incremental costs (the coefficient $\boldsymbol{\beta_1}$) and quality-adjusted life years (QALYs) (the coefficient $\boldsymbol{\gamma_1}$), while accounting for the clustered nature of the data (the clusters were treated as random effects) [49]. A negative result of $\boldsymbol{\beta_1}$ would indicate a cost saving in treated patients, while a positive $\boldsymbol{\gamma_1}$ would mean a positive QALY for treated patients. Individual patient characteristics measured at baseline (*X1*) and variables describing health service use in the 6 months prior to study inclusion (*X2*) were added to the models to adjust for the residual baseline imbalances and control for resulting confounding. Vector *X1* comprised age, sex, quality of life utility, number of chronic conditions and long-term medications, living situation measured by whether the patient was housebound and whether he/she lived in a nursing home, smoking status, educational status, cognitive impairment, medication appropriateness and number of prescribing omissions, all measured at the baseline. Vector *X2* included hours of informal care received, number of GP visits, specialist visits, hospitalizations, and emergency room visits received in the 6 months prior to study inclusion. Finally, incremental cost-effectiveness ratios (ICERs) would be calculated in situations of non-dominance, by dividing the incremental costs ($\boldsymbol{\beta_1}$) by the incremental QALYs ($\boldsymbol{\gamma_1}$).

2.3. Calculation of quality-adjusted life years

We collected information on utilities using the European Quality of Life-5 Dimensions (EQ-5D-5L) instrument [50–54], which was shown to demonstrate validity and responsiveness when administered to older adults with multimorbidity and polypharmacy [55]. We combined the EQ-5D-5L responses with the German value set for the EQ-5D-5L [56], to approximate a Swiss perspective given the absence of a Swiss value set. In a sensitivity analysis, we used the French value set [57]. We calculated QALYs for the 12-month trial follow-up period using the standard area under the curve method following the trapezium rule [58]. For patients who died during the follow-up, we set the utilities to zero from the date of death onwards.

2.4. Calculation of costs

We collected unit cost data in Swiss francs (CHF) from non-trial sources. The following cost items were included in the main analysis: costs of GP visits, specialist visits, emergency room visits, hospitalizations, nursing home stay, home care visits, meals on wheels (meal delivery service), home help visits, rehabilitation, physiotherapy visits, and therapies/care episodes with other non-physician health professionals. Costs of informal care were included in secondary analyses aimed at approximating the societal perspective. The price year used was 2019, as this was the period in which most patients were included into the OPTICA trial. Unit costs only available for different years were corrected for inflation accordingly (e.g., the average price for meals on wheels obtained in 2021 was adapted to the price year 2019).

The unit cost data were obtained from the following sources. Costs of GP visits, physiotherapist visits, emergency room visits, specialist visits, and care episodes with other non-physician health care professionals were obtained from a large provider of statutory health insurance (around 10 % of the Swiss population). We estimated average hospitalization costs per day of hospitalization using reimbursement data based on SwissDRG flat-fee reimbursement codes [59]. The costs of home care visits, nursing home stays, and stays in rehabilitation facilities were derived from national statistical data [60]. The costs of household help visits and meals on wheels were calculated based on publicly available information of different home care associations operating in the Swiss German speaking part of Switzerland. Medication costs were obtained from official sources of the Federal Office of Public Health [59]. Medications with an overall duration of administration of ≥180 days were considered as chronic medications. Medications for which the start and dose were missing, were not costed. Cost information was, in consequence, missing for a percentage of the reported medications at baseline (4.6 %), 6-month follow-up (10.2 %), and 12-month follow-up (9.2 %). The cost of informal, unpaid care provided

to our study participants by people below the age of retirement was self-reported by trial participants and was valued with the average salary in Switzerland. Finally, the costs of the STRIPA was based on the estimated cost of the software as well as on the time spent by GPs on the intervention, which was self-reported by GPs. Please refer to the Supporting Material (**S2**) for more information on the collection of unit cost data.

