Designing a study to test the effect of multi compartment medication devices

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1. Background

Approximately 50% of patients do not take their prescribed medication correctly.[1] The reasons for such patient behaviour have been widely researched and it is believed that it arises from both unintentional and intentional actions. Unintentional non-adherence has been associated with impaired cognitive function and practical problems such as difficulty removing medication from its packaging or swallowing the dosage form. Multi compartment Medication Devices (MMDs) are intended to target unintentional non-adherence [2-4] associated with cognitive problems and perhaps to an extent accessibility via providing medication in a packaging accessible to the patient. It has been estimated that 100 000 people are currently using MMDs in the UK [4]. Assuming that the average number of medicines per patient using an MMD is four, it is estimated that £23 million is being spent annually (includes costs of device plus extra dispensing/professional fees). Some of this cost is borne by the NHS for patients eligible under the disability discrimination act whilst the remainder is paid by patients and their relatives. However, there is no rigorous evidence of the benefit from MMDs[5, 6].

Assuming that MMDs reduce unintentional non-adherence, they may have an important role in the optimisation of therapy. Furthermore, one of the factors which contribute to patients transferring from their own homes into care homes is the inability to safely manage their own medicines. Consequently, MMDs may play an additional role in maintaining patients in their own home and prolonging their autonomy which is in accordance with Government targets to promote independence [7].

Considerable research has been conducted in order to establish the predictors of non-adherence and whilst there is still much uncertainty, a positive association between magnitude of non-adherence and regimen complexity has been frequently reported [8-12]. It is therefore patients prescribed multiple medications that are at the greatest risk of non-adherence and to whom MMDs are most frequently provided [13]. Research suggests that older patients are prescribed an average of three regular medications, thus a large proportion of the older population has at least one risk factor for non-adherence and hence MMDs are most frequently supplied to this population [14].

There are many methodological issues associated with the rigorous testing of MMDs hence the absence of adequate large scale studies. These methodological challenges include, identification of the most appropriate participants, replication and thus testing of standard care versus the MMD intervention, defining and accurately measuring outcomes/effects, and recruiting an adequate number of participants.

Participant identification

Intentional non-adherence is associated with numerous factors such as beliefs about medicines [15] and the quality of the patient–prescriber relationship [16-18]. The proportion of non-adherence that is attributable to intentional factors varies, usually ranging from 4 % to 17 % [17], [19-21] but with reports as high as 37% in older people [22]. It is therefore essential that any MMD trial only targets patients who are unintentionally non-adherent.

The Beliefs about Medicines Questionnaire (BMQ) is an 11 item tool designed to establish whether a patient has a negative attitude towards their prescribed therapy. Trials have demonstrated it to be a strong predictor of intentional non-adherence and it is therefore appropriate for identifying and excluding intentionally non-adherent patients [16]. Similarly the Medication Adherence Report Scale (MARS) is a 5 item questionnaire also designed to identify intentional and unintentional non-adherence [23]. The MARS has demonstrated good internal and test-retest reliability when used to report adherence to medication for the treatment of chronic conditions. A comparative study of Dosage Unit Count (DUC) with the MARS has also reported good correlation between the two measures [17]. As a shorter questionnaire, if effective, the MARS may prove to be a more appropriate tool than the longer BMQ. Consequently both the BMQ and MARS may be suitable tools for screening out those patients for whom an MMD may not be appropriate.

Weekly versus monthly supply

A number of factors have been cited as the rationale for MMDs supporting adherence, including, providing medicine storage which is easily accessible to the patient, reducing the complexity of adhering to a regimen, minimising dose amount and timing errors and acting as a memory aid [5]. A further benefit may be the increased frequency of dispensing which results in greater contact with the pharmacy team or a carer, by virtue of the medication being supplied on a weekly rather than the more usual monthly basis. Research has demonstrated that reducing monitoring frequency from weekly to fortnightly reduces adherence to therapy and therefore it may follow that reducing medication supply frequency may have a similar effect [24]. Studies evaluating patient medication administration errors have cited access to extra medication as a source of errors and therefore reducing the amount of medication to which a patient has access may also be a further source of error reduction [25]. The MMD is therefore a two component intervention; weekly supply and an aide memoire. Clearly, weekly supply in standard containers is cheaper than weekly supply in an MMD and it is important to quantify the added value of the MMD. Current practice is MMD weekly; this proposal is for a factorial design which will compare weekly with monthly supply and MMD with standard containers.

