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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Support for People Starting a New Medication for a Long-Term Condition Through Community Pharmacies: An Economic Evaluation of the New Medicine Service (NMS) Compared with Normal Practice

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Abstract

Background The English community pharmacy New Medicine Service (NMS) significantly increases patient adherence to medicines, compared with normal practice. We examined the cost effectiveness of NMS compared with normal practice by combining adherence improvement and intervention costs with the effect of increased adherence on patient outcomes and healthcare costs.

Methods We developed Markov models for diseases targeted by the NMS (hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease, asthma and antiplatelet regimens) to assess the impact of patients' non-adherence. Clinical event probability, treatment pathway, resource use and costs were extracted from literature and costing tariffs. Incremental costs and outcomes associated with each disease were incorporated additively into a composite probabilistic model and combined with adherence rates and intervention costs from the trial. Costs per extra quality-adjusted life-year (QALY) were calculated from the perspective of NHS England, using a lifetime horizon.

Results NMS generated a mean of 0.05 (95% CI 0.00–0.13) more QALYs per patient, at a mean reduced cost of −£144 (95% CI −769 to 73). The NMS dominates normal practice with a probability of 0.78 [incremental cost-effectiveness ratio (ICER) −£3166 per QALY]. NMS has a 96.7% probability of cost effectiveness compared with normal practice at a willingness to pay of £20,000 per QALY. Sensitivity analysis demonstrated that targeting each disease with NMS has a probability over 0.90 of cost effectiveness compared with normal practice at a willingness to pay of £20,000 per QALY.

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Conclusions Our study suggests that the NMS increased patient medicine adherence compared with normal practice, which translated into increased health gain at reduced overall cost.

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Key Points for Decision Makers

The New Medicine Service (NMS) appears effective and cost effective compared with normal practice.

Increased patient adherence to their new medicine translated into increased health gain at reduced overall cost that is well below most accepted thresholds for technology implementation.

This is a simple intervention which has been popular with community pharmacists and patients, and is transferable into most therapeutic areas.

Consideration should be given to extending and evaluating the NMS in other potentially beneficial areas, and these results are likely to be transferable into health systems less integrated than the UK NHS.

1 Introduction

Adherence to medication is defined as the extent to which individuals take their medication as prescribed [1]. Non-adherence is commonly reported in key prevalent diseases such as chronic obstructive pulmonary disease (COPD): 33% [2]; schizophrenia: 52% [3]; asthma: 67% [4]; and diabetes mellitus: 78% [5]. Non-adherence causes reduced quality of life, increased hospitalisations and premature deaths [5–7]. A recent estimate sets the global economic impact at US $285 billion, 57% of the economic impact of suboptimal medicines use [8]. Estimated opportunity cost to the English National Health Service (NHS England) of health gains foregone because of non-adherence is over £930 million per annum in just five diseases [9]: asthma, type 2 diabetes, high cholesterol/coronary heart disease, hypertension and schizophrenia. Improving adherence from current levels to 80% across these five areas would save the NHS £500 million per annum [9].

One effective way to improve adherence focuses on patients who receive a new medicine for a long-term condition, as they often experience problems that can quickly lead to a proportion becoming non-adherent over time [10, 11]. Barber et al. developed an intervention with a theoretical basis in the self-regulatory model (SRM) [10, 12], designed to elicit patients' experiences with, and concerns about, their new medicine. This intervention significantly reduced non-adherence and was cost effective [13, 14]. Its approach was adopted as government policy [15] and in adapted form was launched as the national New Medicine Service (NMS) in 2011 [15] for people starting a new medicine for asthma/COPD, type 2 diabetes, hypertension or antiplatelet/anticoagulant treatment [16]. The design differs from the original intervention as there are four specified patient groups associated with high rates of avoidable hospital admissions. The original intervention was delivered via a centralised telephone service, whereas NMS is delivered by community pharmacists providing the medicine, either face-to-face or over the telephone. Accredited pharmacies provide NMS, are remunerated for each episode of care and have guidance on how to conduct the intervention [16]. Of 11,495 community pharmacies in England, 10,553 (91.2%) had delivered the NMS to at least one patient between November 2011 and January 2014 [17].

The aim of this study was to evaluate the cost effectiveness of the NMS compared with normal practice in changing medicine-taking behaviour, following published reporting criteria [18]. The incremental cost per extra quality-adjusted-life-year (QALY) generated was determined from the perspective of the funder (NHS England).

2 Methods

A randomised controlled trial (RCT) has assessed NMS effectiveness [19]. At 10 weeks, NMS significantly increased the proportion of patient-reported adherence by 10.2–70.7%, compared with normal practice of 60.5% [20, 21]. Trial design precluded observation of long-term outcomes and costs from changes in adherence. Many benefits of improved adherence are delivered well into the future. Here, we simulated the effect of observed adherence increases on patient outcomes and NHS costs by designing economic models for each drug–disease pair. We developed this method previously in a cross-therapeutic intervention focused on medication errors [22]. Here, we combine the results from the NMS trial with projected harm from non-adherence to generate estimates of patient outcomes and NHS costs (Fig. 1).

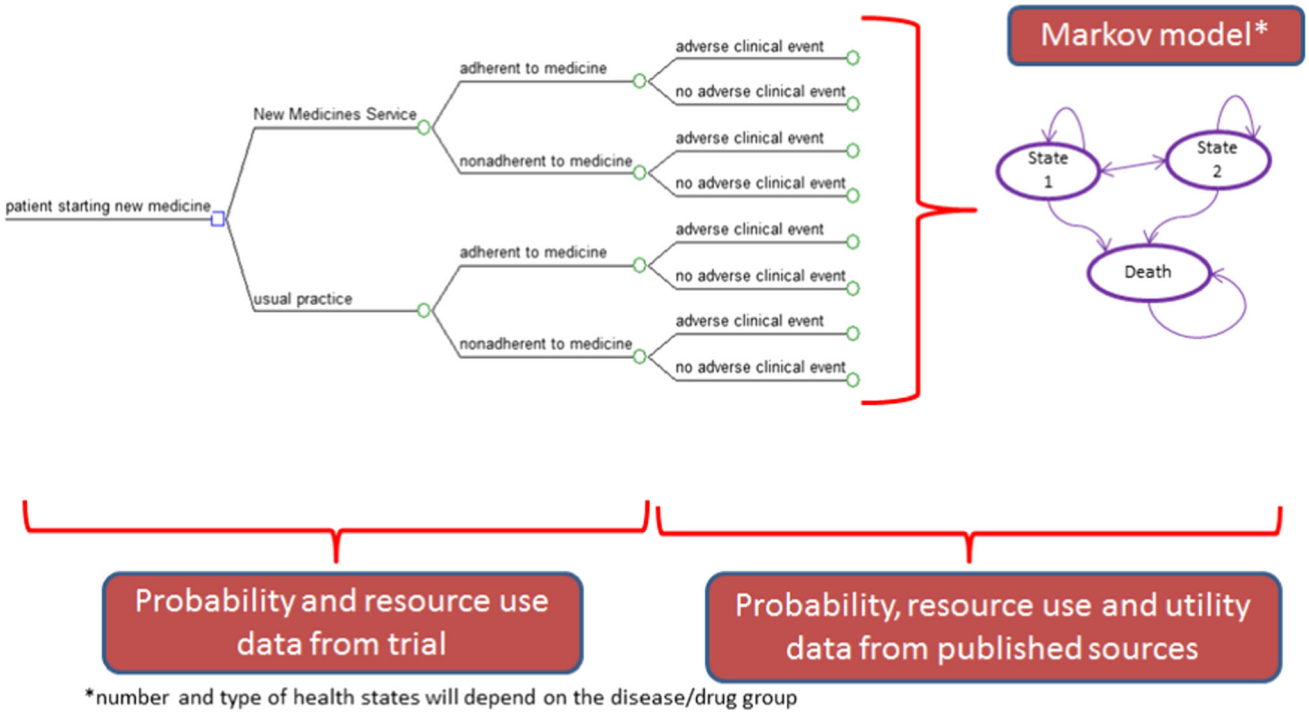

Fig. 1 Overview of economic model developed to combine New Medicine Service (NMS) trial results with estimates of harm caused by non-adherence