2.5. Missing data

After computing QALYs and total costs, and before multiple imputation, 14 % (46 patients) had at least one missing element for the QALY calculation and 12 % (38) had at least one missing cost category value. We assumed a missing at random (MAR) pattern of missing data. We did multiple imputation for any missing EQ-5D-5L score and for each cost category rather than for the aggregated measures of total costs and QALYs [61]. We included baseline and follow-up patient characteristics with no or very few missing values as the basis for imputation (max. 6.8 % missing, see **S3** for variables included). We performed the multiple imputations separately for each trial arm, creating five multiple imputed datasets, each based on 100 iterations [62]. We specified a multiple imputation model with random intercepts and slopes. We estimated the multiple imputed results according to the combination rules by Rubin [63]. We challenged the MAR assumption, by running the main model under several scenarios where a missing not at random (MNAR) structure of missing data was assumed [64].

2.6. Robustness checks

We performed several robustness checks to test and confirm the results of the main GSEM model. First, we computed the simple difference between intervention and control group costs and QALYs without any regression analysis. Second, we ran a simpler Seemingly Unrelated Regression (SUR) model [65] and a linear mixed model of costs and QALYs. Finally, we ran a SUR model using the complete observations only, which excluded participants for whom we had incomplete cost or EQ-5D-5L responses. In a final robustness check, we relaxed the normality assumption of the GSEM model and assumed gamma distributed errors with a log link function for costs.

2.7. Subgroup analyses

We performed analyses for sub-groups defined by the following variables: patient sex (male vs female), age category (65–74, 75–84, and ≥85 years), baseline number of medications (<10 vs ≥10), and baseline median number of chronic conditions (<4, ≥4).

2.8. Sensitivity and uncertainty analyses

In order to assess the impact of related uncertainty on incremental cost-effectiveness, we reduced and increased the external unit costs for each cost category (GP visits, medications, etc.) by 30 %. Next, we combined probabilistic sensitivity analysis with a non-parametric bootstrap-based estimation of first order uncertainty. To do so, we drew a vector of values from the normal distributions representing the uncertainties of the cost parameters, alongside 1′000 bootstrap replications of each of the 5 imputed analysis datasets [66]. In each iteration, resource use was multiplied with the drawn vector of unit costs; the main GSEM model was then re-estimated to derive incremental costs and QALYs. We pooled the samples generated from the 5 imputed datasets and showed results in a cost-effectiveness plane. Finally, we repeated the main analyses using the French value set for the EQ-5D-5L [57].

2.9. Technical implementation

We performed all analyses in Stata version 15.1, except for the multilevel joint modelling multiple imputation, which we did in R using the software package JOMO (https://www.rdocumentation.org/packages/jomo) [67].

Ethical approval

The ethics committee of the canton of Bern (Switzerland) and the Swiss regulatory authority (Swissmedic) approved the study protocol of the OPTICA trial and other documentation on study conduct (BASEC ID: 2018–00914) including the cost-effectiveness analyses.

3. Results

Between January 2019 and December 2020, 323 participants were recruited in 43 GP clusters. 160 patients from 21 clusters were randomized to the intervention group and 163 patients from 22 clusters were randomized to the control group [40,42,46]. The median participant age was 87 years (interquartile range: 65 to 96) and 45 % (146 participants) were female. 12 participants (3.7 %) died during the 12-months follow-up, 12 participants (3.7 %) were lost to follow-up, and 5 participants (1.5 %) opted out from the follow-up by phone. Due to the pragmatic design of the OPTICA trial, we were able to collect information on medications, diagnoses, vital data and lab values from the electronic health records of the treating GPs. The baseline characteristics of participants can be found in **eTable 1**.

3.1. Descriptive statistics of costs and QALYs

Descriptive statistics on QALYs and costs are presented in Tables 1 and 2, respectively based on the observed data (not multiple imputed). At baseline the EQ-5D-5L utility for participants in the control group averaged 0.82 and in the intervention group 0.81. Over the follow-up period, participants in the control group accrued 0.79 QALYs, and participants in the intervention group of 0.82, on average. The non-adjusted total costs per participant, from the healthcare system (direct medical

Table 1
Quality of life of study participants.

