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Appendix

1. Further information about the intervention, its development and rationale

The vast discordant research literature in the field of non-adherence provides limited assistance to guide intervention design. Reviewers frequently conclude that there is insufficient information available to specify effective strategies and to guide decisions about the precise nature of interventions. [1] Nieuwlaat and colleagues, for example, reported that they could identify no common characteristics associated with successful interventions. [2] In the absence of solid evidence about what approaches are most effective, we elected to adapt and refine an existing intervention that had previously shown promise in a large UK based RCT. This research demonstrated that pharmacists can successfully support the optimal use of newly prescribed medicines for long-term conditions in a cost-effective manner through telephone consultation. [3 4] Although, this original proof-of-concept research was limited to a four-week follow-up of self-reported adherence, the patient-centred, tailored intervention had a sound theoretical foundation and as a central telephone-based service was suitable for delivery in a mail order pharmacy context. At the time of the conception of this study, the intervention had recently been adopted as a national NHS-funded New Medicine Service (NMS), provided by community pharmacist in both face-to-face and telephone consultations. In the current study we sought to further develop this intervention and explore its application to other patients already established of long-term medicines, in the context of a mail order pharmacy. The original NMS intervention and its adapted form, named the Medicines Advice Service, are described here.

The New Medicine Service Intervention

The theoretical base of the NMS intervention and the proof of concept research underpinning it is Leventhal's Self Regulatory Model (SRM), incorporating the Necessity-Concerns Framework (NCF). [5 6] This approach recognises that adherence to medication is influenced by each individual's beliefs about their condition and treatment, as well as their experience of it. Alongside theory, empirical evidence suggests that patients' attitudes and beliefs are the factors most closely associated with non-adherence, and reviews have identified individually tailored patient-centred approaches as the most efficacious at improving medication adherence. [7 8]

The NMS intervention is designed to first elicit each patient's experiences with, and concerns about, their new medicine, allowing the pharmacist to tailor the information and advice provided to the individual's specific needs, taking account of their personal beliefs and preferences. The NMS intervention is constructed of three stages:

1. Patient engagement – patient is identified by, or referred to, a community pharmacist and invited to take part in the service when receiving a prescription for a relevant new medicine (NMS is currently targeted at four disease groups: asthma/COPD, hypertension, type 2 diabetes, antiplatelets/anticoagulants).
2. Intervention – 7-14 days later the patient engages in either a face-to-face or telephone consultation with the pharmacist.
3. Follow up – 14-21 days later the patient has a follow up consultation with the pharmacist.

The intervention consultation and follow up are guided by an interview schedule. The pharmacist, having identified any concerns or issues the patient has with their medicine, can then make efforts to resolve these issues, referring the patient back to their GP where necessary. Further information about the NMS can be found in the service specification at http://psnc.org.uk/services-commissioning/advanced-services/nms/.

Adaptation and development - the Medicines Advice Service Intervention

For this study, the original intervention was adapted to be delivered in a new context, targeting different patient groups. The design of the new intervention, which was named the Medicines Advice Service, was influenced by the practical experiences of the research and pharmacy team, guided by theoretical understanding, empirical evidence, and the available resources.

One of the key differences from the NMS intervention was its targeting toward patients already established on medications in the long term, rather than those beginning a new medicine. Although research indicates that the largest decline in persistence occurs within the first 6 months of treatment, there is evidence of subsequent continued steady drop-off in adherence over time. Benner et al. [9] found that adherence to statins was 79 per cent after 3 months, 56 per cent after 6 months, 56 per cent after 12 months, 35 per cent after 60 months, with just about one in four patients still considered adherent at 5 years. This suggests that people may experience problems with their medication that persist well beyond the beginning of a

new therapy, or encounter new problems over time. The Royal Pharmaceutical Society of Great Britain's recently published good practice guidance on medicines optimisation recognises that "the patient's experience may change over time even if the medicines do not." [10, p. 6] Like the NMS, our intervention targeted all patients regardless of their current adherence status.

One pharmacist delivered all the Medicines Advice Service intervention consultations via telephone. The intervention in the original proof of concept study was similarly delivered as a centralised telephone service by a small number of pharmacists from one organisation. However, the intervention has been successfully scaled up, and the NMS can be provided by any accredited community pharmacist, either face-to-face or by telephone, and has been found to produce a similar effect size.