Dispensing and administration errors

The most substantial review to date of errors associated with MMD use was conducted in Australia; the Australian Incident Monitoring Study reported that 0.43% (52/12,000) of all medication related errors were associated with MMDs. In 26 cases, there was a problem with filling the MMD such as wrong dose, dose omission or wrong medication. In 21 of these cases, nursing staff were responsible for the error with the remainder being attributable to pharmacy staff or a carer. On 16 occasions problems using the MMD were cited as a reason for an error, however, the nature of these problems was not reported. Contributing factors to the reported problems included patient confusion/distraction and the MMD being inappropriate for the patient [25]. A further Australian audit of dispensing errors associated with 6,972 dispensed MMDs detected an error rate of 4.3% [26].

A 2007 UK evaluation of dispensing error rate associated with the pharmacy 'usual' dispensing process, reported 1.7% content errors out of 2859 dispensed items. Content errors were errors of omission, incorrect drug, incorrect strength, dosage form, added or missing dose units and expired medication. A similar US based study conducted in 2003 reported an identical 1.7% error rate [27].

Whilst general dispensing error rates are 1.7%, there are no UK data for MMD error rates and thus from Australia suggest widely different potential error rates. It is necessary therefore to record error rates for dispensing into MMDs and usual packaging.

Despite, therefore, the large amount of both NHS and private funds devoted to MMDs, evidence for their value is limited as indicated by a Department of Health commissioned literature review conducted by Bhattacharya [5]. A 2006 Cochrane review concluded that MMDs may improve adherence 'with selected conditions examined to date' however, further research is necessary to improve targeting.[6] In order to achieve this, therefore, the impact of MMDs on a more heterogeneous population needs to be established.

Adherence measurement

No definitive trial demonstrating the effect of MMDs has been conducted to date. The few Randomised Controlled Trials (RCTs) have been limited by small sample sizes, insufficient data to characterize the sample population or focussed on a specific disease area [3, 28-30]. The rationale for focus on a specific disease area is to enable therapeutic outcome or detection of chemicals in body fluids to be used as a measure of adherence. Thus, little guidance is available to guide targeting of the wider population of patients for MMDs in routine practice. Historically, direct measures of adherence such as observation and detection of chemicals in bodily fluids have been considered the 'gold standard'. Observation clearly has significant cost implications for large scale studies and is subject to 'Hawthorne effect'. Detection of chemicals in body fluids has the merit of being objective, however, it can be invasive, costly and is still liable to patients altering their medication taking behaviour in the days prior to sample provision. Some of the disadvantages associated with observation as an adherence measure are exemplified by a trial in which patients were randomised to receive potassium supplementation or placebo tablets. Measurement of urine potassium levels identified a reduction over time which was most likely attributable to reduced patient compliance with 24 hour urine sample collection with trial progression and hence measured potassium levels were artificially low [31]. The taking of blood samples would overcome the issues of patient compliance with inconvenient 24 hour urine samples, however, patient acceptability of frequent blood samples is even lower and has been demonstrated to adversely affect trial recruitment with 52% of patients not consenting to trial participation citing fear of phlebotomy[32]. An additional problem associated with such direct measures is intra- and inter-patient variability in drug metabolism. This can be overcome to a certain extent by estimating individual variation via repeated samples over a short period of time; however, this type of invasive assessment has low patient acceptability. Alternatively, Bayesian methodology can be used, however, this is complex and again only provides an estimate of variability.

The Dosage Unit Count (DUC) is generally accepted as the pragmatic approach to adherence assessment. It is based on the assumption that if the medication is not in the container, it is in the patient. This is problematic when attempting to identify intentional non-adherence because patients may deliberately remove tablets and discard them in order to disguise their non-adherence. However, the assumption is valid if patients are predominantly unintentionally non-adherent. Previous research has demonstrated that conducting DUCs on the older patient population is feasible and acceptable to patients [17]**.**

Recent technological advances have enabled the development of an objective adherence measure which is less susceptible to the 'Hawthorne effect' by virtue of being less intrusive and less conspicuous to the patient than direct adherence measures or DUC. Such electronic Medication Event Monitoring Systems (MEMS) have been widely used in clinical trials to assess medication adherence [12, 31, 33, 34]. MEMS were initially developed as a bottle containing a microprocessor in the cap. The microprocessor then records the date and time of each bottle opening event. However, usual dispensing is now generally in manufacturer issued packaging which in turn is generally in blister pack form. Trials have therefore, generally approached this issue by decanting medication from usual packaging to MEMS in bottle form. This has the limitation of not assessing adherence in a naturalistic setting.

