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Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service

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ABSTRACT

Objective To examine the effectiveness of the New Medicine Service (NMS), a national community pharmacy service to support medicines-taking in people starting a new medicine for a long-term condition, compared with normal practice.

Methods Pragmatic patient-level parallel randomised controlled trial, in 46 community pharmacies in England. Patients 1:1 block randomisation stratified by drug/disease group within each pharmacy. 504 participants (NMS: 251) aged 14 years and over, identified in the pharmacy on presentation of a prescription for asthma/chronic obstructive pulmonary disease, hypertension, type 2 diabetes or an anticoagulant/antiplatelet agent. NMS intervention: One consultation 7–14 days after presentation of prescription followed by another 14–21 days thereafter to identify problems with treatment and provide support if needed. Controls received normal practice. Adherence, defined as missing no doses without the advice of a medical professional in the previous 7 days, was assessed through patient self-report at 10 weeks. Intention-to-treat analysis was employed, with outcome adjusted for recruiting pharmacy, NMS disease category, age, sex and medication count. Cost to the National Health Service (NHS) was collected.

Results At 10 weeks, 53 patients had withdrawn and 443 (85%) patients were contacted successfully by telephone. In the unadjusted analysis of 378 patients still taking the initial

medicine, 61% (95% CI 54% to 67%) and 71% (95% CI 64% to 77%) patients were adherent in the normal practice and NMS arms, respectively ($p=0.04$ for difference). In the adjusted intention-to-treat analysis, the OR for increased adherence was 1.67 (95% CI 1.06 to 2.62; $p=0.027$) in favour of the NMS arm. There was a general trend to reduced NHS costs, albeit, statistically non-significant, for the NMS intervention: saving £21 (95% CI –£59 to £100, $p=0.128$) per patient.

Conclusions The NMS significantly increased the proportion of patients adhering to their new medicine by about 10%, compared with normal practice.

Trial registration numbers ClinicalTrials.gov trial reference number NCT01635361 (<http://clinicaltrials.gov/ct2/show/NCT01635361>). Current Controlled trials: trial reference number ISRCTN 23560818 (<http://www.controlled-trials.com/ISRCTN23560818/>; DOI 10.1186/ISRCTN23560818). UK Clinical Research Network (UKCRN) study 12494 (<http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=12494>).

INTRODUCTION

Adherence to medication is defined as the extent to which individuals take their medication as prescribed.¹ Suboptimal medicines adherence has been reported in many illnesses such as chronic obstructive pulmonary disease (33%),² asthma (67%)³ and schizophrenia 52%.⁴ Adherence reduces with time from initial prescription. In depression, adherence

was reported to drop from 95.5% to 52.6% over a 1-month period.⁵ Low adherence increases risk of hospitalisations and premature mortality.^{6–8} Worldwide, medicines non-adherence constitutes 57% of the estimated US\$500 billion wasted from suboptimal medicines use.⁹ The annual economic impact of non-adherence to five key conditions (asthma, type 2 diabetes, high cholesterol/coronary heart disease, hypertension and schizophrenia) to the English National Health Service (NHS England) has been estimated at over £930 million.¹⁰ Annual savings of £500 million could be realised if adherence were improved.

Many interventions to improve medicines adherence are complex, multifaceted and not grounded in theory about the reasons why people are non-adherent.¹¹ Effective interventions focus on self-management, promoting sustained behaviour change.¹² This may involve more acceptable regimens, removing financial barriers, changing misguided beliefs about the disease and medicines, empowering self-management, improving patient-provider relationships and involving the patient's 'social world'. Overemphasis on the educational needs of patients only is a weakness of many interventions.

When patients receive a new (to them) medicine for a long-term condition, they often experience problems which lead to a proportion becoming non-adherent.¹³ Barber developed an intervention with a theoretical basis in the self-regulatory model,¹⁴ grounded in the patient's perspective and designed to elicit patients' experiences with, and concerns about, their new medicine. This was used as a starting point for the pharmacists to meet each individual's specific needs with information and advice. This theory-based pharmacist-led intervention significantly reduced reported problems and non-adherence in a cost-effective manner.^{15 16}

The New Medicine Service (NMS) in England is the first national service designed to improve medicines adherence¹⁷ and is offered by community pharmacists to people starting a new medicine for asthma/chronic obstructive pulmonary disease, type 2 diabetes, hypertension or antiplatelet/anticoagulant treatment.¹⁸ The design is based on the initial work described above, but the original intervention targeted a wider range of patients whereas the NMS has four specified groups. The original intervention was delivered via a centralised telephone service, whereas NMS is delivered by the pharmacist providing the medicine, either face-to-face or over the telephone. Advanced services are commissioned nationally via the NHS community pharmacy contractual framework and can be delivered following appropriate accreditations. NMS was implemented as an advanced service in October 2011. Community pharmacies in England have to be accredited to provide NMS and are given guidance on how to conduct the intervention and follow-up consultations.¹⁸ This guidance provides a topic guide for pharmacists and an NMS interview schedule. They are

remunerated for each episode of care. Of 11 495 community pharmacies in England 10 553 (91.2%) had claimed for at least one NMS episode up to January 2014.¹⁹ The aim of this study was to evaluate the effectiveness of the NMS compared with normal practice in changing medicines-taking behaviour, using a robust, pragmatic randomised controlled trial (RCT) in community pharmacies in England.