In keeping with the structure of the NMS intervention, our intervention comprised two tailored consultations with a pharmacist, guided by a semi-structured interview schedule. Consultations aimed to identify any particular problems or concerns that the patient may be having and began with an open question "How are you getting on with your cholesterol/diabetes medicines?" The interview guide included questions related to the management of the condition as well as medications to encourage a more holistic approach. Additionally, participants received follow-up written information, comprising a summary of the information and advice imparted over the telephone, and a personalised medicines reminder chart which lists the individual's medicines, what they are for, the times they are to be taken and any other relevant instructions. There is strong evidence to support the provision of combined verbal and written communication. Research indicates that between 40 and 80 per cent of medical information provided by healthcare professionals is forgotten immediately. [11] Moreover, almost half of what people recall is in fact incorrect. [12] [13] Although there is more limited evidence available on the utility of medicines charts, some studies suggest that they are effective in improving knowledge and adherence, and qualitative research had identified a desire among patients for an up-to-date medication list of what to take, as well as when and how. [14-16] Charts were automatically generated within the pharmacy database but could be amended by the pharmacist based on their consultations with the patient to ensure that it was accurate and relevant to the patient's current dosing regimen. The provision of a written summary and a medicines reminder chart was intended to improve both the efficacy and sustainability of the intervention by providing an additional re-iteration and reference of the key points from telephone consultations and clarification of the patient's medication regimen.

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2. Missing data and multiple imputation

The most common reasons for missing data in this study were: participants not returning a questionnaire, participants not fully or correctly completing the questionnaire, participant withdrawal, or participants who became ineligible during the study. Multiple imputation, using the fully conditional specification method in SPSS, was used to impute missing data. Linear regression was used for continuous variables and logistic regression for categorical variables. The imputation model included the primary outcome (self-reported non-adherence at four weeks and six months post-intervention), which was missing for 15.5% and 19.2% of the sample, respectively. Other variables included in the imputation model had no more than 4% missing data (marital status, living arrangements, education, employment, ethnicity, English language, self-reported general health, number of GP visits in three months prior to study, beliefs about medicines, and medication-related problems, concerns and information needs). The variables: group allocation, age, gender, therapeutic group, use of refill reminder service, and number of items on repeat prescription were extracted from the pharmacy database and had no missing values. For outcomes comprising multiple separate questionnaire items, such as the BMQ, each questionnaire item was imputed and the overall outcome score calculated from the imputed data. Twenty complete imputed data sets were created, as recommended in more recent literature (Sterne et al., 2009), which were analysed separately and the results then combined.

3. Study Protocol

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Research Protocol

The Medicines Advice Service Evaluation

-

A randomised controlled trial of a pharmacy-based telephone intervention to support patients taking medication for a long-term condition

UCL School of Pharmacy & Pharmacy2U

Imogen Lyons
PhD Student
UCL School of Pharmacy

CONTENTS

1. Summary 4

2. Background 4

3. Aims and Objectives 5

4. Study Design 5

5. Setting and Participants 5

5.1 Selection Criteria 6

5.1.1 Inclusion Criteria 6

5.1.2 Exclusion Criteria 6

5.2 Recruitment 6

6. Intervention 7

6.1 Intervention Group – Medicines Advice Service 7

6.1.1 Telephone Call and Summary Letter 7

6.1.2 Follow-up Telephone Call 8

6.2 Control Group 9

7. Study Procedures 9

7.1 Randomisation 9

7.2 Intervention procedure 9

7.3 Quality Assurance and Maintaining Intervention Fidelity 10

7.4 Training 10

8. Data Collection and Outcome Measures 11

8.1 Data Collection 11

8.1.1 Postal Questionnaire 11

8.1.2 Qualitative Interviews 11

8.2 Outcome Measures 11

8.2.1 Self-reported Adherence 12

8.2.2 Pharmacy Refill Records 15
8.2.3 Clinical Indicators of Health 15
8.2.4 Healthcare Utilisation 15
8.2.5 Beliefs about Medicines 16
8.2.6 Medicine-related Problems 16
8.2.7 Demographics and General Health 16
8.2.8 Patients' Satisfaction with the Intervention 16

8.3 Process Measures 17

9. Statistical Considerations 17

9.1 Sample Size 17

9.2 Statistical Analysis 17

References 18

Appendix 21

Data Collection and Intervention Time Frame 21

1. SUMMARY

Non-adherence to medication is common and although some interventions have shown promise in improving adherence, the findings are inconsistent. This study aims to examine the impact of a pharmacy-based telephone intervention on medication adherence and health outcomes in patients taking medicines for a long-term condition.