2.1 Intervention and Comparators, Patient Characteristics and Outcomes

2.1.1 New Medicine Service (NMS) Intervention

NMS begins with the patient's initial presentation with a prescription for a medicine that is new to them in a community pharmacy. Patients can be referred by their prescriber, self-refer, or the pharmacist can invite the patient to use the service. The intervention consists of a one-to-one consultation 7–14 days later, with a follow-up 14–21 days after that, the whole episode lasting 5 weeks. These are the points where the pharmacist asks about adherence. Outcomes were collected by researchers at 10 weeks.

The primary aim of the intervention, which can be face-to-face or telephone-based (in this study, all follow-up was via telephone) is the patient-centred identification of any problems with the treatment and provision of appropriate support or action [23]. Action may include referring the patient back to their prescriber (Fig. 2).

2.1.2 Normal Practice

Normal practice was the pharmacist's usual advice. There was no planned follow-up.

2.1.3 Study Outcomes

The RCT primary outcome was self-reported adherence at 10 weeks, considered the minimum time required to demonstrate behavioural change [13].

Patients were contacted by telephone by a researcher and asked about adherence behaviour using the question: "People often miss taking doses of their medicines, for a wide range of reasons. Have you missed any doses of your new medicine, or changed when you take it? (Prompt: when did you last miss a dose?)" [24]. This is the adherence question asked by pharmacists during the NMS intervention and follow-up. The patient was defined as non-adherent if any doses were missed without the advice of a medical professional in the previous 7 days.

Little validation has been carried out for most self-report adherence measures [25]. An existing scale, the Morisky Eight Item Medication Adherence Scale (MMAS-8), validated in hypertension, was used to support our primary outcome measure, and collected via self-completion postal questionnaire [26]. These results are available in [20].

Sample size was determined according to the primary outcome at 10 weeks (see electronic supplementary material and [19–21]). Sample characteristics and study outcomes are reported in Tables 1 and 2. The characteristics

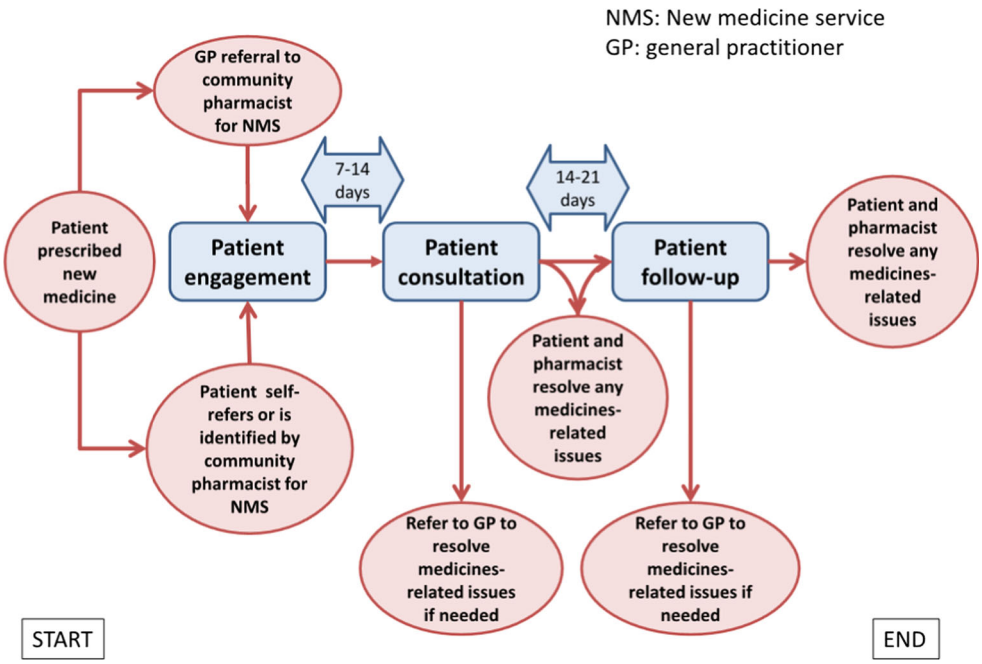

Fig. 2 New Medicine Service intervention

Table 1 Patient and pharmacy characteristics by treatment arm

Patient characteristics	Normal practice	New Medicine Service
Total	253	251
Antiplatelet/anticoagulant ($n = 43$, 8.5%)	19 (7.5)	24 (9.6)
Asthma/COPD ($n = 117$, 23.2%)	58 (22.9)	59 (23.5)
Hypertension ($n = 249$, 49.4%)	128 (50.6)	121 (48.2)
Type 2 diabetes ($n = 95$, 18.8%)	48 (19.0)	47 (18.7)
Female ($n = 260$, 51.6%)	135 (53.4)	125 (49.8)
Age of total cohort (year) *n*; mean (SD)	253; 59.3 (15.0)	251; 59.5 (15.3)
Total withdrawals by week 10; *n* (%)	37 (14.6)	16 (6.4)
Economic deprivation based on IMD rank[a]; mean (SD)		
Pharmacy study sites	10,241.5 (8117.2)	9880.0 (7723.0)
Study patients	13,708.3 (8546.4)	14,325.5 (8906.8)

COPD chronic obstructive pulmonary disease, *n* number, *SD* standard deviation

[a] IMD: Index of Multiple Deprivation (rank)—each area of England is ranked based on its economic deprivation score. The most deprived area of England is ranked 1. The rank only indicates relative position and does not provide a quantifiable comparison. An area ranked 50 is not twice as deprived as the area ranked 100 (English deprivation rank scores range from 1 to 32482)

(age, sex, ethnicity, disease area) of the RCT cohort were very similar to the population accessed from the national PharmOutcomes records of 451,222 NMS consultations recorded from October 2011 to 2 December 2013 [20]. With regards to economic deprivation, the median Index of Multiple Deprivation (IMD) rank for England is 16,241, indicating that our study population is slightly more deprived than average.

