Protocol for Take home naloxone In Multicentre Emergency setting (TIME): Feasibility Study

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Abstract

Background Opioids, such as heroin, kill more people worldwide by overdose than any other type of drug, and death rates associated with opioid poisoning in the UK are at record levels. Naloxone is an opioid antagonist which can be distributed in ‘kits’ for administration by witnesses in an overdose emergency. This intervention is known as Take Home Naloxone (THN). There is a lack of rigorous experimental research into the effectiveness of THN distribution, with fundamental questions remaining unanswered: do THN kits reduce deaths? are there unforeseen harms associated with THN distribution? and is THN distribution cost-effective? We seek to establish the feasibility of a fully-powered cluster Randomised Controlled Trial (RCT) of THN distribution in emergency settings to answer these questions.

Methods We will carry out a feasibility study for a RCT of THN distributed in emergency settings at four sites, clustered by Emergency Department (ED) and catchment area within its associated ambulance service. At two intervention sites, emergency ambulance paramedics and ED clinical staff will distribute THN to adult patients who are at risk of opioid overdose. At two control sites practice will carry on as usual. THN is a peer-administered intervention. We will develop a method of identifying a population to include in an evaluation, comprising people at risk of opioid overdose, who may potentially receive THN. We will gather anonymised outcomes up to one year following a 12 month ‘live’ trial period for patients at risk of death from opioid poisoning. We expect approximately 100 patients at risk of opioid overdose to be in contact with each service during the one year recruitment period. Our outcomes will include: deaths; emergency admissions; intensive care admissions; and ED attendances. We will collect numbers of eligible patients attended by participating emergency ambulance paramedics and attending ED; THN kits issued; and NHS resource usage. We will determine whether to
progress to a fully powered trial based on pre-specified progression criteria: sign-up of sites (n = 4); staff trained (>= 50%); eligible participants identified (>= 50%); THN provided to eligible participants (>= 50%); people at risk of death from opioid overdose identified for inclusion in follow up (>= 75% of overdose deaths); outcomes retrieved for high risk individuals (>= 75%); and adverse event rate (<10% difference between trial arms).

Discussion This feasibility study is the first randomised, methodologically robust investigation of THN distribution in emergency settings. The study addresses an evidence gap related to the effectiveness of THN distribution in emergency settings. As this study is being carried out in emergency settings, obtaining informed consent on behalf of participants is not feasible. We therefore employ novel methods for identifying participants and capturing follow up data, the effectiveness of which are dependent on the quality of the available routine data.

Background Accidental overdose related to the misuse of opioid drugs is an increasingly prevalent public health problem, and opioid related deaths are at record levels in both the United Kingdom (UK) and North America (2,3).

People who misuse either illicit or prescription opioids are at an increased risk of non-fatal overdose, subsequent hospital or emergency service utilisation, and death (4–6). Non-fatal opioid overdose is associated with long-term morbidity and increased demand on health services (7,8). Emergency service contact for drug-related morbidity has been found to be a predictor of future episodes of poisoning or overdose (9,10).

Naloxone is an opioid antagonist used to treat opioid overdose. Naloxone can be supplied to people at risk of opioid overdose by paramedics (11) or by lay people in the form of Take Home Naloxone (THN). Non-experimental studies suggest that THN programs which
involve the training of lay persons to administer a naloxone dose in cases of overdose emergency are safe and effective (12, 13). THN kits typically contain a limited number of doses of naloxone, basic life support instructions, and the means to deliver the naloxone doses either by intramuscular or intranasal administration. THN kits can be used by people without formal medical training in the event of an opioid overdose. Increased access to THN kits via specialist drugs services in the UK and internationally has been motivated by recommendations from influential bodies, including the World Health Organisation (WHO) and the British Advisory Council on the Misuse of Drugs (ACMD) (14,15).

Numerous THN distribution programmes aiming to reduce death from opioid overdose have been implemented by drug service providers in the UK and internationally since the 1990s (16, 17). However, a significant proportion of people at risk of opioid overdose are not engaged with drug services (18). Additionally, high quality empirical evidence to demonstrate the safety and effectiveness of THN is sparse. Observational data suggests that non-serious adverse reactions to naloxone administration are common while serious adverse reactions are rare (19). However, the risks of inadequate response or return to a state of overdose following the administration of naloxone by lay people remain poorly quantified (20,21). Moreover, the uptake of THN kits in at-risk populations remains low (22,23) and appropriate THN intervention by peers and witnesses may not be optimal (24).