Patients will be identified from a database of pharmacy patients. We hope to recruit approximately 600 patients to take part in the study. Half of these will be randomised to receive the intervention, while the other half will continue to receive their usual care from the pharmacy. The intervention will consist of telephone support provided by a pharmacist together with follow-up written information. Participants in the study will be followed up over six months. Data will be collected from both groups prior to the intervention and at two points during and after the study to determine any changes as a result of the intervention. The main outcome of interest is adherence to medication. Other outcomes that we will explore include clinical indicators of health and healthcare service use. The results of this study will be used to guide future intervention development and implementation.

2. BACKGROUND

The World Health Organization (2003) proposed that innovations to improve treatment adherence may have a greater impact on population health than any further developments in specific medical treatments. However, thus far there is a limited evidence base for interventions to increase adherence to medication. Several systematic reviews have been carried out and reported that the literature in this field is of poor quality and the findings are inconclusive as to how best to intervene (Haynes et al., 2008, Van Wijk et al., 2005). The UK Department of Health (2008) also highlighted the need for more robust evidence to strengthen the commissioning of services to support adherence to medicines. This study attempts to address this gap by developing and rigorously evaluating a new adherence intervention based on existing research and theory.

The causes of non-adherence are complex and what evidence exists to date, suggests that multi-faceted, tailored interventions are more effective in improving adherence than single and generalised interventions (Haynes et al., 2008, van Eijken et al., 2003). The 2009 NICE guidelines on medication adherence state that no specific intervention can be recommended for all patients and that any intervention must be tailored to the specific circumstances of the individual patient (Nunes et al., 2009).

Pharmacists have been identified as well-placed and well qualified to deliver tailored adherence interventions (Cutrona et al., 2010). An RCT carried out by Clifford et al (2006) found that a patient-centred telephone intervention, delivered by a community pharmacist and focussing on individuals'

problems and concerns about medicines, resulted in improvements in adherence and cost savings in the use of healthcare costs. However, this study had a follow up of just four weeks and although there is growing evidence that telephone interventions can be effective in improving self-care activities and health outcomes the evidence is inconsistent and requires further study (Walker et al., 2011). It is therefore hoped that this study will provide further insight into the efficacy of a pharmacy-based telephone intervention to improve medication adherence and health outcomes.

3. AIMS AND OBJECTIVES

The overall aim of the study is to evaluate the impact of a pharmacy-based telephone intervention to support patients taking medications for a long-term condition.

Key objectives are to:

- Develop a patient-centred tailored intervention
- Conduct a randomized controlled trial to test the effectiveness of the intervention compared to usual care on the following outcomes:
    - Adherence to medication
    - Clinical health outcomes
    - Medicine-related problems and concerns
    - Beliefs about medicines
    - Health services utilization
- Evaluate the process of intervention implementation and identify factors that may impact on replicability and generalisability.

4. STUDY DESIGN

The study will use a single-site, randomized controlled parallel groups trial with one intervention arm and one control arm to assess the effectiveness of a pharmacy-based telephone intervention compared to usual care in improving adherence to medication and improving health outcomes.

Recruitment will take place over a 6-month period and each participant will be followed up for 6 months. The total duration of participant involvement in the trial is therefore likely to be 12 months from the first randomisation.

5. SETTING AND PARTICIPANTS

The intervention will target patients taking medication for two common long-term conditions: type 2 Diabetes and Hyperlipidemia. Participants will be recruited through Pharmacy2U, an established UK internet and mail-order pharmacy.

5.1 SELECTION CRITERIA

Potential participants will be identified through electronic searches of the active NHS patient cohort contained within the pharmacy's computer database, according to the predefined eligibility criteria below.

5.1.1 INCLUSION CRITERIA

- All NHS patients prescribed medication(s) for at least one of the following conditions:
    - Type 2 Diabetes
    - Hyperlipidemia

5.1.2 EXCLUSION CRITERIA

- Patients living outside of England
- Patients with no access to a telephone
- Patients under the age of 18
- Patients unable to give written informed consent
- Patients on drugs for dementia
- Patients showing signs of dementia or cognitive impairment in conversation
- Patients with substantial hearing or sight impairment
- Patients whose medications are ordered by a caregiver/family member
- Patients with insufficient English to take part in the telephone intervention
- Patients living with someone already taking part in the study
- Patients newly prescribed a medication for the conditions listed in the inclusion criteria

5.2 RECRUITMENT

The number of participants recruited at any given time will be limited by the availability of the intervention pharmacist. Recruitment therefore will be staggered over a period of at least six months. At each recruitment point a random sample of patients who meet the inclusion criteria will be invited to participate in the study. A small pilot study will be undertaken to identify the proportion of selected patients who are likely to consent to take part in the study. These findings will be used to estimate the number of patients who will need to be invited to participate in order to achieve the sample size required. The size of the invitation communication may be adjusted as further experience and understanding of the response rate is developed.