2.1.4 Intervention and Within-Trial Costs

Costs comprised patient-level intervention costs and healthcare contact over the 10-week follow-up period. Subsequent resource use at follow-up was obtained from patient diaries, 116 normal practice and 122 NMS, consisting of NHS (primary care, secondary care, allied health professionals) and non-NHS costs (community-based

Table 2 Adherence results for NMS and normal practice measured using NMS question and MMAS-8 at 10 weeks

ITT[a] at 10 weeks	Unadjusted probability (95% CI)[b]	Unadjusted odds ratio[b] (95% CI)	Adjusted probability (95% CI)[c]	Adjusted odds ratio[c] (95% CI)
Adherence NMS ($N = 378$)				
Normal practice	0.61 (0.54–0.67)	1.58 (1.03–2.42); $p = 0.037$	0.63 (0.55–0.70)	1.67 (1.06–2.62); $p = 0.027$
NMS	0.71 (0.64–0.77)		0.74 (0.67–0.81)	1.62 (1.04–2.53)[d]; $p = 0.032$
Adherence MMAS-8 ($N = 267$)				
Normal practice	0.59 (0.51–0.67)	1.74 (1.04–2.90); $p = 0.036$	0.65 (0.56–0.75)	1.88 (1.06–3.34); $p = 0.030$
NMS	0.72 (0.64–0.80)		0.78 (0.70–0.86)	1.77 (0.96–3.28)[d]; $p = 0.068$

CI confidence intervals, *ITT* intention to treat, *MMAS-8* Morisky eight-item Medication Adherence Scale, *NMS* New Medicine Service

[a] The ITT cohort was defined as all patients within a randomisation arm with measured outcomes, or who were followed up to the end of the study

[b] Simple logistic regression model

[c] Multi-level logistic regression model adjusted for recruiting pharmacy, disease, age, sex and medication count (level 1: patient, level 2: pharmacy)

[d] Model accounting for multiple imputation of missing data

practitioners and allied health professionals including community pharmacists). These data were combined with NHS reference costs [27] and Personal Social Services Research Unit (PSSRU) costs [28] (see electronic supplementary material) to derive patient-level total costs. Comparison between treatment arms at patient level was made using a two-sample *t*-test on the original dataset, or on a bootstrapped dataset, depending on the normality of the distribution of costs [29]. Mean (median, range) total NHS costs for patients in normal practice and NMS are £261 (£121, 0–1669), and £239 (£135, 25–1483), respectively. There was a general trend to reduced NHS costs, statistically non-significant, for the NMS intervention: −£21 (95% CI −59 to 150; $p = 0.1281$).

2.2 Clinical and Economic Impact of Non-adherence

Six Markov models were developed in TreeAge Pro (TreeAge Software Inc, One Bank Street, Williamstown, MA, 01267, USA). The most commonly prescribed medicine within the four NMS areas was used to inform a model representative of that disease group. Asthma and COPD were modelled separately due to the different natural history of the disease and impact of non-adherence. As hypertension represented over 50% of the cohort, two models were built to reflect the two most common medication groups prescribed: calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors—index NMS drugs for 34.4 and 24.1% of hypertensive patients, respectively.

The models were hypertension–amlodipine; hypertension–ramipril; asthma-inhaled corticosteroid (ICS)–beclometasone; COPD–tiotropium; diabetes–metformin; anticoagulants–aspirin. Each model had a lifetime horizon (until the age of 100), an annual (hypertension, diabetes, anticoagulant), monthly (COPD), or weekly (asthma) cycle length with half-cycle correction and the UK treasury recommended 3.5% discount rate for both costs and outcomes. Age-related mortality was included in each model.

Each model described the consequences of being adherent to the medicine, compared with non-adherence. Entry age, disease severity, drug prescribed and health status in the models were those in the RCT cohort.

2.2.1 Sources of Data and Model Design

Each model is described in detail in the electronic supplementary material. For all models apart from aspirin we utilised and adapted existing published models to optimise design (amlodipine [30], ramipril [31], beclometasone [32], tiotropium [33], metformin [34]). We derived the aspirin model structure from case–control studies analysing outcomes in large UK cohorts of patients with a first prescription of aspirin [35, 36].

2.2.2 Literature Searches

A literature search was conducted through Medline, Embase and Web of Science using treatment pathway-specific search terms. Databases were searched to the end of 2013. References in English and limited to humans were

included. After excluding duplicate records, studies were included if they examined issues on the incidence, prevalence, treatment or resource use of the consequences of non-adherence. Reference lists of the retrieved references were hand-searched.

2.2.3 Transition Probabilities

Data came preferentially from up-to-date UK sources that reflected the NMS trial patient characteristics. The quality of evidence varied for the different models. Data were taken from RCTs such as effect of calcium channel blockers [37] or ACE inhibitors [31] on major cardiovascular consequences in hypertension, and effects of inhaled steroids on asthma control [38]. Observational data were available to populate parts of the metformin and aspirin models. In the metformin model, transition probabilities are based on UKPDS68 equations [34], using data on 3642 (type 2 diabetes) patients from UKPDS (United Kingdom Prospective Diabetes Study) for whom annual data on potential risk factors were available [39]. In the aspirin model, data were taken from case–control studies analysing outcomes in large UK cohorts of patients with a first prescription of aspirin [35, 36]. Where no other primary sources were available, transition probabilities estimated in published models were used, such as transition probabilities for exacerbations in COPD [40].

2.2.4 Identifying the Effect of Non-adherence on Outcomes

Quality of evidence for the effect of non-adherence on outcomes varied widely. Where possible, data on the impact of non-adherence were taken from large long-term cohort studies, such as the impact of non-adherence to antihypertensive treatment on long-term cardiovascular outcomes for the amlodipine [41] and ramipril models [42], and for myocardial infarction/chronic heart disease death [35] and for stroke/transient ischemic attack [36] in the aspirin model. The effect of non-adherence in the metformin model was modelled via a higher level of HbA1c [43], which resulted in estimated higher probabilities of diabetes complications. We used data from a study analysing non-adherence to antidiabetic medications (using MMAS-8 [26]) and HbA1c level in 301 patients with diagnosed type 2 diabetes in the US [43], good adherence (MMAS-8 score $\geq$3) was associated with 10% lower HbA1c ($p = 0.0003$).

Little data on the effect of non-adherence on asthma or COPD control was available. We derived the effect of non-adherence on asthma control from baseline data of the SIMPLE study (observational trial of community pharmacy intervention for asthma management), combining adherence to ICS assessed using prescription refill data in the previous 6 months and Asthma Control Test [44] (ACT, $0 \leq \text{ACT} \leq 25$) results [45]. The most relevant results about adherence in COPD were available from Vestbo et al. [7]. Based on the Toward a Revolution in COPD Health (TORCH) study [46], they reported that adherent patients had a 60% [hazard ratio (HR) 0.4; 95% CI 0.35–0.46] lower risk of death and a 44% [relative risk (RR) 0.56; 95% CI 0.48–0.65] lower rate of severe exacerbations [7]. We found no data to inform the effect of adherence on frequency of non-severe exacerbations, so assumed that the HR was equivalent to severe exacerbations.

2.2.5 Health Status

For the amlodipine, ramipril, metformin and aspirin models, utilities were based on EQ-5D data from the Health Survey for England (2003, 2006), adjusted for age, sex and disease status [47]. Asthma utilities were taken from an RCT of ICS, using the Asthma Quality of Life Questionnaire (AQLQ [48]) scores [49]. Utilities for the COPD model were derived from an RCT of tiotropium [33, 50].

2.2.6 Resource Use and Unit Costs

Resource-use data came preferentially from up-to-date UK sources of observation of clinical practice, with disaggregated resource-use data, to allow attachment of current unit prices. If possible, individual patient data were used, with associated measures of mean and variation. If these were not available, point estimates were used, with carefully specified deterministic ranges, and standard methods for allocating distributions to these data were used.

The probability, cost and utility data were assigned beta, gamma and beta distributions, respectively, and are summarised in Tables 3, 4 and 5. Costs are given in year 2014 values.

2.3 Incremental Analysis

In the base case, we applied probabilities of adherence to each model, estimated from 10-week trial results, for the primary adherence outcome measure (Table 2). Adjusted probability of adherence in the NMS group was 74%, probability of adherence in normal practice was 63%, and the odds ratio (OR) (NMS vs normal practice) was 1.67 (1.06–2.62; $p = 0.027$). Adherence was assumed to stay the same in both arms over the time horizon of the model.