METHODS

Study design

The study is reported according to Consolidated Standards of Reporting Trials (CONSORT) criteria.²⁰ The study was a patient-level multicentre, pragmatic RCT involving a parallel group design. The study was overseen by an advisory group. The protocol has been published.^{21 22}

Study setting

Community pharmacies in East Midlands and South Yorkshire and Greater London accredited to provide the NMS were eligible to take part, an area with approximately 870 pharmacies. Pharmacy selection took into account pharmacy ownership (independent, small, medium and large multiples), proximity to general practice (GP), setting (rural vs urban) and economic deprivation.

Study participants

Patients were able to take part in the RCT if they were eligible for NMS, community-dwelling, aged 14 years or over, able to consent to the NMS and the study and willing to provide written consent (parental consent for 14-year-olds and 15 year-olds).

Recruitment

A pragmatic approach was used to include pharmacies covering the range of characteristics listed above, by inviting pharmacies from all groups to participate. No further training on delivering the intervention or normal practice was provided to prevent alteration of the pragmatic status of the study. Individual pharmacists within the pharmacy had the option to participate in the study.

Patients were recruited within community pharmacies by the study pharmacists (see figure 2). Consenting to the NMS was a prerequisite for a patient being invited to the study. It was explained that if they joined the RCT, they could be randomised to normal practice, and not receive NMS. Patients were given as long as they needed to read the study information and ask questions. The normal 24 h grace period for consent was not appropriate as the intervention needed to be scheduled while the patient was in the pharmacy. Therefore, patients received an additional welcome call from the researcher to answer subsequent questions and patients were also reminded that they could withdraw.

Randomisation and blinding

Patients were randomised into one of the two study arms stratified by drug/disease group within each pharmacy using Statistical Analysis Software.²³ Block randomisation was used within each pharmacy to avoid allocation imbalances. Sequentially numbered tamper-proof opaque sealed envelopes were used to conceal sequence allocation. Separate randomisation sequences were produced for patients 16 years and over and for patients aged 14 years and 15 years, due to the age-specific motivators for adherence in this latter group.²⁴ Researchers collecting data were blinded to study arm except in the case of accidental disclosure by study participants or when inviting a participant to the qualitative arm of the study. The qualitative work is available in the main report.²²

NMS intervention

NMS begins with the patient's initial presentation with a prescription for a new medicine in a community pharmacy. Patients can be referred to the service by their prescriber (GP or nurse), can self-refer or the pharmacist can invite the patient to use the service. The NMS intervention itself is relatively rapid and comprises two parts, named 'intervention' and 'follow-up' by the commissioners. The pharmacist invites the patient to a one-to-one consultation 7–14 days later (the 'intervention') with a 'follow-up' 14–21 days after that, meaning the whole episode should be complete within a maximum of 5 weeks. These are the points in the service where the pharmacist would ask about adherence and experiences with the medicine. Primary outcomes were collected by researchers at 10 weeks from initial prescription presentation in both study arms.

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 (including adverse drug reactions) and support or action needed (figure 1). Action may include referring the patient back their prescriber to review their medication.

Normal practice

Normal practice was the pharmacist's usual advice when presented with a prescription for a new medicine for a long-term condition. No follow-up is offered to this group of patients. The episode ceases either until the next prescription is presented or further assistance is sought by the patient.

Outcomes

Primary outcome

The primary outcome is self-reported adherence at 10 weeks from the initiation of the intervention (see table 1). Patients were followed up at 10 weeks, expected to be the minimum time required to demonstrate any behavioural changes from the intervention.¹⁵

Patients were contacted by telephone 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?)".²⁵ 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.