Systems to monitor medication taking events have been developed for blister packs and therefore, this technology can now be applied to enable medication taking events from MMDs to be objectively and accurately recorded. A two month pilot study (N=52) of this technology to assess feasibility and acceptability reported promising results. Adherence data were obtained from 94.3% of participants and 67.4% of participants reported that they would consider using the MEMS for a long term study.

Validation of these systems is carried out prior to release and is achieved via removing medicines from the system when in situ at predefined times. Standards exceeding 90% are frequently reported for the following:

- Functionality – proportion of MEMS functioning at the end of the trial period
- Sensitivity – proportion of recorded medication removal events compared with actual removal events
- Specificity – proportion of recorded removals that correspond to actual removal events [35]

Categorising non-adherence as intentional or unintentional can only be achieved via establishing the motivation for the deviation. A number of self report tools have been developed to identify intentional non-adherence such as the Drug Attitude Inventory [36], Medication Adherence Rating scale [37] and the Brief Medication Questionnaire [38]. However, these have either not been validated for use with patients prescribed multiple medications for chronic diseases or are not specific to intentional non-adherence. The Beliefs about Medicines Questionnaire (BMQ), however, has been validated for use on patients with a number of chronic diseases and is specific to intentional non-adherence [16]. The BMQ is an 11 item questionnaire which establishes patient attitude to their prescribed medication in terms of perceived necessity and concerns. Analyses of questionnaire results yield a necessity–concerns differential. Patients whose concerns score outweighs the necessity score (negative necessity–concerns differential score) are significantly more likely to be intentionally non-adherent ($p<0.001$). This is therefore considered to be an appropriate tool for 'screening out' intentionally non-adherent patients to ensure that they do not inappropriately receive a MMD.

The Medication Adherence Report Scale is a widely used 5 item adherence measure which provides for self reporting of intentional non-adherence. As a much shorter tool than the BMQ it is likely to have greater patient acceptability, but, this may be compromised by reduced sensitivity. It has, however, demonstrated good correlation between patient reported non-adherence and DUC results [17] and therefore, it is appropriate to compare it's sensitivity and specificity to the BMQ.

The Medication Adherence Questionnaire (MAQ) developed by Morisky, is a 4 item self report adherence questionnaire validated with clinical outcome [39]. Blood pressure readings of participants prescribed antihypertensives were monitored for a five year period and self reported adherence using the MAQ was recorded. There was found to be a significant correlation between a high MAQ score predicting good adherence and good blood pressure control.

Patient autonomy

In addition to the impact of MMDs on adherence, it is important to establish patient acceptability. No studies have reported the impact of MMDs on patient autonomy or ability to manage ones own medication, however, there is anecdotal evidence of reduced autonomy as patients are unable to differentiate one medication from another in an MMD and therefore cannot select one type of medication to omit over another where that is desired (e.g. delaying taking a diuretic when taking a long journey) sometimes resulting in omission of all [2]. Conversely, patients may report that they feel enabled by feeling confident about managing their medication. A number of studies have explored patient autonomy with respect to medication taking in the context of describing the extent to which patients feel involved in the decision making process[40-42]. However, exploration of whether patients feel as though they have some control over the medication taking process is limited. The Patient Enablement Instrument whilst initially developed to establish the impact of a GP consultation on patient enablement [43], has been widely used and validated within general practice including the older population. As a 6 item questionnaire, which with minor modification to the opening statement will be applicable to MMDs, it is an appropriate choice for assessing the impact of MMDs on patient confidence in their ability to manage their own medication.

Recruitment rate and methodology

Whilst passive recruitment via medical practice invitation letters is convenient in terms of research administration, response rates have historically been low as the method requires the patient to be pro-active in responding to a letter invitation; consent rates are frequently between 30% and 40% [18, 44] Active recruitment processes such as waiting room recruitment by researcher, however, whilst more labour intensive and thus costly, have yielded substantially higher response rates[45-48]. Identification of the most cost-effective approach to recruitment is therefore required within any feasibility study.