Each model was populated with probability, cost and health status data. This allowed the generation of the outcomes and costs in a cohort who were adherent, and in a

Table 3 NHS and non-NHS costs for normal practice and NMS intervention

Cost category	Normal practice ($n = 116$) Mean cost/£ (n, SE)	NMS ($n = 122$) Mean cost/£ (n, SE)
Primary care total	81.6 (111, 5.76)	72.18 (115, 4.99)
GP total	67.7 (100, 5.26)	60.94 (105, 4.34)
GP contact	59.21 (95, 4.35)	57.13 (98, 4.36)
GP home visit	3.66 (2, 3.02)	0.7 (1, 0.7)
GP phone call	4.83 (19, 1.11)	3.11 (13, 0.93)
Nursing total	13.9 (79, 1.53)	11.24 (73, 1.56)
Nurse contact	12.49 (73, 1.46)	10.73 (72, 1.51)
Nurse home visit	0.92 (3, 0.60)	0.38 (2, 0.28)
Nurse phone call	0.49 (7, 0.29)	0.13 (3, 0.08)
Secondary care total	175.54 (53, 28.76)	141.23 (52, 25.79)
Outpatient	98.85 (47, 16.42)	91.2 (46, 16.19)
Accident and emergency	2.02 (2, 1.42)	0.96 (1, 0.96)
Day case	63.01 (17, 16.00)	49.08 (13, 16.62)
Inpatient	11.66 (1, 11.66)	0 (0, 0)
Allied HCPs (NHS) total[a]	3.73 (19, 1.13)	1.75 (16, 0.48)
Allied HCP contact	2.37 (16, 0.66)	1.48 (13, 0.43)
Allied HCP home visit	1.27 (3, 0.77)	0.15 (1, 0.15)
Allied HCP phone call	0.08 (2, 0.06)	0.12 (3, 0.07)
NMS intervention	0	24.60
Total NHS cost	260.87 (114, 30.23)*	239.66 (121, 26.61)
Community-based practitioner total[b]	4.81 (5, 2.66)	4.71 (2, 4.44)
Community-based practitioner phone call	0.08 (2, 0.06)	0.08 (1, 0.08)
Community-based practitioner contact	0.14 (1, 0.14)	0.27 (1, 0.27)
Community-based practitioner home visit	4.58 (4, 2.54)	4.36 (1, 4.36)
Allied HCPs non-NHS total	7.4 (54, 0.99)	8.69 (64, 1.04)
Community pharmacist	6.31 (48, 0.93)	7.57 (61, 0.91)
Other associated HCPs non-NHS[c]	1.1 (10, 0.35)	1.13 (11, 0.34)
Total non-NHS cost	12.21 (56, 2.86)	13.4 (65, 4.5)

GP general practitioner, *HCP* healthcare practitioner, *NHS* National Health Service, *NMS* New Medicine Service, *SE* standard error

* Mean difference in costs: £21.11 (95% CI −59.01 to 100.24; $p = 0.1281$)

[a] Allied HCPs (NHS) include podiatrists, phlebotomists

[b] Community-based practitioners include social workers

[c] Allied HCPs (non-NHS) include dentists, opticians, chiropractors

cohort who were non-adherent to the medicine. The adherence for each drug–disease pair at 10-week follow-up in the NMS and normal practice arms were combined with the appropriate disease-drug-specific model. Using these models, we generated the difference in patient outcome and costs between NMS and normal practice for each disease–drug pair. Probabilistic estimates of costs and outcomes were derived, the analysis generating 5000 iterations, using Monte Carlo simulation for each disease–drug pair.

The incremental costs and outcomes associated with each disease–drug pair were incorporated additively into the economic model to allow derivation of the total incremental impact of the NMS intervention costs and outcomes for all six disease–drug pairs. At this point the NMS intervention costs were added.

Deterministic and probabilistic incremental economic analyses were carried out. The incremental cost-per-QALY generated by NMS over normal practice was calculated using the following equation:

$$(\text{Cost}_{\text{NMS}} - \text{Cost}_{\text{Normalpractice}}) / (\text{QALY}_{\text{NMS}} - \text{QALY}_{\text{Normalpractice}}).$$

Utilising Microsoft Excel, we used 5000 Monte Carlo simulations to obtain the incremental cost-effectiveness

Table 4 Summary of probabilities in the Markov models in the adherent and non-adherent groups for each of the six models (for full details of parameter derivation for each model, see electronic supplementary material, Table 16)

Parameter	Estimate and source	
1. Hypertension–amlodipine model		
P [stroke for adherent patient]	Age- and sex-dependent risk from ASCOT study [30]	
P [MI/fatal CHD for adherent patient]		
P [stroke for non-adherent patient]	P [stroke for adherent patient] × effect of non-adherence (HR)	
P [MI/fatal CHD for non-adherent patient]	P [MI/fatal CHD for adherent patient] × effect of non-adherence (HR)	
Effect of non-adherence, HR	Intermediate vs high adherence: HR 1.39 [41]	
P [MI/CHD (non-fatal MI or fatal CHD) being fatal CHD]	Age- and sex-dependent risk from ASCOT study [30]	
P [stroke being fatal]		
P [death for MI survivors]		
P [death for stroke survivors]		
P [death from all other causes]	Age and sex dependent [73]	
2. Hypertension–ramipril model		
P [fatal cardiovascular event (MI, stroke,coronary event, heart failure, other cardiovascular events, first events) for adherent patient]	0.0068 [31]	
P [fatal cardiovascular event for non-adherent patient]	0.0083, P [fatal cardiovascular event for adherent patient] × effect of non-adherence (HR)	
P [non-fatal MI for adherent patient]	0.0041 [31]	
P [non-fatal stroke for adherent patient]	0.0075 [31]	
P [non-fatal MI for adherent patient]	0.0050, P [non-fatal MI for adherent patient] × effect of non-adherence (HR)	
P [non-fatal stroke for adherent patient]	0.0092, P [non-fatal stroke for adherent patient] × effect of non-adherence (HR)	
P [death for MI survivors]	Age, sex, number of years from MI dependent [74], personal communication	
P [death for stroke survivors]	Age, sex, number of years from stroke dependent [75], personal communication	
Effect of non-adherence, HR	HR 0.81 (95% CI 0.67–0.98), adjusted for age and sex (base-case scenario) [42]	
P [death from all other causes]	Age and sex dependent [73]	
3. Asthma–beclometasone model		
	Adherent patients [38, 76]	Non-adherent patients [38, 76]
P [successful control → sub-optimal control]	$0.1563 \times (1 - p)^a$	$0.3710 \times (1 - p)$ [45][a]
P [successful control → primary care exacerbation]	$0.0135 \times (1 - p)^a$	
P [successful control → secondary care exacerbation]	$0.0054 \times (1 - p)^a$	
P [sub-optimal control → successful control]	$0.1394 \times (1 - p)^a$	
P [sub-optimal control → sub-optimal control]	$0.8322 \times (1 - p)^a$	
P [sub-optimal control → primary care exacerbation]	$0.0174 \times (1 - p)^a$	
P [sub-optimal control → secondary care exacerbation]	$0.0109 \times (1 - p)^a$	
P [secondary care exacerbation → successful control]	$0.2000 \times (1 - p)^a$	
P [secondary care exacerbation → sub-optimal control]	$0.2000 \times (1 - p)^a$	
P [secondary care exacerbation → primary care exacerbation]	$0.4000 \times (1 - p)^a$	
P [secondary care exacerbation → secondary care exacerbation]	$0.4000 \times (1 - p)^a$	
P [death from all other causes]	Age and sex dependent [73]	