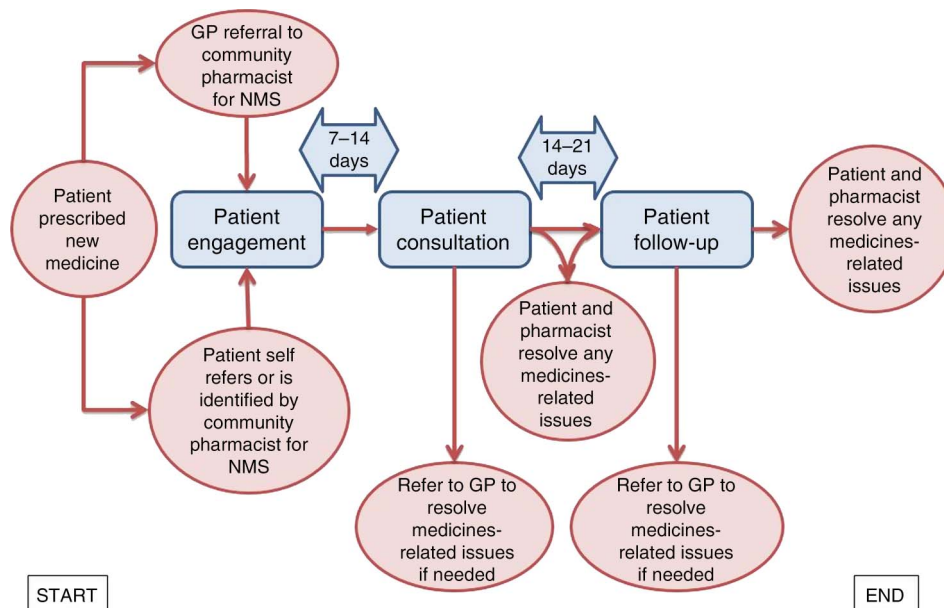


Figure 1 New Medicine Service intervention.