Members of the research team (CM, HS) have previously conducted a randomised feasibility study of THN distributed through the emergency ambulance service in a single urban geographic area (25). The experiences of the researchers, as well as those of other researchers (26), has demonstrated that using traditional methods (e.g. telephone or postal methods) for capturing follow up outcomes of participants in receipt of a kit (and of those not in receipt of a kit despite eligibility) is not feasible.

This paper describes a protocol for a feasibility study of THN distributed in the Emergency
Department (ED) and the catchment area for the associated emergency ambulance service. In carrying out the proposed study, we seek to determine the feasibility of carrying out a fully-powered cluster Randomised Controlled Trial (RCT) of THN in emergency settings using routinely collected, anonymised and linked data to capture outcomes. Should we find that carrying out a full trial is feasible, this subsequent trial would be adequately powered to determine the safety, clinical and cost-effectiveness of THN distribution in emergency settings.

Methods

Setting, recruitment and consent

We will carry out a feasibility study in the emergency care environment, involving study sites defined geographically as an ED and its catchment area within the local emergency ambulance service. For example, one of the study sites consists of the ED at Bristol Royal Infirmary, a large city centre hospital in England, and the catchment area is the surrounding urban area within which patients would be routinely conveyed to the ED at the Bristol Royal Infirmary. The study will be delivered in the form of an RCT clustered by study site, using retrospective anonymised linked routine data to capture patient outcomes. We will also collect qualitative data to gain an understanding of the processes of implementation of the intervention, and experiences of service users and providers. Finally, we will collect data related to patient safety.

Participant recruitment

The target population for this trial is people who are at high risk of a fatal opioid overdose.

We cannot know if the naloxone dose included in any individual THN kit will be administered to a peer of the recipient of the kit, or to the recipient him/herself. Effects of
the THN intervention could extend beyond recipients seen in the ED or by ambulance crews. Therefore, in order to measure treatment effect in those likely to benefit from THN, we define two populations: those eligible for receipt of intervention (at intervention sites); and those at high risk of death from opioid overdose at all sites.

Population A: eligible for receipt of THN (at intervention sites)

Our first population is the target population for the intervention, comprised of adult patients who arrive at the ED, or who are attended by ambulance paramedics for a problem related to opioid misuse (e.g. opioid overdose or injuries due to opioid use). ED and ambulance service clinicians will undertake initial clinical assessment as per routine practice, adults presenting with an opioid misuse related problem and who have capacity to consent to receipt of the kit will be identified as potentially eligible to receive THN. These patients will be eligible to be offered THN following standard treatment by a participating paramedic or ED clinician.

Patients who lack capacity; are aggressive or exhibit otherwise challenging behaviour; who are seen by untrained staff; who have already been recruited; or who are in custody at the time of their presentation will be excluded.

Population B: predicted to be at high risk of death from opioid overdose

We will identify people to include in outcome follow up who are at high risk of opioid overdose and may be able to benefit from THN. Population B thus extends the target population for follow-up of outcomes beyond original recipients of THN kits. We will define a discriminant function as a predictive tool, similar to a risk index, incorporating known and routinely recorded predictors of opioid-related events. We will use existing linked data on opioid deaths in Wales, including ED and in-patient data, to define criteria most closely associated with those who died from opioid poisoning and then use these criteria to identify participants to be included in the ‘high risk population’ (Population B) for outcome
analyses in the trial study areas. As ambulance service records are not included in nationally available datasets that can be linked anonymously, we will assess whether the inclusion of potential participants from routine ambulance service data e.g. patient records including flags such as ‘naloxone administered’ or ‘drug overdose’ improves the performance of the predictive tool. If this is the case these data will be included in the final dataset for generation of the population in whom outcomes will be compared between intervention and control sites.

We will gather prospective clinical data at each intervention site related to eligibility and distribution of THN kits. We will also gather retrospective and prospective data from all participating ambulance services related to indicators of high risk of death from opioid overdose e.g. naloxone administration (for use in defining population B). These data will be sent by participating ambulance services and EDs using ‘split-file’ format to National Health Service (NHS) Digital in England and to NHS Wales Informatics Service (NWIS) in Wales (with identifiable data separated from clinical data) for matching and linkage to routine centrally held datasets. All study data will be transferred to the Secure Anonymised Information Linkage (SAIL) Gateway for analysis (27).