Each potential participant will receive an invitation letter with a patient information sheet, consent form and prepaid return envelope. Patients who do not return a consent form within 2 to 3 weeks may be contacted by telephone by a member of the Pharmacy2U customer care team and again invited to participate if they wish and have the opportunity to have any questions answered. The same process will be repeated at each subsequent round of recruitment, with all those previously invited to take part excluded from the search.

6. INTERVENTION

The intervention being studied is a patient-centred telephone service to support patients taking prescribed medicines for a long-term condition. The intervention will include three communications: two telephone consultations and written information by post. The intervention is intended to target medication adherence but the specific emphasis will be tailored to the individual participant's specific medication and condition-related needs.

6.1 INTERVENTION GROUP – MEDICINES ADVICE SERVICE

Participants in the intervention arm will receive a scheduled telephone consultation with a pharmacist, a written summary of the consultation and a medicines reminder chart. A second follow-up telephone call completes the intervention.

The intervention will be delivered by fully qualified pharmacists. Wherever possible the same pharmacist will conduct all the sessions for a given participant. During each interaction with the patient the pharmacist will focus on developing rapport with the patient, establishing a collaborative relationship and encouraging open communication. Pharmacists will aim to be non-judgemental and encouraging, in a supportive rather than a directive manner.

All patients will continue to be treated according to the clinical discretion of their GP, hospital specialists or any other healthcare providers throughout the trial.

6.1.1 TELEPHONE CALL AND SUMMARY LETTER

The first intervention telephone call will take place within 3-4 weeks of enrolling in the study.
At the beginning of the first intervention telephone call the pharmacist will check the participant meets the selection criteria, briefly reiterate the overall structure of the intervention, and will confirm that the participant is happy to continue.

The initial consultation will follow a semi-structured condition-specific interview guide designed to establish the patient's adherence to medicines, identify any problems the patient may be having and assess the patient's needs for further information or advice. The interview schedule has been

adapted from one successfully used in previous research studies (Clifford et al 2006) and currently being used as part of the recently established New Medicine Service. The pharmacist will also have access to the patient's pharmacy record and will be able to see a complete list of the patient's medications and dispensing history.

Based on the information elicited the pharmacist can confirm and prioritise the issues identified with the patient and together explore potential solutions. The pharmacist can tailor advice to each patient's individual needs. The intervention will take a holistic approach, focussing not only on the medicines used in the selection criteria but also taking into account any other prescribed or over-the-counter medications, or co-morbid conditions.

The components used in the intervention will address both intentional and unintentional non-adherence and may include:

- Information or suggestions to help address any concerns about taking medication
- Information or suggestions to help address any existing problems with medicines
- Tips and tactics to avoid common side effects
- Advice about how to deal with side effects.
- Information about strategies to help patients remember to take their medications as prescribed e.g. alarms, multi-compartment compliance aids, phone/tablet apps, etc
- Signposting to educational videos and websites – e.g. video of accurate inhaler technique.
- Discussion about potential formulation or dosing schedule changes
- Referral to prescriber where necessary

At the end of the interaction the pharmacist will summarise the outcomes of the discussion and actions to be taken, and will schedule a follow-up telephone call. The pharmacist will record any issues identified and interventions provided using a specially designed intervention page on the pharmacy database. The outcomes of the intervention will be documented and a summary will be posted to the patient. All participants will also receive a personalised printed medicine reminder chart, which will be discussed with them during the intervention phone call.

6.1.2 FOLLOW-UP TELEPHONE CALL

Four to six weeks after the first telephone call, the patient will receive a follow-up phone call from the pharmacist as scheduled. The follow-up intervention will follow a similar process and will focus on assessing medication adherence, reviewing progress, addressing any new problems or concerns, and providing healthy lifestyle advice.

6.2 CONTROL GROUP

Participants in the control group will continue to receive their existing dispensing service from Pharmacy2U. This includes ordering their prescribed medications online or through a dedicated telephone service and having their prescriptions delivered to their home or office by recorded delivery. Customers ordering by telephone usually speak to a member of the customer care team. It is therefore unlikely that the intervention pharmacist(s) will have contact with control group participants.

Participants in the control group who have previously opted to avail of Pharmacy2U's prescription reminder service, either via telephone or email, will continue to do so throughout the study period. Patients who use this service are contacted by a member of the customer care team when their prescription is due for renewal and if requested Pharmacy2U arrange for the prescription to be approved by their doctor and dispensed on their behalf.