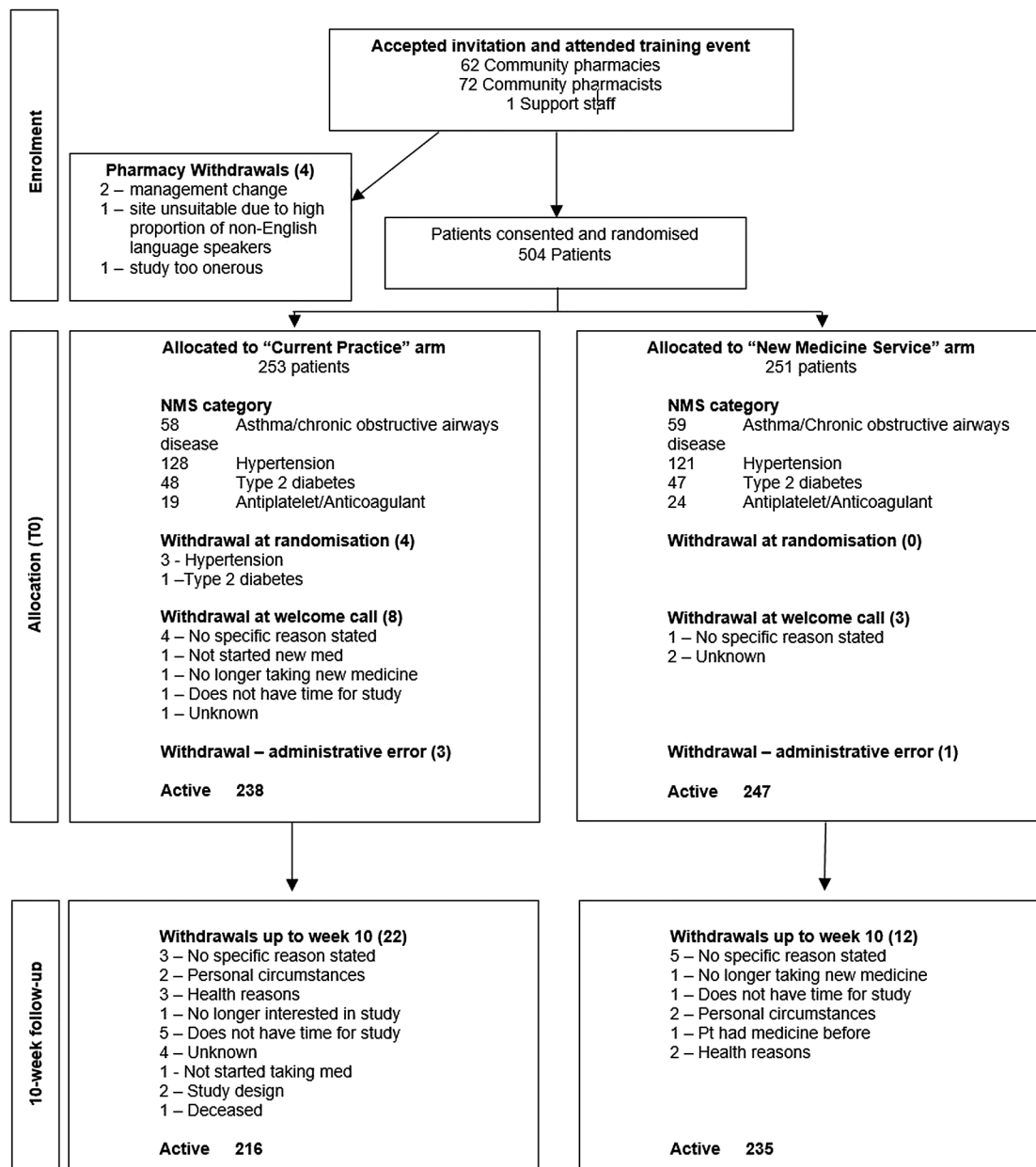


Figure 2 Overview of pharmacy and patient recruitment (CONSORT). ‘Active’ patients indicates how many patients are contributing data to the study at each time point, by arm. As part of the study pharmacies were asked to provide a 4-weekly return indicating the number of patients approached, but who declined. Despite significant efforts by the study team throughout, only 25% of these were returned, meaning an accurate indication of patients approached was not possible. Of the 369 4 week recording periods over the 61 pharmacies, data were received for 94 of these periods. In the remaining periods either pro forma were not returned or returned not completed. Across the 94 periods, 470 declines were recorded. Declines by pharmacy ranged from 1 to 150. It was therefore not possible to report the number of patients approached. Patients who did not wish to receive the New Medicine Service (NMS) service were given a short questionnaire to complete and return to the study team. There were 11 responses from 117 questionnaires issued with the majority (7/11) stating they did not see the need as their general practice would be reviewing them in due course.

The Morisky Eight Item Medication Adherence Scale (MMAS-8), validated in hypertension, was used to support the primary outcome measure, and collected via self-completion postal questionnaire (expected to result in a lower response rate).²⁶

The main intention of the NMS intervention is to enhance adherence to the newly prescribed medicine. Situations will inevitably present, such as experiencing severe side effects, where it would be inappropriate

for a patient to continue taking their prescribed new medicine. Therefore, the medicine can also be stopped or changed appropriately by the prescriber, with or without referral from the pharmacist during the NMS intervention. Patients’ medicines may also be stopped or changed appropriately in the normal practice arm. When a patient’s new medicine was substituted by another medicine this patient was classed as having their new medicine changed. On the other

Table 1 Summary of outcome measures collected at 10 weeks

Outcome measure	Method of recording
Adherence NMS question	Telephone interview*
Adherence Morisky's Medication Adherence Scale 8-item version (MMAS-8) ^{26†}	Self-completed postal questionnaire‡
Medicines stopped or changed by the prescriber	Telephone interview*
Health status EuroQol-5 Dimension-3 Level Instrument (EQ-5D-3L) ²⁷	Self-completed postal questionnaire‡
Medicines understanding Beliefs About Medicines Questionnaire (BMQ) ²⁸	Self-completed postal questionnaire‡
Healthcare resource use	Self-completed diary§

*Participants were asked to specify optimal contact times at registration. Up to seven attempts were made for each time point if unsuccessful.

†Use of the MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

‡Questionnaires were issued prior to telephone interviews. Return status was checked during the telephone interview and actioned as necessary.

§Interactions with primary, secondary, social care and allied health professionals were recorded on an episodic basis. Wasted medicines were not recorded.

NMS, New Medicine Service.

hand, if a prescriber had directed that the patient stop their new medicine this was classified as stopped new medicine. A composite measure of success is the patient either being adherent to the first medicine, or it being appropriately stopped or changed. The outcome is reported as proportion of patients adherent to newly prescribed medicine, or appropriately stopped or changed by the prescriber (composite outcome=adherence plus stopped/changed).

Composite outcomes were constructed for the NMS question and the MMAS-8 by including those patients adherent to the initial medicine and those whose medicines had been stopped or changed appropriately by the prescriber:

- ▶ 'Composite NMS' (Patients successfully managed composite outcome using NMS question): adherent plus (stopped or changed appropriately by the prescriber);
- ▶ 'Composite MMAS-8' (Patients successfully managed composite outcome using MMAS-8): adherent plus (stopped or changed appropriately by the prescriber).

Other outcomes

Health status, medicines understanding and healthcare resource use were also recorded.

Costs

Resource use associated with the interventions (time spent, costs of telephone calls) was recorded for each patient. Subsequent NHS contact or patient costs were recorded by the patient in diaries for 10 weeks after the intervention. Resource use data were

combined with NHS reference costs²⁹ and Personal Social Services Research Unit costs³⁰ to derive total costs per patient. Unit costs are summarised in online supplementary appendix tables 1 and 2. Comparisons between treatment arms were made using a two-sample t test on the original data set, or on a bootstrapped data set, depending on the normality of the distribution of costs.³¹

Sample size

Estimation of sample size was based on the effect observed by the intervention in the original work.¹⁵ Prevalence of non-adherence behaviour measured by the NMS question at 10 weeks follow-up (primary outcome) was expected to fall from 20% to 10%. A sample size of 200 patients/arm was required to detect this change with 80% power, 5% significance level (two-tailed). Up to 100 patients were expected to be lost to follow-up, withdraw from the study or change/stop medication. To maintain study power 250 patients/arm was the planned sample size (table 2).