We will also assess whether the newly introduced Emergency Care DataSet (ECDS) provides reliable data about attendances for opioid overdose and related problems that could be used within the predictive tool.

Consent

We will not attempt to gain consent to participate in the trial prospectively, at the time of attendance for opioid related emergency, because the situation contradicts the requirements of informed consent (32). We will not gather consent retrospectively, as the population is likely to be very hard to reach and low contact rates could invalidate research findings. In addition, the wider population for inclusion in follow up (Population
B) will be identified through anonymised routine data sources, we will not have
identifiable data with which to contact people for consent purposes. Rather, clinicians will
consent patients to receive the intervention, and we will offer the option to dissent from
the research at all sites via patient information leaflets supplied with THN kits and made
available at ED waiting areas. We will also include this information on the Wales Centre
for Primary and Emergency (including Unscheduled) Care Research (PRIME) website. We
have gained ethical, research and information governance permissions to follow this
approach in this trial in which all information about processes and outcomes of care will
be anonymised to the research team except for clinical members at each site who will
split identifiable from clinical and operational data before sending files to NHS Digital in
England and NHS Wales Informatics Service (NWIS) for linkage to outcomes held centrally.
In regards to the qualitative component of the study, we will obtain informed consent to
participate on behalf of service users in a routine way using a written consent form.
Service user participants will be identified by members of the care team at NHS and third-
sector drug treatment services. Eligible participants who agree to participate will also be
eligible to receive a thank you gift card voucher for their time in participating should they
so wish.

Sample Size

We aim to include enough patients to test our trial methods, study intervention and
outcome data collection. Site enrolment and allocation, and follow up of participants prior
to analysis are summarised in Fig. 1.
(Fig. 1 goes here)

We expect 200 people at high risk of overdose and thus eligible for the intervention (THN)
to make contact with the ED or ambulance service at each study site over the course of
1 year (100 via ED; 100 via the corresponding ambulance service).
We will use routine linked data to identify the population to be included at each site in outcome analyses via a predictive model to be fully specified within our study. The model will include opioid users who have made contact with included services over a period of 24 months previous to our recruitment phase. These individuals, predicted to be at risk of death from opioid overdose, represent those attending during the recruitment phase and their peers. We expect the follow up population to be at least 1520 people across four sites.

**Case ascertainment**

In order to identify people at high risk of opioid overdose we will develop a predictive tool and then externally validate this algorithm prospectively during the recruitment period of the study. We will test the sensitivity (prediction of true cases) and positive predictive values (minimisation of prediction of true non-cases) of the algorithm as well as our ability to retrieve outcomes. Data held at intervention sites related to patients at high risk of opioid overdose (and therefore eligible to be offered THN) will be linked to other routinely held ED, in-patient and mortality datasets using a split-file approach in which identifiable and clinical data are separated to ensure anonymity (26).

**Randomisation**

We approached all UK ambulance services and received five positive responses from potential sites with matched EDs, who were able to demonstrate the capacity and resources to participate. Of these potential sites, four demonstrated sufficient geographic separation from other study sites to mitigate potential cross-contamination of study populations. From these four sites we randomly selected two to be intervention sites, and two to be control sites by having a member of the research team (MJ) pick four of five randomly generated study site allocations within sealed opaque envelopes.
**Intervention**

The intervention, described following the template for intervention description and replication (TIDieR) checklist (28), chosen for use in TIME is Prenoxad – a multi-dose THN kit containing 2 mg naloxone hydrochloride 1 milligram/1 milliliter solution for intramuscular injection. This kit contains simple textual and pictorial instructions which reiterate face-to-face training each participant receives as part of the intervention, on: preparing and administering the naloxone dose; basic life support; the importance of calling the emergency services; duration of effect (and hence why it is important that paramedics attend the patient as soon as possible); the safety of naloxone in terms of adverse events and overdose; and the legality of bystander administration of naloxone.

Participants will not be able to receive part of the intervention only – e.g. the training and not the kit – and so will need to consent to the whole intervention or decline the whole intervention.