MMD selection

A number of MMDs are commercially available; produced by different manufacturers, they vary considerably in terms of their size and method via which medication is accessed from the device [5]. Four MMDs (Venalink®, Nomad Clear®, Dosett® and Medidose®) represent the four different types of device that are most widely used, collectively accounting for over 90% of the market share [13]. The

Venalink® is a cold sealed device which is also similar to most commercially available heat sealed devices and most closely represents blister packaging. The Nomad Clear® represents monitored dosage systems which are tamper evident systems and are sealed once the medication has been dispensed into the device. The Dosett® is one of the oldest commercially available MMDs and is similar to most MMDs sold within community pharmacies for patients to fill themselves or to be filled by non trained carers [49]. The Medidose® is the only device that allows patients to carry one day's doses rather than a full week.

Patient characterisation

Given the variations in MMD design and that patients have differing abilities and needs, it follows that choice of MMD should be as a result of discussion with the patient and assessment of ability to use the MMD. A survey of 10 purposively sampled pharmacists reported that eight would select a MMD without involving the patient in the decision making and all pharmacists had a preferred MMD thus suggesting that patient needs would not be the primary driver of MMD selection [4]. A larger survey of 105 pharmacists, however, reported that pharmacists perceived that checking patient ability to use an MMD was the most important factor when considering whether or not to provide a patient with a MMD [13].

Aside from the issues associated with intentional non-adherence, the most commonly reported factors to impair patient ability to adhere to their prescribed regimen are cognitive function, manual dexterity and visual acuity [5]. An Australian survey of older patients (N=120) with a mean age of 81.8 years characterised participants in terms of cognitive function and visual acuity and then assessed ability to open a variety of commercially produced medication packaging. It was reported that 78.3% of participants were unable to open one or more of the medication packaging in order to access the medication. It was found that inability to access medication was significantly associated with lower cognitive function and manual dexterity [50]. There is, therefore, a clear need to ensure that any MMD provided is suited to the patient.

A study conducted by Bhattacharya *et al.* (N = 50) assessed patient ability to use MMDs via presenting participants with different MMDs and asking them to rank each MMD on a visual analogue scale in terms of ease of reading the text on the MMD, ease of opening the MMD in order to access placebo medication, ease with which placebo medication could be removed from the MMD, convenience with which the participant felt that they would be able to transport the MMD and overall rating of preference. Participants were then further characterised in terms of manual dexterity, visual acuity and cognitive function in order to identify any trends in preference of and/or ability to use MMDs with functional ability measured using validated tools [51].

Participant acceptance of visual acuity [52] and cognitive function [53] measurement was good, however, manual dexterity measurement using the standardised Purdue peg board test yielded low participant completion rates [54]. As might be expected, correlation between each of the validated test scores and patient performance in the corresponding skill required for using the MMDS was very high (R> 0.8). In order to reduce the assessment burden, it therefore seems more appropriate to provide patients with the different types of MMD and assess their ability to use each device plus preference for device to inform MMD selection rather than using additional validated tests that are also less practical for use in the natural healthcare setting.

In summary, the current evidence base provides a basic framework for the design of a trial to comprehensively estimate the effects of MMDs. However, further preliminary work is necessary such as stakeholder involvement in order to optimise the feasibility of such a trial.

2. Aim

The aim of the study is to capture service user and provider opinion regarding the optimum design of a study to trial the effect of multi compartment medication devices.

3. Objectives

The objectives of the study are, in a sample of patients and their carers to:

- Gain a better understanding of some of the practical difficulties experienced by patients and their carers in adhering to complex medication regimes
- Explore the appropriateness and acceptability of MMDs including issues such as desired level of patient choice in the type of MMD with which they are provided and the appropriateness and feasibility of proposed adherence measures
- Establish the patient/carer perceived benefits and disadvantages of MMDs including any potential adverse outcomes such as loss of autonomy, routine etc
- Explore the acceptability of trial participant procedures including recruitment documentation, participant information sheets and survey tools

and in a sample of healthcare practitioners to assess opinion on:

- The appropriateness and feasibility of the research design in terms of patient recruitment, outcome measures, costs and benefits
- Potentially suitable patients for MMD provision and MMD selection including characterisation of patient ability (e.g. visual acuity, manual dexterity & cognitive function)
- The size of a clinically important difference in patient adherence

4. Research methods

4.1. Literature review

A literature review will be undertaken to identify the study design approaches which have been utilised within previous studies and therefore identify any appropriate enhancements to study design that may be trialled. Strategies and inclusion criteria of the recent systematic review will be adopted and thus the review updated. Additional considerations for RCT design not assessed by this search e.g. information regarding appropriate measures of functional assessment will be addressed by additional searches. The research management group will consider the literature review findings when designing the pilot RCT.