Table 4 continued

Parameter	Estimate and source	
4. COPD–tiotropium model		
Probability of exacerbation	Adherent patients [7, 77]	Non-adherent patients [7, 77]
Moderate COPD → exacerbation	0.051	0.089
Moderate COPD → severe exacerbation given an exacerbation occurs	0.097	0.165
Severe COPD → exacerbation	0.075	0.129
Severe COPD → severe exacerbation given an exacerbation occurs	0.136	0.229
Very severe COPD → exacerbation	0.096	0.164
Very severe COPD → severe exacerbation given an exacerbation occurs	0.192	0.316
Effect of non-adherence on exacerbations rate, HR	44% (HR 0.56; 95% CI 0.48–0.65); lower rate of severe exacerbations for adherent patients [7]	
Effect of non-adherence on death rate, HR	60% (HR 0.4; 95% CI 0.35–0.46); lower risk of death for adherent patients [7]	
P [moving between chronic health states] year 1, subsequent years	[77]	
5. Diabetes–metformin model		
P [fatal first diabetes complication (MI, CHF, stroke, renal failure, amputation) for adherent patient]	Patient characteristic and HbA1c-dependent value from UKPDS68 [34] and UKPDS34 [39]	
P [fatal first diabetes complication for nonadherent patient]		
P [non-fatal first diabetes complication (MI, CHF, stroke, renal failure, amputation, blindness, IHD) for adherent patient]		
P [non-fatal first diabetes complication for nonadherent patient]		
P [second non-fatal diabetes complication after the first complication]		
P [death from all other causes]	Age and sex dependent [73]	
Effect of non-adherence	HbA1c multiplier for non-adherent patient: 1.105 (95% CI 1.047–1.166)	
	HbA1c for non-adherent patient (age) = HbA1c for adherent patient (age) × 1.105 [43]	
6. Antiplatelets/anticoagulants–aspirin model		
	Adherent patient	Non-adherent patient
P [event-free → non-fatal MI[b]]	0.0056	0.0086 [35]
P [event-free → non-fatal stroke[b]]	0.0019	0.0028 [36]
P [event-free → fatal MI/CHD[b]]	0.0015	0.0023 [35]
P [event-free → fatal stroke[b]]	0.0002	0.0003 [36]
P [non-fatal MI → death]	Dependent on age, year after the first MI, sex [74]	
P [non-fatal stroke → death]	Dependent on age, year after the first stroke, sex [75]	
P [death from all other causes]	Age and sex dependent [73]	

CHD coronary heart disease, *CHF* congestive heart failure, *CI* confidence intervals, *COPD* chronic obstructive pulmonary disease, *HbA1c* glycosylated haemoglobin, *HR* hazard ratio, *IHD* ischaemic heart disease, *MI* myocardial infarction, *p* probability, *SE* standard error, *UKPDS* United Kingdom Prospective Diabetes Study

[a] Transition probabilities between asthma states from [76, 38] with mortality (P[death from all other causes]) incorporated (*p*)

[b] Probabilities for three age groups, 50–64 years, 65–74 and 75–84 years, respectively. Probabilities calculated from incidence rates reported. In the case of non-adherent patients, incident rates adjusted by the effect of non-adherence (reported rate ratios for events, comparing non-adherence vs adherence)

Table 5 Summary of utilities and costs for the Markov models in the adherent and non-adherent groups for each of the six models (for full details of parameter derivation for each model, see electronic supplementary material, Table 17)

Health state	Utility weights	Mean cost/patient (£; 2014 values)
1. Hypertension–amlodipine		
Well	Age- and sex-dependent, no cardiovascular event [47]	Mean annual cost of medication (amlodipine): 13.4 [78, 79]
Non-fatal MI	Age- and sex-dependent + MI history	1st year: 5704.6
	Utility decrement (MI) added [47]	≥2nd year: 986.7 [78–81]
Non-fatal stroke	Age- and sex-dependent + stroke history	1st year: 4161.8
	Utility decrement (stroke) added [47]	≥2nd year: 770.9 [78–81]
2. Hypertension–ramipril		
Well	Age- and sex-dependent no cardiovascular event [47]	Mean annual cost of medication (ramipril): 95.8 [78, 79]
Non-fatal MI	Age- and sex-dependent + MI history	1st year: 5787
	Utility decrement (MI) [47]	≥2nd year: 1069
Non-fatal stroke	Age- and sex-dependent + stroke history	1st year: 4244
	Utility decrement (stroke) added [47]	≥2nd year: 853
3. Asthma–beclometasone		
Successful control	0.900 [49, 82]	13.4 [32, 81]
Sub-optimal control	0.842 [49, 82]	34.9 [32, 81]
Asthma exacerbation	Primary care-managed: 0.57	Primary care-managed: 105.6
	Hospital-managed: 0.33 [83]	Hospital-managed: 2013.1 [76, 81]
4. COPD–tiotropium		
Moderate COPD	0.787 [84, 85]	46.53 per month [86]
Severe COPD	0.750 [84, 85]	79.32 per month [86]
Very severe COPD	0.647 [84, 85]	125.13 per month [86]
COPD exacerbation	Non-severe decrement: 0.01	Non-severe: 75.97
	Severe decrement: 0.042 [50, 87]	Severe: 1372 [86]
5. Diabetes–metformin		
Well	Age- and sex-dependent, no cardiovascular event [47]	Mean annual cost of medication (metformin): 8.05 [78, 79]
Other diabetes health states	Utility decrement [88]	Fatal event; non-fatal event 1st year; non-fatal event ≥2nd year [81, 88, 89]
IHD	−0.090	N/A; 2916.4; 963.8
MI	−0.055	1477.7; 5624.0; 926.0
CHF	−0.108	3252.8; 3252.8; 1140.2
Stroke	−0.164	4338.9;3440.0; 650.1
Amputation	−0.280	11,200.4; 11,200.4; 646.9
Blindness	−0.074	N/A; 1469.0; 622.0
Renal failure	−0.263	32,452.5; 32,452.5; 32,452.5
6. Antiplatelets/anticoagulants–aspirin		
Event-free	Age- and sex-dependent + utility decrement for MI/stroke history [35, 47]	1510.9 [35, 47, 79–82]
Non-fatal MI	Age- and sex-dependent + utility decrement for MI [47] [35]	1st year after MI: 6662.5
		≥2nd year: 1597.1 [35, 47, 78–81]
Non-fatal stroke	Age- and sex-dependent + utility decrement for stroke [36, 47]	1st year after stroke: 4593.5
		≥2nd year: 1817.5 [36, 47, 78–81]

CHF congestive heart failure, *COPD* chronic obstructive pulmonary disease, *IHD* ischaemic heart disease, *MI* myocardial infarction; *N/A* not applicable

ratio (ICER) distribution. Negative ICERs are difficult to interpret and often arise when one of the interventions is either 'dominant' (more effective, less costly) or 'dominated' (less effective, more costly). It is not possible to tell this from the ICER itself. We report the proportion of ICER estimates in each of the four quadrants

of the cost-effectiveness plane. We present mean ICERs for all results, indicating for negative ICERs whether the intervention is dominant or dominated.

Cost-effectiveness acceptability curves (CEACs) [51] were constructed to express the probability that NMS is cost effective as a function of the decision maker's ceiling cost-effectiveness ratio (λ) [52].

2.4 Sensitivity Analysis

Deterministic analysis was conducted using the MMAS-8 adherence measure, for which probabilities of adherence were 78 and 65% in the NMS and normal practice groups, respectively, with OR of 1.88 (1.06–3.34), (Table 2).