The kit is manufactured by Martindale Pharma (Woodburn Green, UK) and supported by ‘train-the-trainer’ materials for participating paramedics and ED staff developed by Stephen Malloy, an independent consultant. Each Prenoxad kit retails at £21.00 before VAT (Value Added Tax). The decision to use the Prenoxad kit, as opposed to an intranasal alternative, comes from evidence regarding the bioavailability of naloxone following intramuscular versus intranasal administration (29, 30); and the time taken for improvement in respiratory rate to be observable (31). We also based our decision on feedback from drug service workers who were approached in the initial setting up of the study.

Paramedics, nurses and doctors at intervention site ambulance services and EDs registered with their respective professional bodies will be invited to participate in the study and volunteers will be trained in delivering the intervention in accordance with the
study protocol. Patient Group Directions (PGDs) will be established at participating services within intervention sites to allow non-prescribing paramedics and nurses to distribute THN kits. Training will be provided in a flexible manner to suit the working practices of individual departments and services. This will involve face-to-face group based training, as well as utilising a ‘cascade’ approach whereby research support paramedics and nurses will continue to train others on an ad-hoc basis. Online resources produced by Martindale Pharma will be available as refresher content for staff (http://www.prenoxadinjection.com/). Training per person will take up to 15 minutes. Staff will complete and sign a ‘Record of Completion of Training’ form once they have been deemed competent by their trainer.

At intervention sites, participating healthcare professionals based in the specific ambulance service region or hospital ED and caring for patients eligible to receive the intervention will offer these patients the THN kit, with an explanation of its purpose. If the patient consents to receiving the kit, the healthcare professional will provide training regarding preparation and administration of the naloxone dose using the kit materials. The healthcare professional and the patient will then complete a training checklist document which will be made available to research support staff and stored as evidence that training was provided as part of the intervention.

At control sites patients who attend for opioid poisoning or overdose, or other drug related problems will receive treatment as usual. This will not include the offer of THN prior to discharge.

Blinding

Due to the nature of the intervention the study will not include blinding of participants or intervention providers. However, the trial statistician will remain blinded to allocation during analysis and until data lock.
Outcomes

We will measure outcomes related to the feasibility of the study in terms of the intervention and methodology, including whether we can capture sufficient data to measure clinical outcomes and health economics.

Outcomes related to the feasibility of the study include: sign up of sites; proportion of eligible staff recruited and trained to deliver the intervention; proportion of eligible participants identified, number of kits issued; and the adverse event rate in intervention and control sites.

We will also assess the feasibility of collecting clinical outcomes from anonymised linked routine health records, acknowledging that feasibility will be reliant on the quality and availability of the routine data.

The proposed primary outcome is deaths (all deaths and those known to be opioid related). Secondary outcomes will include Intensive Treatment Unit (ITU) admissions, ED visits and in-patient admissions (all visits/attendances as well as those known to be opioid related) as well as THN kits issued and costs. Our feasibility study will not be adequately powered to detect statistically significant differences between intervention and control sites in regards these proposed outcomes.

We will test the feasibility of using routine data sources to estimate health care costs. Total NHS costs for each patient will be calculated based on the staff training costs, patient training costs and other NHS costs (e.g. those for 999 calls, ED attendances and admissions). Training costs will be calculated using records of completion of training, staff recall of patient training and then combined with NHS salary data. Other NHS costs will be based on routine data for the relevant hospital and ambulance service Trusts.

We will use qualitative data to explore patient experiences of overdose, the experiences of friends and family and the views of providers including paramedics, clinical ED staff and
health service managers at participating sites regarding THN in emergency settings.
Service users will be identified by co-operating staff at specialist drug treatment units in
the immediate geographic areas of one intervention and one control site. These data will
include responses and outcomes; awareness and experiences of naloxone; perceived
benefits and challenges of THN; and views on the feasibility and acceptability of
distributing THN via ambulance paramedics and hospital EDs. Interviews will be recorded,
with participants’ consent, and professionally transcribed prior to analysis.

Progression Criteria

We will assess whether or not to proceed to a fully powered RCT using the following
progression criteria,

Green
indicates that we have either met a criterion (in which case no modifications to the
relevant aspect of the study protocol may be needed), or we are within 10% of our stated
progression targets (in which case we will review the reasons for this and consider
appropriate modifications to study methods)

Amber
indicates that we are within 20% of our stated progression target, in which case we will
critically review reasons for this and assess whether major changes to study methods are
likely to realise significant improvements

Red
indicates that we are more than 20% from our target, in which case we will not, in the
absence of clear extenuating circumstances, consider progression to a full trial

All % change will be measured as relative.