7. STUDY PROCEDURES

7.1 RANDOMISATION

Randomisation will be at the level of the individual participant and will take place after the participant has completed the baseline data collection. Participants will be randomly allocated in equal numbers to either the intervention or control group. If necessary, minimisation will be used to ensure groups are balanced on factors such as use of the pharmacy refill reminder service. According to the Consort guidelines (Moher et al., 2010) minimisation is considered an acceptable alternative and methodological equivalent to random assignment to ensure that a balance is maintained between groups for several patient factors identified prior to the beginning of the study. Using minimisation, the first patient is randomly assigned to a group; all subsequent patients are allocated to the group which will ensure the groups remain as closely balanced as possible on the characteristics selected.

The researcher will contact the pharmacy to inform them that consent has been received and the allocated group for each consented participant. Each participant will also receive a letter from the researcher informing them of their allocation. Due to the nature of the intervention it will not be possible to blind participants or pharmacy staff to the patient's allocated group.

7.2 INTERVENTION PROCEDURE

Participants who have been randomized to the intervention group will receive either a call or an email from the Pharmacy2U customer care team to arrange an appointment with the pharmacist.

Emails will provide a link to available time slots for the participant to book as convenient. Participants who schedule an appointment using this system will receive email confirmation of the appointment time and date. Customers who do not have an email address registered with Pharmacy2U or do not respond to the initial appointment scheduling email will receive a call from the customer care team to schedule an appointment.

In most cases the pharmacist will arrange the follow-up intervention appointment with the participant at the end of the first intervention telephone consultation. Where this is not possible, the customer care team will schedule the next appointment using a similar process.

7.3 QUALITY ASSURANCE AND MAINTAINING INTERVENTION FIDELITY

Limiting the study to one site allows greater control over the intervention. There will be a small number of pharmacists involved in the study, which will reduce the impact of variation in individual practices. However, a detailed intervention manual will be developed to help ensure adherence of the intervention pharmacist(s) to the study protocol. The intervention manual will be developed in consultation with the intervention pharmacists to ensure it is relevant and user-friendly, and will be updated as the study progresses and more experience is gained.

The pharmacist will be responsible for tailoring the intervention to the specific needs of each individual. The intervention pharmacists will carefully document the participants' responses and each component of the intervention applied for each patient, using a specially designed intervention page on the pharmacy database. All intervention telephone calls will be recorded and a random selection will be reviewed to monitor quality and give feedback to the intervention pharmacist(s). The researchers will maintain regular contact with the pharmacy staff to resolve any emerging issues.

7.4 TRAINING

The intervention will be delivered by fully qualified pharmacists, who will have received training in the implementation of the study protocol and specific procedures. This training will be supported by a written manual. Customer care staff who will be involved in the recruitment and scheduling of intervention appointments will also receive training in the background and rationale for the study, and in the implementation of the study protocol and the intervention and control procedures.

8. DATA COLLECTION AND OUTCOME MEASURES

8.1 DATA COLLECTION

Both quantitative and qualitative data will be collected. Data will be collected via self-complete postal questionnaire at three time points: baseline, four weeks and six months.
A qualitative telephone interview will be conducted with a subsample of participants in the intervention group approximately 4 months into the study. Further data may be extracted from pharmacy records and the NHS hospital episodes statistics secondary usage data. Further information on the data collected at each time point can be found in the Appendix.

8.1.1 POSTAL QUESTIONNAIRE

The postal questionnaire at baseline will include demographic questions, a measure of general health, a section on medication beliefs, problems and adherence, and questions on healthcare utilisation. A second questionnaire posted to participants at four weeks will include questions on medication beliefs, problems and adherence, and healthcare utilisation. Participants in the intervention group will receive a supplementary questionnaire assessing their satisfaction with the telephone service. A similar questionnaire will be posted to participants 6 months post intervention.

8.1.2 QUALITATIVE INTERVIEWS

Qualitative interviews will be conducted with a purposive sample of approximately 30 participants in the intervention group. Interviews will explore participants' experiences of the study and will examine their perceptions of and satisfaction with the telephone service.

The aims and objectives of the qualitative component of the study are to:

- Provide in-depth information about how the intervention works from the perspective of participants
- Identify and understand outcomes of the intervention from the perspective of the participants
- Collect information to explain the success or failure of the intervention, such as the mode of communication, structure and components of the intervention.
- Identify areas needing improvement in future implementation of the intervention

8.2 OUTCOME MEASURES

The primary outcome of interest in this study is self-reported adherence to medication. Secondary outcome measures will include: pharmacy refill adherence, clinical health outcomes, healthcare resource use, beliefs about medicines, and medicine-related problems and concerns.