4.2. Focus Groups

The lack of evidence for the effects of MMDs may be partially attributable to the complexities of developing a randomised controlled trial to test these devices. Challenges include developing an effective and acceptable method of measuring adherence, selecting appropriate MMDs for testing, measuring and recording relevant outcomes i.e. advantages and disadvantages and then achieving acceptable patient uptake to the trial. This project is therefore intended to capture information from stakeholders via focus group discussions to inform the design of a subsequent trial to test MMDs. One or two focus groups will be convened with each of patients, informal carers and carers in sheltered housing. A separate focus group will be convened with healthcare practitioners.

4.2.1 Sample size

Each focus group will be of six to ten participants. For patients/carers, there will be one or two focus groups. To account for attrition owing to unforeseen circumstances, up to 16 participants will be recruited as per criteria outlined in section 4.2.2. For healthcare practitioners there will be one focus group.

4.2.2 Participant identification and recruitment

Generic inclusion and exclusion criteria applicable to all focus group participants are outlined below. Additional criteria relevant to the individual categories of participants are indicated in the appropriate following sections.

Inclusion criterion

- Aged over 18 years

Exclusion criteria

- Unable to read or speak English
- Unable to provide informed consent

I) Patient/carer focus groups

I a) Patients and informal carers

Patients and informal carers will be identified and recruited via medical practices. The term 'informal carer' refers to friends and relatives who support patients in their medication organisation and/or taking but receive no remuneration. Six medical practices and the pharmacies geographically close to these medical practices in NHS Norfolk have expressed an interest in being involved with this study and any subsequent pilot trial of MMDs. Patients and informal carers will be purposively sampled by clinical members of these medical practices. Patients and informal carers will be identified by medical practice staff initially via a computerised search for patients aged over 75 years of age, prescribed more than three regular medications and excluding patients with recorded severe cognitive impairment such as Alzheimer's disease. The resulting list will be manually searched by the most appropriate member of the medical practice team which may be a GP or a non-medical member of the prescribing team. The search will be conducted to identify patients that meet the following criteria:

- Patients representing a range of medication taking behaviour:
    - Some suspected of intentional and some of unintentional non-adherence plus patients considered to have excellent adherence
- Patients representing a range of regimen complexity:
    - From, three regularly prescribed medicines through to five or more
    - Prescribed multiple formulations e.g. inhalers, eye drops and creams or ointments
- Patients using MMDs
- Patients that declined the use of a MMD
- Patients with mild cognitive impairment (sufficient in the clinician's opinion to allow provision of informed consent and engagement with a focus group)
- Patients with manual dexterity problems
- All patients will be over 75 years of age
- Informal carers who manage medication

These patients and carers will be recruited via letter posted from the medical practice for return to the research team. Written, informed consent will be sought. After two weeks, a follow up letter will be sent to non-responders.

Additional inclusion criteria for patient participants

- Aged 75 years or over
- Registered with one of six participating medical practices
- Prescribed three or more oral solid dosage form medications

Additional inclusion criteria for informal carer participants

- Registered with one of six participating medical practices
- Known by medical practice staff to support a person aged over 75 years in managing his / her medication

I b) Carers in sheltered housing

Independence in terms of medication administration generally declines with progression from patient's own home through sheltered housing, residential homes and then homes with nursing. Carers in the latter two organisations will therefore have little experience of MMDs and patient self administration difficulties as residents of these institutions tend not to self administer their medication.

Wardens of sheltered housing, however, are likely to be aware of any regular informal care received by people within the sheltered housing complex. A list of contact details of sheltered housing complexes and their wardens will be obtained from Norfolk County Council Adult Social Services. Wardens will be contacted by mail and requested to distribute the carer information leaflets and consent forms to carers supporting people in the sheltered housing. . Written, informed consent will be sought for contact from the researchers to arrange the focus groups. After two weeks, a follow up letter will be sent to non-responders if a desirable response rate is not achieved.