Intervention feasibility:
1.
Sign up of four sites, including ≥ 50% eligible staff to complete training in delivering the intervention at each intervention site

2. Identification of ≥ 50% of people who have presented to ED or ambulance service with opioid overdose or an opioid use related problem

3. THN kits offered to ≥ 50% eligible patients at intervention sites

4. Serious adverse event rate of no more than 10% difference between intervention and control sites during the live trial period and prior to the conclusion of data collection

Trial methods feasibility:

5. Identification and inclusion for outcome follow up of ≥ 75% of people who died of opioid poisoning in the following year

6. Matching and data linkage in ≥ 90% of cases not dissented at the conclusion of quantitative data collection

7. Retrieval of primary and secondary outcomes for ≥ 75% of included participants from NHS Digital and National Welsh Informatics Service within one year of projected timeline

Safety Monitoring

We will regard data on service usage (emergency and ITU admissions, and emergency attendances) and death as surrogate markers of adverse behavioural change in relation to opioid misuse, such as taking larger doses at one time. In doing so we assume that increased rates of service usage and death correlate with increased volume of higher risk drug-taking behaviour. We will also monitor for instances of serious adverse events, including deaths following THN use.

Data Analysis

We will develop a formal Statistical Analysis Plan (SAP) to summarise all planned analyses, including conventions on the treatment of missing data, principles of retention of explanatory factors and covariates in statistical models, and the reporting of raw and adjusted outcomes.

Our primary analyses will address the progression criteria as presented above. These will
be largely descriptive in nature.

We will produce a CONsolidated Standards Of Reporting Trials (CONSORT) flowchart for patient recruitment appropriate for cluster trials (33). Study data will be summarised by intervention or control group, and we will further summarise key demographic and outcome variables by site. Although this feasibility study is not intended to provide a definitive assessment of the THN intervention, we will assess and report differences in outcomes via appropriate generalised mixed linear models, adjusting for key covariates and factors.

In order to develop the discriminant function to be used for defining our population for outcome comparison, we will partition the available routine (retrospective) linked dataset, using one part (training data) to determine inclusion thresholds and the other (testing data) to check performance of the function. We will use the actual number of recorded opioid poisoning deaths during the trial period to validate the function. We will summarise performance by calculating sensitivity (the proportion of actual opioid poisoning deaths included in our defined high risk population; denominator = all actual opioid poisoning deaths, a/a + c) and positive predictive value (the proportion of our defined high risk population who die of opioid poisoning in the following year; denominator = all defined high risk, a/a + b) as shown in Table 1.

|                  | Actual opioid death | No opioid death |
|------------------|---------------------|-----------------|
| Predicted high risk | a                   | b               | a+b             |
| Not predicted high risk | c                   | d               | c+d             |
|                   | a+c                 | b+d             |
We will report on whether our discriminant function can, via Fisher’s Linear Discriminant Function, be usefully reduced to a single individual-level risk score, consider thresholds used in its definition, and evaluate its performance as a predictive tool using test datasets compiled specifically for this purpose.

For the follow up population (B), we will summarise linkage rates and characteristics for those not linked versus those linked, coding completion rates for ED and ambulance service events, and carry out a comparison of data obtained from routine sources. We will report these data by site and in total. We will provide details on data completeness related to the criteria for determining progression to a full trial.

We will use NVIVO to manage the qualitative data and carry out thematic analysis of interview transcripts. Transcripts will be imported into NVIVO and be read and re-read to ensure familiarity with the data before coding. One researcher will develop and refine initial codes, with coding undertaken both with reference to Normalisation Process Theory (NPT) as a theory for evaluating the potential for normalisation of the intervention as a change of working practices in emergency settings (34) and ‘grounded’ in the data. Codes will be reviewed and emerging concepts used to develop themes. A second researcher will independently code a subsample of transcripts for comparison and discussion before further refinement of the coding structure and themes by the first researcher. PPI members will be involved in the qualitative analysis by co-developing themes and reviewing drafts of findings. Data from service providers at intervention sites will be compared within sites across time and also between sites for commonalities and divergence in themes.

**Trial Management**

A Trial Management Group (TMG) will manage the project and report to the Trial Steering Committee (TSC) at appropriate intervals. The Chief Investigator will chair the TMG which
will meet every three months. The TMG will comprise all co-applicants, named collaborators, Patient and Public Involvement (PPI) members and researchers. An independent TSC will oversee the conduct and progress of the trial and adherence to the protocol, patient safety and the consideration of new information of relevance to the trial. Two PPI members are full members of the TSC. 