8.2.1 SELF-REPORTED ADHERENCE

The primary outcome measure in this study is self-reported medication adherence. A range of methods are available to measure medication adherence, including: electronic monitoring of medication containers to record each opening, pill counts, pharmacological or biochemical markers in blood or urine, dispensing records, patient diaries and self-report. All these methods are indicative rather than absolute measures of adherence, each with its own advantages and disadvantages. Previous research indicates that in the absence of a 'gold standard' measure, researchers must choose the most appropriate measure in the specific context (Garfield et al., 2011).

Self-report measures have long been the most widely used method of assessing adherence in both research and practice settings (Williams et al., 2012). Patient-report methods are relatively inexpensive, simple and convenient to use (Osterberg and Blaschke, 2005, Bosworth et al., 2006). Self-reported adherence rates tend to be higher than those obtained from more objective measures such as electronic monitoring data, however, recent reviews and meta-analysis have reported moderate correlations between self-report, electronic monitoring, pill counts and pharmacy refill data, indicating that self-reports are still a valid measure (Garfield et al., 2011, Shi et al., 2010). Self-reported adherence measures have also been found to have good predictive validity with clinical outcomes, such as viral load in HIV and blood pressure (Garfield et al., 2011, Williams et al., 2012). Furthermore, self-report measures can be qualitatively informative, providing an opportunity to help understand and interpret adherence behaviours (Kyngas et al., 2000, Bosworth et al., 2006, Williams et al., 2012).

Many self-report instruments have been developed to assess both generic and disease-specific medication adherence, a number of which have been explored for use in this study (Bosworth et al., 2006). A recent systematic review carried out by Garfield et al (2011) identified 58 different self-report measures, with limited evidence available to help decide which types of scales are most acceptable, reliable and obtain the most accurate information. Among the most commonly used self-report adherence measures are the 4-item or 8-item Morisky Medication Adherence Scale (Morisky et al., 1986, Morisky et al., 2008) and the Brief Medication Questionnaire (Svarstad et al., 1999). The evidence for validity and reliability for these existing scales remains inconclusive and each scale has limitations. For example, Garfield et al. (2011) reported that approximately half the papers reporting reliability data for the Morisky scale found low internal reliability, while the other half reported acceptable reliability. The Morisky instrument has been found to be a poor predictor of low adherence or clinical outcome (Farmer, 1999, Dunbar-Jacob et al., 2012). Moreover, this scale measures adherence as a categorical variable and does not allow for the quantification of individual

patient's adherence or adherence for different drugs within a regimen (Doró et al., 2011). Finally, the Morisky Scales are not time specific and are therefore impractical for measuring changes in adherence over time. None of the questions on the 4-item scale and six of the eight items in the Morisky-8 ask about general adherence rather than specifying a time period.

The Brief Medication Questionnaire (BMQ), developed by Svarstad et al (1999) to screen for adherence and perceived barriers to adherence, requires participants to list all the medications they have taken in the previous week, with detailed information about doses times and number of pills taken and missed. It also collects information about what the medicine is being taken for, whether the patient thinks it is working, whether medicines bother the patient, and about common problems with medicines. It is a long, complex and cumbersome instrument, and does not address medicines which the patients may have been prescribed but has not taken in the previous week. Furthermore, although it was found to have good sensitivity for predicting non-adherence of more than 20% of prescribed medicine, it has very low sensitivity for identifying sporadic non-adherence (defined as taking 1-19% more or less medicine than prescribed).

In the absence of a suitable standardised questionnaire, a measure was sought that could meet the following criteria:

- Generic rather than disease-specific and therefore suitable to use for multiple conditions
- Suitable for patients taking a single medication or multiple medications for one or more conditions.
- Brief and acceptable, not overly time consuming or intrusive
- Sensitive to change over time
- Provides continuous outcome data

The measure selected consists of three questions; two about the amount of medication taken and one about the reasons medication was missed. The first question asks people to estimate their adherence using a visual analogue scale (VAS). The VAS requires participants to mark a point along a scale indicating their best guess about how much of the medicines they have taken within the previous month. The VAS is a quick, simple measure and has shown promising evidence of validity in recent studies (Giordano et al., 2004, Oyugi et al., 2004, Pearson et al., 2007). Moderate to high correlations have been reported between the VAS and other self-report measures, unannounced pill counts and prescription refill data, as well as with HIV viral load suppression (Nau et al., 2007, Kalichman et al., 2009).