Starting new medication for one of these long-term conditions is not that common an event per pharmacy. Pharmacies initiating at least two NMS consultations/week were recruited, to provide 52 eligible patients in 6 months. Assuming that 50% of eligible patients consented, approximately 20 pharmacies were needed. There was lower than predicted NMS uptake within study pharmacies either because eligible patients were not presenting, or because the pharmacist could not identify that the prescription was for a new medication, due to lack of access to patient medical records. In 2013 the number of recruiting pharmacies was expanded to 61, of which 46 ultimately provided patients. Recruitment was stopped once the required sample size was reached.

Statistical analysis

Intention-to-treat (ITT) analysis was used.^{32 33} Adherence rates were analysed using the χ^2 test or Fisher's exact test. The ITT cohort was defined as all patients within a randomisation arm with measured outcomes, or who had withdrawn from the study.

Simple logistic regression analysis assessed unadjusted effect of NMS on the outcome (Model 1: 'naïve' results). Multilevel logistic regression analysis adjusted effect size for clustering of data and confounding by disease, age, sex and medication count (Model 2). Two levels were defined in the multilevel analysis: (1) Patient, (2) Pharmacy.

Full application of ITT analysis can only be performed where there is complete outcome data for all randomised subjects. To include such participants in an analysis, the outcome data were imputed which involves making assumptions about the outcomes in the lost participants.^{34 35} Generalised estimating equations^{36 37} techniques took account of correlated outcome data. Multiple imputation by chained

Table 2 Patient characteristics

Patient characteristics	Normal practice n (%)	New Medicine Service n (%)
Total N (%)	253 (100.0)	251 (100.0)
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)
Male (n=244, 48.4%)	118 (46.6)	126 (50.2)
Age of total cohort (years) (N: Mean (SD))	253: 59.3 (15.0)	251: 59.5 (15.3)
Age (female) (years) (N: Mean (SD))	135: 58.7 (15.4)	125: 56.8 (16.0)
Age (male) (years) (N: Mean (SD))	118: 60.0 (14.6)	126: 62.2 (14.1)
No of NMS eligible new medicine(s) at study entry (n (%))	Total NMS medicines: 257	Total NMS medicines: 262
1	249 (98.4)	241 (96.0)
2	4 (1.6)	9 (3.6)
3	0 (0.0)	1 (0.4)
Mean (SD) number of other medicines	3.6 (3.4)	3.5 (3.4)
Most commonly prescribed medicines (% medicines prescribed in that disease category)		
Antiplatelet/anticoagulant	Aspirin 10 (52.6) Clopidogrel 7 (36.8) Dipyridamole 1 (5.3) Warfarin 1 (5.3)	Aspirin 11 (45.8) Clopidogrel 9 (37.5) Dipyridamole 1 (4.2) Warfarin 3 (12.5)
Asthma/COPD	Salbutamol 11 (18.0) Beclometasone (<i>Clenil</i>) 7 (11.5) Budesonide and formoterol (<i>Symbicort</i>) 7 (11.5) Tiotropium (<i>Spiriva</i>) 7 (11.5) Formoterol and beclometasone (<i>Fostair</i>) 6 (9.8)	Salbutamol 20 (30.8) Beclometasone (<i>Clenil</i>) 12 (18.5) Tiotropium (<i>Spiriva</i>) 10 (15.4) Fluticasone and salmeterol (<i>Seretide</i>) 6 (9.2) Ipratropium 5 (7.7)
Hypertension	Amlodipine 40 (30.8) Ramipril 29 (22.3) Indapamide 11 (8.5) Bisoprolol 10 (7.7) Losartan 10 (7.7)	Amlodipine 38 (30.2) Ramipril 24 (19.0) Losartan 11 (8.7) Bisoprolol 10 (7.9) Indapamide 10 (7.9)
Type 2 diabetes	Metformin 22 (44.9) Gliclazide 11 (22.4) Insulin (various) 7 (14.3) Sitagliptin 5 (10.2) Saxagliptin 2 (4.1)	Metformin 25 (53.2) Gliclazide 12 (25.5) Sitagliptin 5 (10.6) Acarbose 1 (2.1) Insulin various 2 (4.2)
Economic deprivation based on IMD Score* (Mean (SD))		
Pharmacy study sites	30.7 (14.0)	31.1 (13.6)
Study patients	25.0 (15.0)	24.2 (15.3)
Location of pharmacy study site (n (%))		
Derbyshire	46 (18.2)	55 (21.9)
South Yorkshire	35 (13.8)	31 (12.4)
Leicestershire	15 (5.9)	10 (4.0)
Nottinghamshire	117 (46.2)	114 (45.4)
Greater London	40 (15.8)	41 (16.3)
Pharmacy ownership† (n (%))		
Independent	65 (25.7)	56 (22.3)
Large multiple	63 (24.9)	68 (29.1)
Small multiple	122 (48.2)	123 (49.0)
Supermarket	3 (1.2)	4 (1.6)

*Economic Deprivation Index (Score)—Data from the Office of National Statistics was used to ascertain the deprivation index for each pharmacy using the postcode as the lookup reference.⁴¹ Data were collected for two variables: (i) IMD score and (ii) rank of IMD score. The IMD score is directly proportional to the level of deprivation (higher IMD score; higher level of deprivation) while the IMD rank is inversely proportional to the level of deprivation (lower IMD rank; higher level of deprivation). The Office of National Statistics data records the English deprivation scores as ranging from 0.5 to 87.8 and deprivation rank scores ranging from 1 to 32482.