Baseline EQ-5D utilities			
	All participants (n = 315)	*Control (n = 156)*	*Intervention (n = 159)*
Mean (SD)	0.82 (0.20)	0.82 (0.20)	0.81 (0.21)
Median (IQR)	0.89 (0.77–0.96)	0.88 (0.80–0.94)	0.89 (0.76–0.97)
Min-Max	0.07 to 1	0.08 to 1	0.07 to 1
QALYs per patient over one year*			
	All participants (n = 277)	*Control (n = 141)*	*Intervention (n = 136)*
Mean (SD)	0.80 (0.18)	0.79 (0.20)	0.82 (0.18)
Median (IQR)	0.87 (0.74–0.93)	0.86 (0.72–0.92)	0.88 (0.78–0.93)
Min-Max	0.07 to 1	0.10 to 1	0.07 to 1

Legend: *QALYs were estimated over the 12-month trial observation period. This table is based on the observed, non-multiple imputed data.

Table 2
Total medical costs (CHF) per patient over one year.

Healthcare system perspective*			
	All participants (n = 323)	*Control (n = 163)*	*Intervention (n = 160)*
Mean (SD)	16′897 (24′605)	17′350 (23′951)	16′436 (25′321)
Median (IQR)	6′057 (3′428 to 17′044)	6′690 (3′178 to 18′258)	5′587 (3′801 to 15′967)
Min-Max	345 to 122′201	429 to 108′046	345 to 122′201
Societal perspective**			
	All participants (n = 323)	*Control (n = 163)*	*Intervention (n = 160)*
Mean (SD)	17′098 (24′660)	17′630 (24′057)	16′555 (25′322)
Median (IQR)	6′150 (3′484 to 17′949)	6′690 (3′238 to 18′258)	5′658 (3′813 to 16′967)
Min-Max	345 to 122′201	429 to 108′046	345 to 122′201

Legend: *The healthcare system perspective includes costs from: GP visits, specialist visits, emergency room visits, hospitalizations, nursing home stay, home care visits, meals on wheels, home help visits, rehabilitation, physiotherapy visits, and other therapies.
**Societal perspective costs additional include indirect costs of informal care provided by persons aged younger than 65 years. | This table is based on the observed, non-multiple imputed data.

costs only) and societal (direct medical costs and indirect costs from informal care) perspectives are shown in Table 2. Direct medical costs were slightly lower for participants in the intervention group (CHF 16′436, with 1 CHF≅ 1.11 as of November 2023) than for those in the control group (CHF 17′350).

Cost differences between the trial groups for each cost item are presented in Fig. 1. Participants in the intervention group were more costly in terms of nursing home stays, medications, GP visits and other therapies, but less costly in terms of hospitalizations, nursing visits at home, home help, physiotherapy visits, meals on wheels, rehabilitation, specialist visits and emergency room visits. eTable 2 in the supporting material shows further details on the cost items.

3.2. Results of cost-effectiveness analyses

Table 3 shows the results of the main GSEM-based cost effectiveness analysis of the OPTICA trial, including all covariate effects. In the trial-wide GSEM analysis, the medication review intervention was estimated to generate 0.026 incremental QALYs (95 % confidence interval (CI): 0.013 to 0.040, p-value <0.001) and to reduce healthcare costs by CHF -1′857 (95 % CI: CHF -3′620 to -93, p-value <0.039). Thus, the intervention strategy dominated the control strategy. The analysis results from the societal perspective were similar; they showed a cost reduction of CHF-1′966 (95 % CI: CHF -3′733 to -200, p-value: 0.029) and an increase in QALYs of 0.026 (95 % CI: 0.013 to 0.039, p-value: <0.001) (eTable 3).