Several recent studies report that general estimates of adherence over longer periods produce similar or more accurate rates than more specific measures of missed doses (Walsh et al., 2002, Giordano et al., 2004, Simoni et al., 2006, Lu et al., 2008, Doró et al., 2011). The VAS question

asks about adherence over a one-month period. Williams et al (2012) state that for general estimates of adherence, a one-month period is a reasonable time frame for most patient groups. One advantage of using a one-month time period is that it is more likely than shorter time frames to be reflective of general patterns of adherence over time, and therefore more likely to be linked with clinical outcomes.

Although estimation recall measures such as the VAS appear promising, they lack more detailed information about patterns of adherence and may be more susceptible to recall bias (Garfield et al., 2011). The second question, drawn from the Diagnostic Adherence to Medication Scale (DAMS), therefore, requires participants to recall how many doses of each of their cholesterol and/or diabetes drugs they have missed taking in the previous 7 days (Garfield et al., 2012). A review comparing self-report and objective adherence measures in HIV found that the most common self-report item was an open-ended question about the number of doses missed over a defined period of time (Simoni et al., 2006). When asking participants to provide more specific details shorter time periods are more appropriate (Williams et al., 2012). Adherence rates reflecting a shorter time period are generally thought to be less likely to be affected by recall bias. Some researchers have reported that the accuracy of adherence reports decline after just 24 hours (Wagner and Miller, 2004). However, others have contradicted this finding moderately strong correlations between 1, 2, 3, 4, 5, 6 and 7-day measures, and reporting no difference in adherence recall between 1 and 3 days, when compared to MEMS data (Pearson et al., 2007, Jerant et al., 2008). A 7-day recall period was chosen as it always incorporates a weekend, when adherence behaviours have been found to differ. Haynes et al. (2002) assert that missing one or more pills in a week is an indication of a problem with low adherence.

Research suggests that patients sometimes have difficulty remembering the names of their medications and their prescribed dosing regimen (Catz et al., 2000, Gagné and Godin, 2005). Williams et al. (2012) recommend that prior to collecting recall information about doses taken or missed the prescribed regimen should be reviewed with the patient. Therefore the 7-day adherence recall question will be personalised for each participant, listing their relevant medicines and dosage prescribed based on pharmacy data.

Both adherence questions include a permission statement to normalise non-adherent behaviour and reduce the potential effect of social desirability bias. The final question, from the DAMS, asks participants to select reasons for missing doses of their medication from a list provided. This is intended to allow distinction between intentional and unintentional non-adherence.

8.2.2 PHARMACY REFILL RECORDS

As there is currently no gold standard measure for assessing adherence, it is often recommended that more than one measure be used. The WHO (2003) reported that the current state-of-the-art in measurement of adherence is a multi-method approach combining a self-report measure and another more objective measure. In this study pharmacy refill records will be used to allow for triangulation between measures. This method of measuring adherence focuses on the amount of medication an individual has available rather than the ingestion of medication (Williams et al., 2012). While this approach cannot provide detail on what medications are taken when and how, it can provide an estimate of the highest possible level of medication consumption. Pharmacy refill records are considered a reliable and objective measure of adherence and can be used to corroborate other measures such as self-report without any additional burden on patients (Osterberg and Blaschke, 2005, Bosworth et al., 2006). Pharmacy refill measures have been found to have good predictive validity with HIV viral load and CD4 response, and to correlate well with blood pressure and glycaemic control (Steiner and Prochazka, 1997, Gonzalez and Schneider, 2011, Williams et al., 2012).

8.2.3 CLINICAL INDICATORS OF HEALTH

A systematic review of studies to improve adherence by Haynes et al (2008) advocates the inclusion of clinical outcome measures in a trial of an adherence intervention on the basis of an ethical imperative to have a clinical benefit. A finger prick blood test will be used in this study to test the impact of the intervention on HbA1c levels in patients with Diabetes and cholesterol levels in patients on lipid-lowering drugs. Patients will receive a kit supplied by The Doctor's Laboratory (TDL) London with clear instructions for use. Using this method, participants will use a spring-loaded lancet to draw blood from the finger and fill a collection tube with approximately 20-30 drops of blood. The participant then posts the sample back to the laboratory in a freepost addressed envelope.

8.2.4 HEALTHCARE UTILISATION

Healthcare resource use will be measured in two ways. In the postal questionnaire, patients will be asked to self-report the number of times they have used a range of health services in the previous 3 months. Further data may be sourced using the NHS Information Centre's trusted data linkage service. With patient consent this service can provide data on specific patients' secondary care usage.