The deterministic analysis was repeated to determine the effect of reducing the effect size, by reducing the adherence in the NMS arm, keeping the probability of adherence in the current practice arm unchanged. The difference in adherence between NMS and normal practice that would be required to attain an ICER of £20,000 per QALY was determined.

The probabilistic analysis was repeated in the disease-specific subgroups.

2.5 Model Validation

Validity testing (conceptual model, input data, assumptions, model outcomes) was carried out iteratively as part of the development of the model throughout the project, with general practice, clinical pharmacy and health economics experts on the project team and the independent advisory panel [53]. This was carried out as multiple 'walk-throughs' and review of specific written summaries of model structure, inputs and outcomes. There is no comparable model of a cross-therapeutic intervention to assess adherence. However, cross validity of individual models was maximised by using published models to derive a model for each disease where possible. The computerised individual and composite models were developed by LT and GG and examined by RAE, who has built a composite model in a previous study. Models were only accepted if there were no illogical or illegal inputs or outputs.

3 Results

3.1 Incremental Analysis

Tables 6 and 7 summarise the lifetime costs and outcomes derived from each disease-drug-specific model, their relative contribution to the economic model, and the overall results for the incremental analysis of NMS versus normal practice.

NMS generated a mean of 0.04 more QALYs per patient than normal practice, at a mean reduced cost of −£139, with probabilistic means of 0.05 (95% CI 0.00–0.13) and −£144 (95% CI −769 to 73). Therefore, NMS dominates normal practice, with an ICER of –£3166 (probabilistic mean −£2638). The probability that NMS dominates normal practice is 0.78. NMS has a high probability (0.96) of cost effectiveness compared with normal practice at a willingness to pay of £20,000 for one QALY (see Figs. 3, 4).

3.2 Sensitivity Analysis

The results were robust to changing adherence outcome. When MMAS-8 was used to estimate changes in adherence, the incremental QALY was 0.06, incremental cost was −£164, with an ICER of −£2953 (see electronic supplementary material). The threshold

Table 6 Results from individual models and incremental economic analysis of NMS versus normal practice: deterministic analysis

Model	Percentage of NMS cohort	Mean cost (£)		Mean QALY		Incremental		ICER (£/QALY)
		NMS[a]	Normal practice	NMS	Normal practice	Cost (£)	QALY	
Amlodipine	25.3	1496.9	1512.0	14.22	14.17	−15.1	0.04	−338.0
Ramipril	24.1	2925.4	2922.9	16.37	16.30	2.6	0.07	37.9
Aspirin	8.5	22,881.6	22,830.1	10.04	10.03	51.5	0.01	5151.0
Beclometasone	17.5	71,539.9	72,432.2	16.56	16.54	−892.3	0.02	−44,614.0
Tiotropium	5.7	10,508.6	10,250.3	6.99	6.85	258.3	0.14	1845.2
Metformin	18.8	15,285.7	15,279.8	9.55	9.53	5.9	0.02	293.0
Overall	100	19,013.2	19,151.8	13.49	13.45	−138.6	0.04	−3166.1

ICER incremental cost-effectiveness ratio, *NMS* New Medicine Service, *QALY* quality-adjusted life-year

[a] Incorporating cost of intervention equal to £24.6

Table 7 Results from individual models and incremental economic analysis of NMS versus normal practice: probabilistic sensitivity analysis

Model	Percentage of NMS cohort	Mean cost (95% CI[b])/£		Mean QALY (95% CI[b])		Incremental		ICER (£/QALY)
		NMS[a]	Normal practice	NMS	Normal practice	Cost, £ (95% CI[b])	QALY (95% CI[b])	
Amlodipine	25.3	1230.2 (498.9–2201.1)	1242.4 (481.9–2265.8)	13.96 (11.63–16.36)	13.90 (11.59–16.31)	−12.2 (−119.7 to 37.4)	0.06 (−0.04 to 0.23)	−1996.2
Ramipril	24.1	2946.4 (2280.0–3876.5)	2943.9 (2264.8–3882.8)	16.35 (13.93–18.82)	16.28 (13.87–18.76)	2.5 (−40.8 to 24.0)	0.07 (0.00 to 0.18)	−42.8
Aspirin	8.5	22,870.4 (17,855.9–30,396.3)	22,816.6 (17,822.8–30,300.3)	10.12 (8.94–11.28)	10.10 (8.93–11.26)	53.82 (23.9 to 108.3)	0.01 (0.00 to 0.04)	5585.7
Beclometasone	17.5	75,418.05 (21,472.3–253,610.9)	76,279.6 (21,475.9–257,102.1)	16.53 (15.61–17.14)	16.50 (15.58–17.13)	−861.5 (−4414.6 to 269.8)	0.02 (0.00 to 0.07)	−48,996.6
Tiotropium	5.7	11,184.9 (3150.8–25,321.4)	10,987.5 (3072.7–24,732.0)	7.27 (4.33–10.01)	7.14 (4.22–9.93)	197.4 (−234.9 to 979.9)	0.13 (0.00 to 0.39)	1819.1
Metformin	18.8	15,079.2 (9400.5–29,221.8)	15,073.5 (9409.0–29,152.1)	9.55 (8.77–10.31)	9.52 (8.74–10.29)	5.7 (−54.0 to 73.9)	0.03 (0.00 to 0.07)	1564.4
Overall	100	20,201.8 (9843.1–50,750.5)	20,345.8 (9840.2–51,749.6)	13.48 (12.59–14.39)	13.43 (12.53–14.34)	−144.0 (−768.7 to 72.9)	0.05 (0.00 to 0.13)	−2638.4

CI confidence interval, *ICER* incremental cost-effectiveness ratio, *NMS* New Medicine Service, *QALY* quality-adjusted life-year

[a] Incorporating cost of intervention equal to £24.6

[b] 95% CIs were obtained from 2.5% and 97.5% percentiles for costs, QALYs and ICERs in probabilistic sensitivity analysis

analysis demonstrated that the effect size of NMS compared with normal practice would need to be reduced to an OR of 1.01 to derive an ICER of £20,000 per QALY or above (see electronic supplementary material).

The disease-specific sensitivity analysis showed that if the NMS intervention targeted one of the disease areas only, NMS generated more QALY gain than normal practice in all models. NMS generated lower lifetime costs than normal practice for amplodipine–hypertension and asthma models. Higher costs in the NMS arm were generated for ramipril–hypertension, diabetes, COPD and aspirin models. In all cases, higher lifetime costs were the effect of reduced mortality for adherent patients (deaths from COPD exacerbations and from cardiovascular events). The mean ICERs were hypertension only (amlodipine plus ramipril): −£115; asthma only: −£44,614; COPD only: £1845; diabetes only: £293; aspirin only: £5151 (Table 8). Targeting individual disease areas with NMS has a probability over 0.90 of cost effectiveness compared with normal practice at a willingness to pay of £20,000 per QALY (Fig. 4).

3.3 Model Validation

Where possible, outputs from individual models were compared with published model outputs. The output of four of our individual models was comparable with published studies. The amlodipine model generated 14.3 QALYs in the adherent group, similar to another UK hypertension model [54] and a German model [55]. The ramipril model generated 16.6 QALYs in the adherent group, similar to another ACEI model [56]. The diabetes model generated 9.62 QALYs in the adherent group, similar to UKPDS68 [34]. The aspirin model generated 10.07 QALYs in the adherent group. There were no lifetime horizon models available for comparison, but a 10-year model generated 8.2–8.4 QALYs [57]. We were not able to find models with time horizons similar to our asthma and COPD models, so relied on feedback from clinical experts regarding model outcome validity.