3.3. Subgroup analyses

Table 4 shows the incremental costs and QALYs from the subgroup analyses. The results of the subgroup analyses suggested stronger effects in men, older adults aged 65–74 years and those aged ≥85 years (Table 4).

3.4. Robustness checks

We present the results of additional robustness checks for the main analyses from the healthcare system perspective in the supporting material. In these alternative analyses, the directions of both effects were consistent (lower costs, higher QALYs in the intervention arm) but the results were not always statistically significant. The simple unadjusted cost-effectiveness analysis presented incremental costs of CHF -1′454

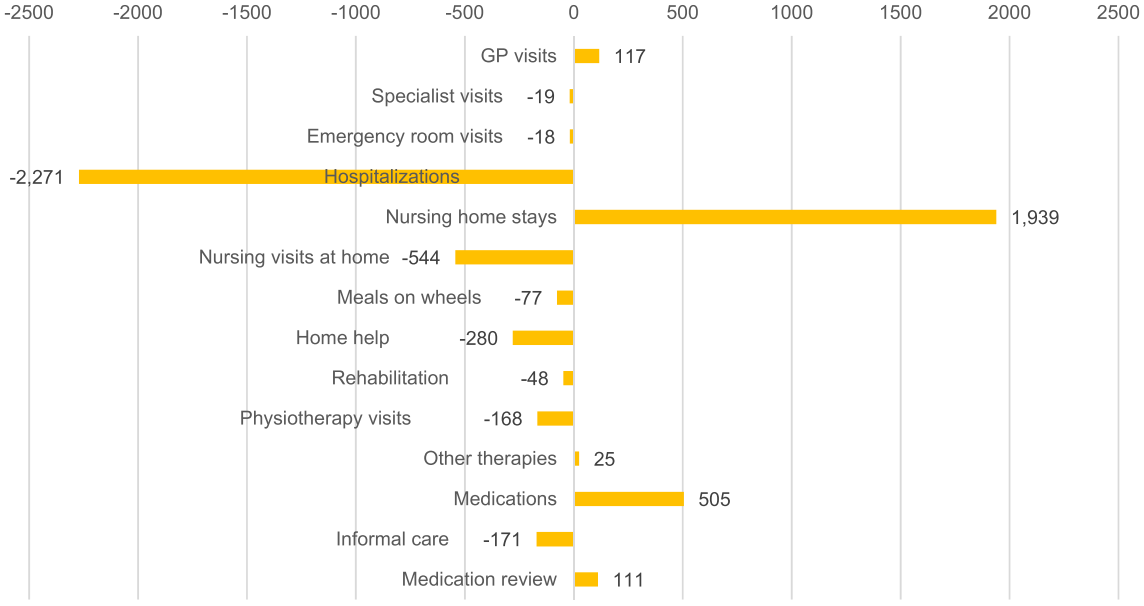

Fig. 1. Mean cost differences between intervention and control group patients (in CHF) broken down into cost categories, per patient. Legend: A positive cost difference (bar on the right hand-side of the figure) means that costs were higher in the intervention arm, while a negative cost difference (on the left hand-side) indicates that costs were higher in the control arm. Costs are presented in Swiss Francs (CHF). The cost category 'medication review' represents the intervention costs. | This figure is based on the observed, non-multiple imputed data.

Table 3
Results of the main cost-effectiveness analysis from the healthcare system perspective, GSEM.