8.2.5 BELIEFS ABOUT MEDICINES

Research has suggested that patient's medication adherence is related to their beliefs about their medicines. Influencing beliefs about medicines may, therefore, present an opportunity for improving adherence. In this study participant's beliefs about medicines will be assessed using the Beliefs about Medicines Questionnaire (BMQ) (Horne et al., 1999). The BMQ has shown good validity and reliability in a range of chronic conditions, including asthma, diabetes, psychiatric, renal and cardiovascular disease.

The BMQ has two sections: the BMQ-general covers beliefs about medicines in general, while the BMQ-specific addresses beliefs about particular medicines the patient is taking. This study will use the BMQ-specific scale only. The BMQ-specific comprises two 5-item subscales: a necessity scale that assesses the perceived need for the medication and a concerns scale that gauges the strength of concerns about potential adverse effects of taking medicines. Participants rate each item on a five-point Likert scale from strongly agree to strongly disagree. The difference between the two subscales can be calculated and the resulting 'necessity-concerns differential' has been related to patients' adherence. A high score on the necessity scale and low concerns beliefs have been linked to good adherence (Horne and Weinman, 1999, Phatak and Thomas, 2006, Tibaldi et al., 2009).

8.2.6 MEDICINE-RELATED PROBLEMS

The questionnaire also includes items assessing the problems people experience with their medicines. The items have been developed based on problems related to medicines that have been identified by patients in previous studies in the UK (Barber et al., 2004, Gordon et al., 2007).

8.2.7 DEMOGRAPHICS AND GENERAL HEALTH

Socio-demographic information and a single item assessing general health will be collected to determine whether randomization was successful, to assess their moderating influence on adherence and to determine whether some types of patients are more likely than others to benefit from the intervention.

8.2.8 PATIENTS' SATISFACTION WITH THE INTERVENTION

Participants in the intervention group will receive a supplementary questionnaire at the second and third data collection points. No suitable validated questionnaire was found to assess patient satisfaction with a pharmacist telephone intervention. Some questions were derived from existing scales used in the literature and others were developed to evaluate specific components of this intervention.

8.3 PROCESS MEASURES

A number of process measures will also be extracted from pharmacy records to help assess the fidelity to the intervention protocol and the future practicality of the service. These will include:

- Time and duration of each intervention
- Person providing the intervention
- Number of sessions delivered to each participant
- Number of attempts made to reach participants
- Length of time between each intervention session

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE

A sample size calculation was carried out for the primary outcome (self-reported non-adherence) based on the ability to detect a reduction in self-reported non-adherence from 15% to 7.5% in the intervention group compared with the control group at 6 months. This effect size is based on a pharmacy intervention study in a UK population with chronic conditions (Clifford et al., 2006). With 80% power, at a 0.05 significance level (two-sided), and assuming a 10% dropout rate, the sample size required is 612 individuals (306 in the intervention and 306 in the control group).

Based on the data from the pharmacy customer database, this sample size should be feasible within the time frame of the study. Pharmacy records indicate there are approximately 3800 patients on lipid-lowering drugs, and over 1000 patients on drugs for type 2 diabetes.

9.2 STATISTICAL ANALYSIS

Intention to treat analyses will be performed in this study. Multiple imputation method will be used to deal with missing data. Data will be summarized as mean (SD) for continuous variables and number of participants (percent) for categorical variables. Chi-square and analysis of variance tests will be performed to determine significant differences for baseline characteristics between the two groups. A logistic regression model or a mixed regression model will be used to analyze the non-compliance in the intervention and control groups. A number of exploratory analyses will be carried out to assess the differences in health outcomes, healthcare utilization and health related quality of life between the two groups. P values of less than 0.05 will be considered to indicate statistical significance. All statistical analyses will be carried out using SPSS.

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APPENDIX

DATA COLLECTION AND INTERVENTION TIME FRAME

Data Collection	Month	Intervention
	0	**Recruitment and consent** Letter
Postal questionnaire *Demographics* *General health* *Beliefs about medicines* *Medication-related problems* *Medication adherence* *Health service utilization*		
	1	**First telephone consultation** Written information by post
	2	**Follow-up telephone consultation**
Postal questionnaire **(4 week follow-up)** *Beliefs about medicines* *Medication-related problems* *Medication adherence* *Health service utilization* *Satisfaction with service (intervention group only)*	3	
Qualitative telephone interviews ~30 patients	4	
Postal questionnaire **(6 month follow-up)** *Beliefs about medicines* *Medication-related problem* *Medication adherence* *Health service utilization* *General health*	8	
Pharmacy refill adherence	12+	
HES/SUS data *Hospitalizations*		