†Definition of large multiples and supermarkets—the 10 largest pharmacy entities in England, Small multiples—pharmacies with six or more branches and Independents—pharmacies with one to five 5 branches.⁴²

COPD, chronic obstructive pulmonary disease; IMD, Index of Multiple Deprivation; N, number; NMS, New Medicine Service.

equations analysis of Model 2 dealt with missing data (Model 3: sensitivity analysis to check the effects of the missing data on the outcome).

Predetermined subgroup analyses³⁸ explored whether effect varied by disease, age, gender, pharmacy ownership, pharmacy location, number of other medicines prescribed and deprivation index. Exploratory analyses of secondary outcome measures were also carried out.

Study data (disease, age, gender, ethnicity, number of NMS medicines) were compared with anonymised national records of completed NMS episodes from service inception (1 October 2011) to 2 December 2013. (<https://www.pharmoutcomes.org/pharmoutcomes/>, Health Information Exchange, Hampshire).

Statistical analyses were conducted using Statistical Package for the Social Sciences V.20³⁹ and Stata V.13.0.⁴⁰

Pilot study

The study was piloted in four pharmacy sites to ensure that training, set-up of the pharmacy to operationalise the study, recruitment methods, study materials and processes were satisfactory before full roll-out to all phase 1 pharmacies. Four patients were recruited as part of the pilot prior to wider roll-out.

RESULTS

The pilot study lasted from July to September 2012, and no changes were made to the methods prior to the full study from October 2012 to September 2013. Between July 2012 and September 2013, 504 patients

were recruited from 46 of the 61 pharmacies (range 1–99 patients).

Researcher blinding was broken 75 times in the course of the study, (42 in the NMS arm and 33 in the normal practice arm) accounting for 14.9% of recruited patients. Of these, 66 instances were purposeful due to checking eligibility for qualitative arm of the study. The remaining nine were due to either patient or pharmacist accidentally disclosing their study arm at phone call.

The two groups were well matched (figure 2) for patient characteristics (table 2), most commonly prescribed drugs being amlodipine, ramipril and metformin. There was also a similar disease distribution overall and by gender, age and ethnicity to the national data set cohort (see online supplementary appendix table 3).

Effect of NMS on adherence

Results at Week 10 are shown in table 3. By Week 10, 37 and 16 patients had withdrawn from the normal practice and NMS arms, respectively.

Primary outcome: NMS question

In the unadjusted ITT analysis of 378 patients still taking the initial medicine, 115/190 (60.5%) and 133/188 (70.7%) ($p=0.037$) patients were adherent in the normal practice and NMS arms, respectively. Predictions of adherence were calculated on an ITT basis giving an OR (95% CI) of 1.58 (1.03 to 2.42, $p=0.037$), in Model 1. In the adjusted analysis (Model 2), adherence gave an OR (95% CI) of 1.67 (1.06 to 2.62, $p=0.027$), in favour of NMS. In the

Table 3 Reported adherence by patients to their new medicine and intention-to-treat analysis of the intervention as a predictor of adherence at Week 10—frequency counts, unadjusted, adjusted and imputed ORs

N=patients with outcomes recorded plus withdrawn patients	Number of adherent patients/total responses N (%), p	Model* 1 OR (95% CI, p)	Model* 2 (Adjusted) OR (95% CI, p)	Model* 3 (Imputation) OR (95% CI, p)
Adherence NMS (N=378, 126 responses missing)				
Normal practice	115/190 (60.5)	1.00	1.00	1.00
NMS	133/188 (70.7), 0.037	1.58 (1.03 to 2.42, 0.037)	1.67 (1.06 to 2.62, 0.027)	1.62 (1.04 to 2.53, 0.032)
Composite NMS (N=443, 61 responses missing)† (adherent+stopped+changed)				
Normal practice	144/222 (64.9)	1.00	1.00	1.00
NMS	165/221 (74.7), 0.025	1.60 (1.06 to 2.40, 0.025)	1.68 (1.09 to 2.58, 0.018)	1.64 (1.08 to 2.50, 0.021)
Adherence MMAS-8 (N=267, 237 responses missing)				
Normal practice	85/143 (59.4)	1.00	1.00	1.00
NMS	89/124 (71.8), 0.035	1.74 (1.04 to 2.90, 0.036)	1.88 (1.06 to 3.34, 0.030)	1.77 (0.96 to 3.28, 0.068)
Composite MMAS-8 (N=321, 183 responses missing)† (adherent+stopped+changed)				
Normal practice	108/167 (64.7)	1.00	1.00	1.00
NMS	116/154 (75.3), 0.038	1.67 (1.03 to 2.71, 0.039)	1.78 (1.06 to 3.00, 0.029)	1.81 (1.07 to 3.05, 0.027)