n = 323	Effects on costs (in CHF)	Effects on QALYs
Intervention arm (Reference: control group)	-1′857* [-3′620 to -93]	0.026*** [0.013 to 0.040]
Age groups (Reference: 65–74 years)		
75–84 years	794 [-1′258 to 2′847]	-0.021** [-0.037 to -0.006]
≥ 85 years	-1′464 [-4′243 to 1′315]	-0.06*** [-0.08 to -0.040]
Female sex (Reference: male sex)	1′687 [-280 to 3′653]	0 [-0.015 to 0.014]
Utility at baseline	-8′886*** [-13′636 to -4′137]	0.558*** [0.522 to 0.593]
Number of chronic conditions	118 [-81 to 318]	0.004*** [0.002 to 0.005]
Number of long-term medications	262 [31 to 494]	-0.004*** [-0.005 to -0.002]
Housebound (Reference: not housebound)	1′881 [-3′121 to 6′884]	-0.101*** [-0.139 to -0.063]
Living in nursing home (Reference: community-dwelling)	30′386*** [25′613 to 35′159]	-0.086*** [-0.122 to -0.049]
Smoker (Reference: non-smoker)	2′076* [116 to 4′037]	-0.013*** [-0.027 to 0.001]
More than mandatory schooling	-742 [-2′645 to 1′161]	0.015 [0.001 to 0.029]
Cognitive impairment (reference: none)	18′002*** [12′274 to 23′729]	0.004* [-0.039 to 0.047]
Hours of informal care received during baseline period (per 1-unit increase)	-220* [-417 to -23]	-0.002** [-0.004 to -0.001]
Number of GP visits (per 1-unit increase)	1′025*** [875 to 1′174]	-0.002** [-0.003 to -0.001]
Number of specialist visits (per 1-unit increase)	-188 [-502 to 127]	0.003* [0.001 to 0.005]
Number of hospitalizations (per 1-unit increase)	-1′892 [-4′656 to 872]	0.015 [-0.006 to 0.035]
Number of emergency room visits (per 1-unit increase)	1′915* [90 to 3′739]	0.011 [-0.002 to 0.025]
Observation time (in days)	4 [-11 to 20]	
Number of prescribing omissions as measured by the Assessment of Underutilization	4′230** [1′661 to 6′798]	-0.004 [-0.022 to 0.014]
Averaged Medication Appropriateness Index[a]	194 [-61 to 449]	0.001 [-0.001 to 0.003]
Constant	1′998 [-6′539 to 10′534]	0.37 [0.323 to 0.416]
Observations	323	323

Legend: GSEM models. 95 % confidence intervals in brackets. This table is based on the multiple imputed data. Costs are expressed in Swiss Francs (CHF). The main results of the GSEM-based analysis, i.e., the incremental costs and incremental QALYs representing differences between the intervention and control arms, are equivalent to the coefficients of the variable "intervention arm". Results always represent average values per patient. A positive value of the coefficient for 'intervention arm', for costs/QALYs, indicates that the intervention is associated with higher average costs/QALYs per patient, and vice versa. Intervention arm, female, housebound, smoker, living in nursing home, education status, and cognitive impairment are dichotomous variables. Age was measured in years and presented in categories. Utilities at baseline are ranged from −0.2 to 1. The number of medications (at baseline) and the number of chronic conditions (at baseline) are integers. Observation time was measured in days.
*p < 0.05, **p < 0.01, *** <0.001.
[a] Averaged for the total number of chronic medications.

(95 % CI: CHF -3′699 to 791, p-value: 0.204) and incremental QALYs of 0.024 (95 % CI: 0.007 to 0.043, p-value: 0.007) (eTable 4). The SUR model estimated incremental costs of CHF -2′859 (95 % CI: CHF -4′655 to -1′063, p-value: 0.002) and incremental QALYs of 0.027 (95 % CI: 0.013 to 0.040; p-value: <0.001). Separate linear mixed models of costs estimated a reduction of CHF -1′834 (95 % CI: CHF -5′517 to 1′848; p-value: 0.329) and incremental QALYs of 0.030 (95 % CI: 0.002 to 0.058; p-value: 0.038) (eTable 5). The GSEM model with only observed, non-multiple imputed data showed a cost reduction of CHF -3′462 (95 % CI: 8′312 to 1′468; p-value: 0.170) and incremental QALYs of 0.041 (95 % CI: 0.007 to 0.075; p-value: 0.017) (eTable 5). The GSEM model assuming gamma distributed errors and using a log link function for the costs equation showed similar trends as the main GSEM model (eTable 6), but the results were not statistically significant.