A Data Monitoring Committee (DMC) will monitor study data at interim periods and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. Members will have access to comparative data and interim analyses and may request the un-blinding of such data at any time. The DMC will also consider requests for the release of data. The DMC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies. If new evidence becomes available during the course of the trial, it is the responsibility of the Trial and/or Data Manager to provide that information to the DMC to allow them to consider such issues and make recommendations on the continuation of the trial to the TSC.

Any risks identified throughout the trial will be documented in a Risk Log and monitored. This will be reported to the TMG and escalated to the TSC if appropriate.

Public and Patient Involvement

We have involved public and patient members throughout this study to strengthen research rigour (35). PPI members have experience of opioid addiction through family and voluntary networks. They have contributed to developing this study using personal experience to highlight relevance of the research questions and comment on data collection methods and selection of outcomes. We also discussed the project with drug service users and voluntary sector service providers in the community. PPI members were named as co-applicants on the funding proposal. They will remain involved as members of
the Trial Management Group and relevant subgroups. They will contribute to study management, reporting and dissemination through papers. Additionally we have recruited two more individuals with relevant experience to be involved in the Trial Steering Committee. We will support all public and patient members to collaborate as equal members throughout the study (36).

Dissemination

In addition to publishing results in scientific journals, we will engage with third sector organisations, and media and communications departments at participating institutions, we will disseminate findings and raise awareness about the trial and wider issues related to implementation. We will develop a proposal for funding for a fully powered trial, should this be supported by our findings

Discussion

This study is the first to our knowledge to use routine anonymised linked data to identify the target population and measure outcomes related to a peer administered anti-overdose intervention such as THN in emergency settings. Our novel approach to capturing outcome data comes from previous research to indicate that the target population for the intervention are peripatetic and therefore difficult to follow up using traditional methods. The study design incorporates the development and testing of a predictive tool also, which is a necessity due to the difficulty in establishing treatment effect related to an intervention which is administered by lay people to their peers who may or may not be the original recipient of the THN kit.

The strength of this study lies in its novel approach establishing evidence for an intervention which is already being distributed, albeit patchily, in response to opioid overdose as a growing public health concern. The study is being carried out by a team
well placed to apply expertise and prior experience in the use of routine data in RCTs to contribute to the evidence base for THN in emergency settings, which is in urgent need of expansion.

Abbreviations

ACMD – Advisory Council of the Misuse of Drugs

CONSORT - CONsolidated Standards Of Reporting Trials.

DMC – Data Monitoring Committee

ECDS – Emergency Care DataSet

ED – Emergency

ITU – Intensive Treatment Unit

NHS – National Health Service

NPT – Normalisation Process Theory

NWIS - NHS Wales Informatics Service

PGD – Patient Group Direction

PPI – Patient and Public Involvement

PRIME - Primary and Emergency (including Unscheduled) Care Research

RCT – Randomised Controlled Trial

SAIL – Secure Anonymised Information Linkage

SAP – Statistical Analysis Plan

THN – Take Home Naloxone

TIDieR - Template for Intervention Description and Replication

TIME - Take home naloxone In Multicentre Emergency setting

TMG - A Trial Management Group

TSC - Trial Steering Committee

UK – United Kingdom
VAT – Value Added Tax

WHO – World Health Organisation

Declarations

Ethics approval and consent to participate

The TIME study has been approved by the HRA (Health Research Authority), CAG (Confidentiality Advisory Group) and REC (Research Ethics Committee) 18/WA/0337.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The study design was conceived in response to an NIHR HTA funding call by HS advised by CM and further developed by AW, MJ, AJ and the rest of the study team SG, GF, JB, JJ, JH, FS, FB, SB, PB, SD, AE, BAE, RH. BL and EP are the patient and public involvement representatives, whose involvement is facilitated by BAE. FS will lead the qualitative component of the study supported by JH. The discriminant function for use as a predictive tool will be developed by AW and TD supported by MJ. AW will lead the quantitative analysis, and SD will lead the health economics component. MJ contributed to the development of this manuscript and all other authors contributed to and approved the
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Figures

Site enrolment and allocation, and follow up of participants prior to analysis are summarised in Figure 1.