4 Discussion

This economic evaluation suggests that NMS will deliver better patient outcomes than normal practice at overall reduced costs to the NHS in the long term. In the short term, extra costs incurred by remunerating community pharmacists were absorbed by small reductions in other NHS contact-related costs.

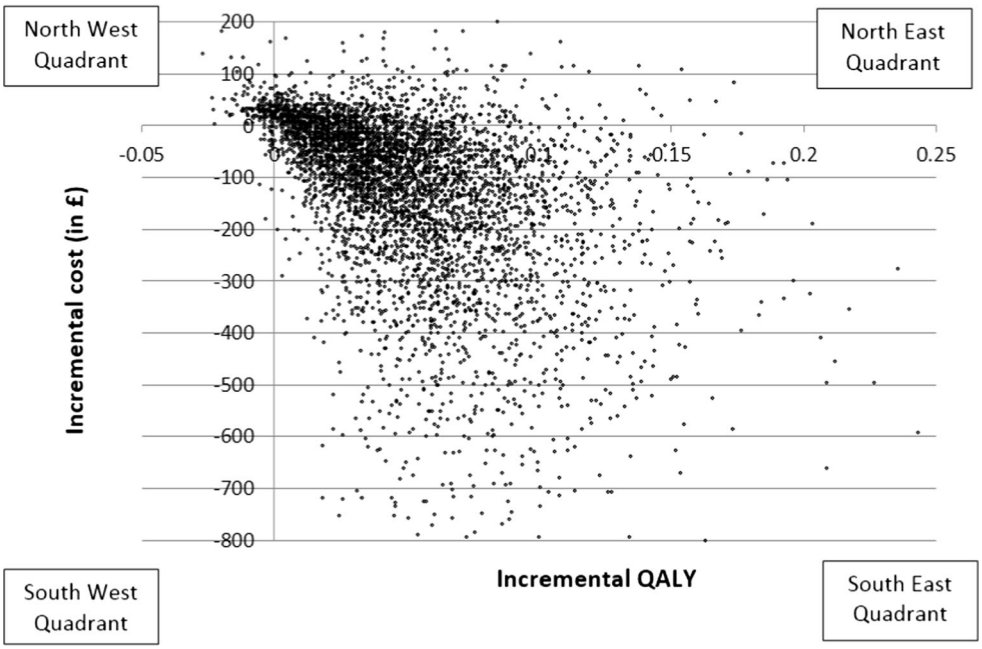

Fig. 3 Incremental cost-effectiveness plane: New Medicine Service (NMS) intervention versus normal practice. 5000 iterations in composite and medicine-specific models. In composite model, cost and QALY in NMS and normal practice arms are calculated as weighted cost and QALY from each medicine-specific model. Iterations were ordered by the index reflecting the strength of NMS effect (incorporating adherence effect from medicine-specific model and trial effect of NMS on adherence). *QALY* quality-adjusted life-year

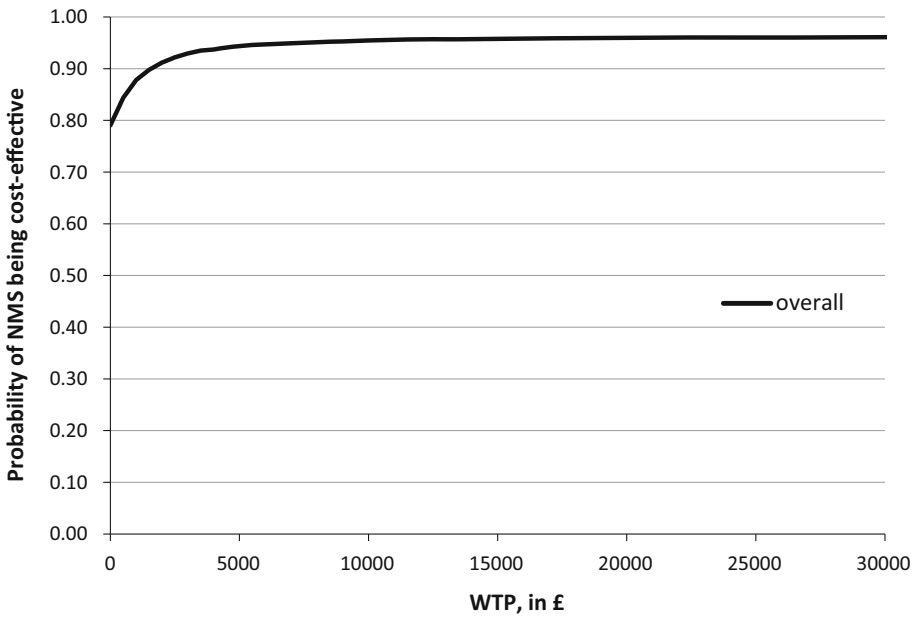

Fig. 4 Cost-effectiveness acceptability curve for New Medicine Service (*NMS*) intervention versus normal practice. This graph demonstrates the probability of cost effectiveness at a range of decision-maker ceiling willingness to pay for the NMS intervention overall. See electronic supplementary material (Section 4, Fig. 7) for Cost-effectiveness acceptability curves when only one disease group is considered at a time. *WTP* willingness to pay

Interventions to improve adherence were assessed in a recent Cochrane review as "mostly complex and not very effective", and in need of better design [58]. Most strategies to improve medicines have been costly and atheoretical with little evidence of cost effectiveness [59, 60]. In contrast, NMS is an effective, relatively simple intervention with a strong theory base, transferable across diseases and healthcare settings, and which we estimate here to be cost effective for the NHS when compared with normal practice.

4.1 Strengths and Limitations

The current UK evaluative framework requires a cost per QALY to compare the value for money of different healthcare interventions. Patient adherence is an intermediate process indicator assumed to lead to changes in patient outcomes, but criticised as insufficient to demonstrate patient benefit [58]. Our analysis has moved beyond adherence, giving an estimate of clinical and economic

Table 8 Incremental effectiveness analysis of NMS intervention versus current practice in specific disease groups (base-case adherence outcome)

	Incremental		ICER, £/QALY	% ICERs in each quadrant				Probability C/E at $\lambda <$ £20 K
	Cost/£	QALY		SE[a]	NE	SW	NW	
Base case	−138.6	0.04	−3166.1	78.5	17.9	0.5	3.0	0.96
Hypertension only[b]	−6.5	0.06	−115.5	46.9	47.1	0.0	6.0	0.93
Asthma only	−892.3	0.02	−44,614.0	88.6	7.1	0.2	4.2	0.93
COPD only	258.3	0.14	1845.2	13.1	84.3	1.1	1.5	0.97
Diabetes only	5.9	0.02	293.0	40.7	57.2	0.0	2.1	0.97
Aspirin only	51.5	0.01	5151.0	0.0	96.8	0.0	3.1	0.93

C/E cost effective, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *ICER* incremental cost-effectiveness ratio, *NMS* New Medicine Service, *QALY* quality-adjusted life-year

[a] Probability of dominance

[b] Probabilities of dominance are 50.0 and 36.2% and probabilities of cost effectiveness at $\lambda <$ £20,000 are 83.7 and 98.0% for amlodipine and ramipril models, respectively. Probabilistic means with 95% CI for hypertension patients are −£4.5 (95% CI −69.4 to 28.4) and 0.06 (95% CI −0.01 to 0.20) for difference in costs and QALYs, respectively; ICER (£/QALY) was −£39,236.1 (95% CI −4049.2 to 5096.9), with a median of −£28.9

impact of the intervention, and is an important development.