3.5. Sensitivity analyses

Deterministic sensitivity analysis of unit cost parameters showed no substantial impact on the main results (eTable 7). The results of the combined first order uncertainty and probabilistic sensitivity analysis are shown in eFigure1. The majority of the bootstrap replications (61 %) were in the lower right quadrant of the cost-effectiveness plane,

Table 4
Results of cost-effectiveness analyses by subgroups, coefficients of main interest only.

n = 323	Incremental Costs	95 % confidence interval	Incremental QALYs	95 % confidence interval	ICER
Main results	-1′857*	[-3′620 to -93]	0.26***	[-0.013 to 0.040]	dominant[a]
Sex					
Female (n = 177)	-610	[-3′349 to 2′129]	0.041***	[0.024 to 0.059]	dominant
Male (n = 146)	-4′924***	[-7′096 to -2′753]	0.010	[-0.009 to 0.029]	dominant
Age					
65–74 years (n = 111)	-5′775***	[-8′535 to -3′014]	0.009	[-0.010 to 0.028]	dominant
75–84 years (n = 150)	1′688	[-999 to 4′376]	−0.004	[-0.023 to 0.016]	-422′000
≥85 years (n = 62)	-10′737***	[-16′125 to -5′349]	0.105***	[0.070 to 0.140]	dominant
Number of medications					
5–10 (n = 215)	-2′134*	[-4′179 to -88]	0.020*	[-0.004 to 0.036]	dominant
≥10 (n = 93)	-4′808*	[-9′210 to -405]	0.067***	[0.040 to 0.094]	dominant
Number of chronic conditions[b]					
< 4 (n = 43)	4′668***	[2′976 to 6′360]	0.003	[-0.069 to 0.074]	1′556′000
≥ 4 (n = 259)	-3′519**	[-5′568 to 1′471]	0.025**	[0.010 to 0.039]	dominant

Legend: This table is based on the multiple imputed data. Results are shown in Swiss Francs (CHF). The first column characterizes the analysis performed. All analyses were run with the same set of covariates as were used for the main analysis. Column 2 and column 4 report the coefficients of the variable "Intervention arm", representing incremental costs and incremental QALYs respectively. ICER: incremental cost-effectiveness ratio in CHF per QALY gained. The positive ICER values represent saving per QALY lost.
*p < 0.05, **p < 0.01, *** <0.001.
[a] Intervention dominant.
[b] As defined in the statistical analysis plan from the OPTICA trial, the median of 4 was used to define the two categories for the subgroup analyses.

implying dominance of the medication review intervention. Overall, results were robust and not sensitive to the MAR assumption (section S5 of the supporting material, eTable 8). The analyses using the French EQ-5D-5L value set led to similar results as the main analyses based on the German value set (eTable 9), but the results for the cost reduction were not statistically significant.

4. Discussion

In the present analyses, we assessed the cost-effectiveness of an intervention in primary care settings, namely a medication review intervention centered around the use of an electronic clinical decision support tool. According to our main analysis from a healthcare system perspective, the intervention resulted in cost savings of CHF 1′857 per patient and a gain of 0.026 QALYs over the 12-month trial observation period. Results from a societal perspective suggested increased costs savings of CHF 1′966 and a QALY increase of 0.026, confirming the saving of indirect costs as well. The conduct of different robustness and sensitivity analyses confirmed the trends found in the main analysis, but the results were not always statistically significant. For instance, the results of the GSEM analysis of the observed data found a numerically increased but non-significant cost reduction of CHF 3462. Similarly, the GSEM analysis assuming gamma distributed errors and using a log link function for the costs equation found a numerically increased but non-significant cost reduction of 2′529 CHF.