*Model 1: Simple logistic regression model; Model 2 (Adjusted): Multilevel logistic regression model adjusted for recruiting pharmacy, disease, age, sex and medication count; Model 3 (Imputation): Adjusted logistic regression model incorporating imputation of missing data.

†The difference in numbers of patients with composite and simple adherence outcome is larger for the NMS adherence question, when compared with MMAS questionnaire (65 and 54, respectively). This is because, at 10 weeks, more patients whose medicine was changed responded to the NMS adherence question, compared with the MMAS questionnaire (34 and 23, respectively; 11 patients more for the NMS question). MMAS-8, Morisky's Medication Adherence Scale 8-item version; N, number; NMS, New Medicine Service.

full sample (Model 3), the OR (95% CI) was 1.62 (1.04 to 2.53, $p=0.032$) in favour of NMS.

MMAS-8 and composite outcome

By Week 10, across both groups, there were 37 (8.2%) reports of patients with changed medicines and 31 (6.9%) reports of patients with stopped medicines. Amlodipine was most often cited as the medicine that was stopped or changed.

When the ITT analysis was carried out using the composite outcome, or MMAS-8 to measure adherence, similar results to the primary analysis were obtained.

Exploratory analysis suggested that effect size was similar across the four therapeutic areas, although none of the findings were statistically significant (see online supplementary appendix table 4).

Effect of NMS on other outcomes

No change in beliefs about medicines or health status was observed (see online supplementary appendix tables 5 and 6).

Further exploration of contributors to the effectiveness of the NMS suggested that pharmacy characteristics (ownership and location) rather than patient characteristics had an impact (see online supplementary appendix table 7). The likelihood of being more adherent following an NMS consultation is almost double if conducted by a small multiple compared with an independent (OR 1.00 vs 0.57, $p=0.042$). However, as one small multiple recruited 99 patients, this may have influenced the results unduly. Removal of this subset of patients did not affect the effect size. The data for large multiples and supermarkets did not suggest any difference.

Patients most frequently attributed factors such as forgetting, experiencing side effects and their beliefs about their prescribed medicine to their non-adherent behaviour (see online supplementary appendix table 8).

Effect of NMS on costs

Mean (median, range) total NHS cost for patients in normal practice and NMS are £261 (£121, £0–1669), and £239 (£135, £25–1483), respectively (see online supplementary appendix table 9). The NMS intervention incurred slightly lower NHS cost, albeit statistically non-significant, for: £21 (95% CI –£59 to £150, $p=0.1281$).

No reports of patient harm due to the intervention or study participation were reported.

DISCUSSION

The NMS significantly increased the proportion of patients reporting adherence to their new medicine by 10.2–70.7%, compared with normal practice, 60.5%. These results were consistent across two adherence measures and taking account of

confounders and missing data. The cost to the NHS of paying community pharmacists to deliver NMS was absorbed by small reductions in other NHS contact-related costs.

Effect size appeared to be constant across disease areas. The proportion of non-adherent patients in each therapeutic group of our sample varies between disease, which is widely known⁴³ and the proportions reflect those in the literature.^{44–50} This consistent effect supports the theoretical approach of the intervention to allow patient concerns to take priority. This supports the consideration of offering the service in diseases currently outside the remit of the current NMS specification, including mental health. The lack of consistent direction of effect with increased age,^{51 52} sex¹² and deprivation status^{12 24} has been previously observed.

Pharmacy ownership and location may affect the effectiveness of NMS but our data are inconclusive and further work is needed to establish their validity.

Strengths and limitations

This was a pragmatic trial of an existing commissioned service to make sure that results were as generalisable to real-world practice as possible, and was also a methodologically rigorous trial, such that effect sizes reported can be considered internally robust. Sites were closely followed up and supported in running the trial face-to-face and over the telephone. Where recruitment was particularly hampered, most common reasons were NMS conducted in languages other than English; and pharmacists and patients with time constraints.

A cluster RCT design was rejected as this would mean a set of pharmacies would not be able to participate in NMS and this was unlikely to be acceptable to pharmacies, which would lose income and competitive advantage. A quasi-experiment (comparing pharmacies providing NMS with those not providing NMS) was rejected because of possible differences in the two populations of pharmacies. The research team would have had no control over subsequent decisions of pharmacies to start providing NMS, so would have potentially lost substantial numbers of the control group. Patient-level randomisation allowed for control of pharmacy characteristics. Contamination between NMS and normal practice patients from the same pharmacy was very unlikely due to the low frequency of NMS-eligible patients. The difference between NMS and normal practice is the presence or absence of two one-to-one consultations, meaning that the delivery of one arm is unlikely to be affected by the delivery of the other arm.