Pharmacist-led interventions often reflect their cross-therapeutic role around prescribing safety and patient adherence, bringing a significant challenge to the evaluative framework, which is historically disease-specific. Evaluations of pharmacist-led interventions often rely on generic process measures such as errors [61, 62], medication changes [63] or patient adherence [14], and tend to report ICERs such as cost per adherent patient or cost per error avoided [14, 61]; or utilise assumptions about the level of disutility incurred [64]. In a previous study examining the economic impact of a pharmacist-led information technology-based intervention (PINCER) to reduce medication errors in general practices, we developed a novel approach where economic models were developed for each of six errors, and generated a cost per QALY [22]. We applied this method in the economic evaluation of NMS. Therefore, this study differs from most other economic evaluations in this area, and we have been able to generate cost-per-QALY statistics to inform decision making.

The effect size of an absolute 10% improvement in adherence from normal practice to NMS is similar to that reported in the original work by Clifford [65]. Although the effect sizes here might initially be considered small, we anticipate significant benefits for two reasons. First, large numbers of patients have experienced the service. Second, we suggest that this is a conservative effect size, given probable patient recruitment bias, use of self-report of adherence, and the assumption that all the patients in the intervention arm actually received the NMS.

There is no gold standard for measuring patients' medicines adherence. Each approach has limitations. More than one adherence measure should be used to provide an internal check on validity [1]. In this study, we chose two self-report measures. Prescription filling was not an option for routine adherence monitoring in England due to lack of interoperability between community pharmacy and general practice systems. Although self-report tends to return a higher rate of medication adherence (+15%) than some objective measures, it correlates with objective clinical measures [66]. It is possible to minimise biases through confidential interview [67], as is carried out as part of NMS; normalising non-adherence by recognising the challenges of taking regular medications; avoiding negative or positive questions which may encourage a biased response; and asking about a missed dose in the few days or a week prior to data collection rather than months or years [68].

A key limitation is the paucity of data upon which to base the estimates of economic impact of adherence in the individual disease–drug pairs, particularly the link between adherence and outcome. The wide range around the point estimates of cost effectiveness reflects the uncertainty in some of the individual adherence models.

Weaknesses in the models centre on assumptions made. It is assumed that the incremental effect of NMS compared with normal practice on adherence is the same over a patient's lifetime. Published estimates of persistence to new hypertension medicines at 1 year are around 48% [69, 70] and 51% [71] dropping from 6-month rates of 65–68%. This suggests that adherence is likely to drop in the cohort not having NMS at the beginning of their

treatment. Our study suggests that the effect of NMS appears to be an absolute increase in adherence of 10% at 10 weeks post-initiation of the new medicine. It is not clear whether this effect will:

(a) disappear, such that there is no difference in adherence at 6 or 12 months;
(b) be maintained, such that adherence in both the NMS and control groups drops over time at the same rate, so the current benefit is maintained; or
(c) initiate a change in the patient's motivation or ability to adhere that leads to sustained adherence to the medicine such that the usual drop in adherence over time is prevented.

In the absence of any evidence to support which of these scenarios reflects reality, the economic analysis assumes scenario (b) for the basis of extrapolation of effect size. Sensitivity analysis suggested that the OR had to be reduced from 1.67 to 1.01 for NMS to stop being cost effective at a ceiling willingness to pay of £20,000 per QALY.

Apart from general limitations associated with the use of modelling, specific model limitations in our study include the use of the same effect of NMS on adherence for each disease-specific model since the trial was powered to analyse the effect of NMS in the entire NMS trial population. However, the effect of NMS on adherence may differ between disease groups and, in this case, the results of disease-specific models would be different than those assuming the same effect of NMS on adherence. The effects of adherence incorporated in the models were observed in the studies with different time horizons, from 1 year to longer (with maximal follow-up 4–5 years), while in the model we assume that effect of adherence is kept over a lifetime. We did not incorporate adverse event states in the models that may affect cost effectiveness (e.g. in older people, antihypertensive drugs may increase the risks of falls).

4.2 Implications for Policy and Practice

From inception of the NMS to the end of August 2016, 3.59 million consultations have been claimed for with over 820,000 in the year 2015/16 [90]. From the results of this economic evaluation, this suggests £75.4 million short-term savings to the NHS, £517.6 million long-term cost savings to the NHS and 179,500 QALYs gained.

The research presented above suggests that the NMS is cost effective for each disease population than normal practice, with high (above 97%) probability of cost effectiveness at a willingness to pay set at £20,000. On the basis of this evidence, it is recommended that this service continue to be commissioned in the future.

Where there is evidence suggesting therapeutic areas with significantly poor adherence, especially when non-adherence has significant effect on outcomes, consideration should be given to expanding the NMS. Potential areas might include conditions where medicines can have early adverse effects that subside over time such as anti-depressants.

5 Conclusions

This study suggests increased health gain with NMS over normal practice at a cost per QALY well below most accepted thresholds for technology implementation [72]. This intervention could be extended to other groups of medicines. The findings are likely to have applicability to other healthcare systems, including those based on insurance.

5.1 Data Availability Statement

Several datasets were used for this analysis: (1) efficacy, patient-reported outcomes and healthcare resource utilisation data collected in the NMS randomised controlled trial (RCT). The patient-level data are not publicly available, but the results of the trials have been presented in several publications. The trial results supporting the findings of this analysis are available within the article and its electronic supplementary material. (2) The six individual models use RCT, observational data and estimation tools from multiple sources, for which references are provided in the article. (3) Cost data used in the model were obtained from referenced publicly available sources. (4) The model was developed in Data TreeAge and is not publicly available, but is available from the authors upon request.

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Author contributions RAE designed and led the economic analysis, led drafting of the manuscript, was study principal investigator and contributed to the analysis of the RCT. LT designed and built the economic models, including collection of input data on transition probabilities, utilities and costs; carried out the economic analysis (including method and estimation of overall cost effectiveness); contributed to leading and design of the economic analysis; contributed to the COPD model; and contributed to the analysis of the RCT. GG designed and built the COPD model, including collection of input data on transition probabilities, utilities and costs; contributed to the economic analysis and carried out intervention and within-trial costing; and contributed to the analysis of the RCT. MJB led the delivery of the RCT including design of data collection tools and oversight of data collection. AJA contributed to model design and reviewed all models for clinical face validity. NB was involved in intervention design and costing and informed and reviewed the economic analysis for practice face validity. AL was involved in the delivery of the RCT and informed and reviewed the economic analysis for practice face validity. RM led the statistical design and analysis of the RCT and derived the estimates of effect for the economic evaluation. AC provided patient and public input to the project and interpretation of the economic evaluation. JW led the process evaluation of NMS and informed and reviewed the economic analysis for practice and policy relevance. All authors were involved in the drafting of the manuscript. Prof. RE is the guarantor and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Compliance with Ethical Standards

Ethical approval This report is independent research commissioned and funded by the Department of Health Policy Research Programme (Grant no. PR-IC-0711-10010) ('Understanding and Appraising the New Medicines Service in the NHS in England'–PRP 029/0124). The views expressed in this publication are those of the authors and not necessarily those of the Department of Health. The RCT (ClinicalTrials.gov Trial reference number NCT01635361; http://clinicaltrials.gov/ct2/show/NCT01635361) had full ethical approval.

Conflict of interest Rachel A. Elliott, Lukasz Tanajewski, Georgios Gkountouras, Anthony J. Avery, Nick Barber, Rajnikant Mehta, Matthew J. Boyd, Asam Latif, Antony Chuter and Justin Waring have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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