Although the results of the OPTICA trial were inconclusive on whether the medication review intervention led to an improvement in medication appropriateness, or a reduction in prescribing omissions, at 12 months compared to a medication discussion in line with usual care [40,46], there was evidence of successful implementation of prescribing recommendations generated by the STRIPA during the intervention. We thus speculate that the implementation of these prescribing recommendations to stop or start specific medications may have translated into lower healthcare costs in certain categories (e.g., hospitalizations, nursing visits at home) and higher QALYs, but did not affect the main outcomes of the trial measuring overall medication appropriateness and the number of prescribing omissions. Our baseline results pertaining to health-related quality of life are in line with results from previous, international studies with similar study populations of older adults with multimorbidity and polypharmacy and who also used the EQ-5D-5L questionnaire [68–70]. For instance, Lozano-Hernández et al. showed that in their primary care-based clinical trials with older adults aged $\geq$65 with $\geq$3 chronic conditions and $\geq$5 medications conducted in Spain, the mean EQ-5D-5L utility was 0.77 which is very similar to our estimate of 0.80 [70]. With a value of 0.84, the EQ-5D-5L reference values for older German adults aged 65 years and over were reported to be slightly higher than our estimates [69]. This difference is likely due to the fact that all our study participants had multimorbidity and polypharmacy, which was not the case in the German study sample.

Interestingly, the effect of medication reviews centered around the STRIPA seems to have been similar in hospital and primary care settings. Health economic analyses in both hospital and primary care settings (through the OPERAM [38] and the OPTICA trial respectively) found that the medication review interventions were numerically dominant. In OPERAM, the intervention resulted in cost savings of CHF 3′588 per patient over the 12-month trial observation period for all 2′008 trial participants in four countries (95 % CI: 7′716 to 540) and of CHF 7′027 CHF (95 %CI: CHF -13′130 to -924) for patients in Switzerland only. The cost saving was higher than in the OPTICA trial, possibly due to the older and sicker multimorbid patients with more hospitalisations. With regards to quality of life, in both the OPERAM and the OPTICA trials the intervention led to a gain of QALYs over the 12-month trial observation period. Despite the lack of statistical significance in OPERAM, the similarity of results of both trials strengthens the notion that medication review interventions based on the STRIPA may have effects accumulating to improve QALYs and lower costs.

The current evidence on the cost-effectiveness of interventions to improve pharmacotherapy in older adults is mixed [35–37]. A systematic review of economic evaluations of interventions designed to optimize medication use in older adults with multimorbidity and polypharmacy found that the conduct of interventions was generally associated with reductions in healthcare costs [35]. However, it also found that the quality of studies was generally low and key cost elements were often omitted, which leads to difficulties with the interpretability of these results. Similarly, a systematic review of interventions to reduce inappropriate prescribing showed that most interventions led to a reduction in the number of potentially inappropriate medications, but were not cost-effective [36]. Another systematic review of health economic evaluations of deprescribing interventions showed that 85% of interventions were cost-effective, but that results varied across settings, observation periods, and types of intervention [37]. These systematic reviews, however, show the persisting challenges of doing cost-effectiveness analyses of medication optimization interventions and the difficulties of comparing results across interventions, countries and healthcare settings. Our findings are in line with these systematic reviews, as they point towards a cost reduction but also show differences across settings if we compare results from OPTICA to OPERAM.

As the evidence on the clinical outcomes and cost-effectiveness of medication review interventions remains mixed, more research is still needed to better understand the socioeconomic implications of such interventions in primary care settings. Primary care is the first point of contact for many patients with the healthcare system. GPs working in primary care settings are commonly responsible for multimorbid patients with long-term conditions and for managing their treatments [71]. Therefore, it is extremely important that the medication review is done at the first healthcare level, where possible. Additionally, evidence was found that procedures of medication review and deprescribing that should occur regularly in primary care, are often neglected due to physicians' lack of time, perception of increased workload and also physician's concerns about stopping medications, especially when they were prescribed by other colleagues [72]. If such interventions are confirmed to be effective and beneficial, there is a need to identify and address barriers to their scaling-up, such as the current incentive structures for healthcare providers and patients, the integration of such interventions into clinical workflows and workforce planning [35], as a basis for formulating specific policy recommendations for policymakers and healthcare providers. This will help with a better allocation of available healthcare resources for making sure that inappropriate medication use is reduced in older adults and the effectiveness of primary healthcare systems is improved.