Additional inclusion criteria for sheltered accommodation carer participants

- Employed as a carer in sheltered accommodation within Norwich

II) Healthcare practitioners
Participants will be recruited by letter from the six medical practices and pharmacies taking part in the study and from the local hospital trusts. Purposive sampling will be used to ensure representation from general practitioners, pharmacists, community nurses and consultants specialising in the care of older people. Written, informed consent will be sought (appendices 2 and 4). After two weeks, a follow up letter will be sent to non-responders.

4.2.3 Focus group conduct
The focus groups will be moderated by the study Research Associate (RA) and Dr Salter will attend as second moderator. Permission will be sought from participants for the RA to record the focus group. These will then be transcribed verbatim and entered into NVivo 8 to manage, sort and facilitate analysis of the data. All data will be kept securely and destroyed at the end of the project.

I. Patient/carer
Each focus group will last between 60 minutes and 90 minutes. The focus groups will take place at a local and convenient centre such as a community centre and refreshments will be served. Participants will be offered transport or reimbursed for all travel costs incurred. A £20 voucher will be provided to patient/carer participants as thanks. Consent for proceedings to be audiotaped will be reaffirmed at the start of the focus group.

Topic guide for patient/carer focus group

The focus group topic guide will be informed by the literature review and designed to address the study objectives. It is likely to include:

- What are your thoughts and experiences of taking medication or helping others to take their medication?
- What are your thoughts and experiences of medication organisers?
    - Good aspects and not so good aspects
- What are your opinions about how much choice is given to patients about the type of medication organiser that is provided and how much guidance is given in selection?
- We are planning to measure how medication is taken by putting the medicines in a clear case which records every time that it is open, what are your thoughts about this?
    - Good aspects and not so good aspects

The group will be managed to encourage free discussion and to generate a wide range of ideas and opinions. Participants will also be provided with samples of questionnaires and information leaflets that may be used in the main trial to determine their opinion on the appropriateness of this material for patients.

II. Healthcare practitioners
The focus group will last last between 60 minutes and 90 minutes and refreshments will be served. The focus groups will take place either at an NHS site such as one of the local study medical practices, the hospital or the University of East Anglia. Expenses will be reimbursed including locum cover. Consent for proceedings to be audio taped will be reaffirmed at the start of the focus group.

Topic guide for healthcare practitioners
The focus group topic guide will be informed by the literature review and designed to address the study objectives. it is likely to include:

- From your experience, what types of problems do patients experience with adhering to their medication regiments?
- What types of action have you taken to address these issues?
- What types of patients may benefit or not from receiving a MMD?

  - What types of patients do you recommend that we should include and exclude in the study?
- What factors do you think may be important in determining the effect of medication organisers for example a patient's cognitive function, visual acuity, manual dexterity etc.?
- What do you think that we should be measuring to fully capture the benefits and potential problems of medication organisers?
- Participants will be presented with recruitment ideas and asked whether they foresee any problems or have thoughts about how recruitment could be better targeted and uptake further enhanced
- What size/change in adherence do you think is clinically relevant and therefore financially worthwhile for the NHS to achieve?

4.2.4 Analysis

A framework style analysis will be applied as it is particularly appropriate in research where clear policy and practice solutions are sought (http://www.scpr.ac.uk). It is also proven to be useful where in-depth methods are being used to inform further larger scale study design [55]. Framework analysis is a five-stage process that ultimately allows for sensitive analysis of the relationship between concepts and typologies across and within individual focus groups [56]. The stages of the analysis will be shared with the study trial management committee and steering group to enhance the transparency and validity of interpretation.

5. Research governance

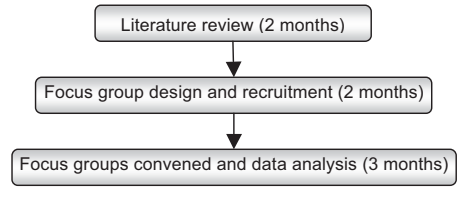
The University of East Anglia will act as sponsor and has appropriate insurance policies in place to provide professional indemnity and public liability cover for any harm to participants or researchers arising from the design of the research.

The Trial Steering Committee (TSC) will ensure that the project is appropriately managed, reports are sent to the HTA and all ethical and governance requirements are met. This project is a feasibility study and therefore a separate data management committee will not be required.

6. Service Users

The Patient and Public Involvement in Research (PPIRes) project is a local initiative to enable and encourage volunteer members of the public to actively participate with researchers in trial development and delivery. Two members of PPIRes have agreed to join the trial steering committee

7. Flow diagram



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