The evaluation was of the implementation of a commissioned service in the real-world setting so the research team did not standardise intervention delivery. To retain the pragmatic design of the study it was not practicable to quality assure each episode in situ.

Qualitative work has investigated the variability of intervention delivery.²²

There is no gold standard for measuring patients' adherence. In this study there were few measurement options. Direct measures such as measuring plasma levels are invasive and impractical, and indirect measures such as 'pill counts' are open to bias. Prescription-filling⁵³ was not an option for routine monitoring in England due to lack of interoperability between community pharmacy and GP systems and patients may use more than one pharmacy. It should be remembered that the most commonly used objective adherence measure, prescription-filling, has the limitation that it assumes that a prescription filled is actually taken by the patient.

Recommended practice is that more than one adherence measure is employed in a study to provide some assessment of validity.¹ In this study, we chose two self-report measures. Patient-reported measures of behaviour and outcome are important.⁵⁴ Self-report tends to return higher rates of medication adherence (+15%) than some objective measures, due to social desirability and memory bias. However, when patients report they have been non-adherent, these accounts are generally accurate,⁵⁵ and patient-reported adherence correlates with objective clinical measures.⁵⁶

It is likely that adherence was overestimated by patients in both arms of the RCT. Patients in the NMS arm could have felt under more pressure to report adherence to their medicine. Reporting bias was minimised through confidential interview,⁵⁷ normalising non-adherence by recognising the challenges of taking regular medications, avoiding leading questions and asking about missed doses in the week prior to data collection rather than 1 month or year.⁵⁸

Patients' adherence was assessed in the previous 7 days at 10 weeks after the intervention, rather than as continuum or over the longer term, so it provides a snapshot of adherence. NMS is designed to improve adherence early in the therapy, which it has been demonstrated to achieve. NMS is not intended to be a one-off intervention that is isolated from care pathways, but to be integrated into longer-term medicines optimisation strategies.

Patient outcomes including hospital admissions and premature death are improved with increased medicines adherence.^{59–62} Specific disease pathology and pharmacology of the medicine moderate the link between non-adherence and outcomes. For example, the consequences of non-adherence in epilepsy become apparent quickly, whereas in hypertension, non-adherence may not cause morbidity for many years. Appropriate time intervals after non-adherence begins need to be incorporated into any appraisals. To know that patient outcomes will improve as a result of NMS requires a sufficiently powered study, long enough to assess impact on patient outcome, with

associated higher research costs, maybe not delivering timely evidence for policy decision-making.

Comparison with other studies

Community pharmacists can improve adherence to medication,⁶³ and improve outcomes.⁶⁴ The effectiveness in this study is similar to the effectiveness of more complex adherence interventions, and could be more effective if recommendations made here are followed. It should also be remembered that, given the high proportion of patients taking medicines, relatively small increases in percentages can affect large numbers of patients. The intervention developed by Barber *et al*, and the basis for design and implementation of the NMS, produced an absolute 10% increase in adherence, similar to NMS.¹⁵ Interventions to improve adherence are often multifaceted, without clear rationale for each part.⁶⁵ Simpler designs such as the NMS are needed. Telephone follow-up is a flexible and relatively low-cost approach. An RCT of telephone follow-up for patients prescribed a statin for the first time who hadn't filled the initial prescription showed an increase in adherence from 26% to 42.3% ($p=0.001$).⁶⁶ This and our study suggest that a simple but theory-driven intervention can be effective.

Implications for clinicians and policy-makers

The NMS is an initiative that encapsulates the priorities and aims of current policies around medicines optimisation, helping patients and payers.⁶⁷ However, the future success of the NMS relies partly on its integration into primary care provision. Viewing medicines management as an integral part of providing care for people with long-term conditions provides support for the continued use of the NMS.⁶⁸ An environment enabling a triangular model of relationship and engagement between the patient, GP and pharmacist is desirable if optimal medicines use is to be realised. Factors including insufficient integration, underdeveloped relationships between a patient's pharmacist and GP, relatively inaccessible patient records, poorly devised strategies for targeting services and the unwillingness by some pharmacists to offer NMS have hampered the implementation of community pharmacy-led clinical services.^{69 70}

Facilitation is needed at local levels, such as tailoring information technology systems to help foster local relationships. This requires decision-makers at a higher level to make funding available. Electronic integration would allow routine use of prescription-filling to assess adherence, a proxy measure associated with limitations, but easier to collect routinely than self-report if integrated systems exist. Finally, feedback pathways which incorporate mentoring and opportunities for peer review are recommended for practitioners to enhance their own skills.

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