5. Limitations

Our analysis has several limitations. First, the sample size of the OPTICA trial was calculated based on the two main primary outcomes (i.e., medication appropriateness and prescribing omissions) and not powered to detect differences in costs and quality of life. Second, the cost-effectiveness analyses were limited to a time frame of 12 months. Future cost effectiveness analyses would benefit from increasing the time horizon, adding scenario analyses of how results could change based on decreased or increased effectiveness due to contextual factors, incorporating quality measure impacts, and including additional value elements associated with reducing the burden of taking many medications and aligning treatment plans with patient care goals [73]. Third, despite the pragmatic approach to data collection in the OPTICA trial and despite using multiple imputation to address the issue of missing data, they remain a potential source of bias. Fourth, there were some unclear data points in the trial data, especially regarding medication use (e.g. medication without a stop date, etc.). To some extent, this could have led to data distortion. Next, in the absence of a Swiss EQ-5D value set, we used the German value set for the main analyses and the French value set in secondary analyses, which led to consistent results. Finally,

around 10 % of trial participants had been recruited in winter 2020, right before the onset of the COVID-19 pandemic, which could have affected their health services use during the 12-month follow-up period. However, this would have affected both trial groups in a non-differential way.

6. Conclusion

This study sheds light on how to deal with a healthcare system decision problem, namely making medication-related treatment decisions in older multimorbid patients. We did this by assessing the cost-effectiveness of a medication review intervention used in primary care settings. The medication review intervention studied in the OPTICA trial in a Swiss primary care setting, centered around the use of an electronic clinical decision support system, was dominant with a potential saving of about CHF -1′857 and a gain of 0.026 QALYs per patient over a 12-month time horizon. In robustness analyses, directions of effects were fully consistent, albeit some effect estimates non-significant. The similarity of results of the OPERAM [38] and OPTICA trials strengthens the notion that medication review interventions based on the STRIPA may have effects accumulating to better QALYs and lower costs.

Our study indicates that medication review interventions potentially contribute to the effectiveness of primary healthcare systems by supporting GPs to be more effective in their practice. If confirmed by more research, our results would lead to a better allocation of available healthcare resources by making sure that inappropriate medication use is reduced in older adults and the effectiveness of primary healthcare systems is improved. At the same time, since older patients with multimorbidity are among the most vulnerable patients, such interventions have the potential to improve the equity of primary healthcare systems.

Conflict of interest disclosures

All authors do not have any conflicts of interest to declare.

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Role of the funder

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical approval

The study protocol of the OPTICA trial and other documentation was approved by the competent ethics committee of the canton of Bern (KEK), Switzerland, and the Swiss regulatory authority (Swissmedic) (BASEC ID: 2018–00914). The KEK and Swissmedic received annually safety reports and were informed about the end of the study. All participants gave their written informed consent. The OPTICA trial was performed in accordance with relevant regulations and guidelines.

Data sharing statement

We will make the data for this study available to other researchers upon request. The data will be made available for scientific research purposes, after the proposed analysis plan has been approved. Data and documentation will be made available through a secure file exchange platform after approval of the proposal. In addition, a data transfer agreement must be signed (which defines obligations that the data requester must adhere to with regard to privacy and data handling). Deidentified participant data limited to the data used for the proposed project will be made available, along with a data dictionary and annotated case report forms. For data access, please contact the corresponding author.

CRediT authorship contribution statement

Katharina Tabea Jungo: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paola Salari:** Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rahel Meier:** Writing – review & editing, Investigation. **Michael Bagattini:** Writing – review & editing, Investigation. **Marco Spruit:** Writing – review & editing, Investigation. **Nicolas Rodondi:** Writing – review & editing, Investigation, Funding acquisition. **Sven Streit:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Matthias Schwenkglenks:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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