Virtually Observed Therapy (VOT)

RCT

Andrew C Hayward – Chief Investigator

7/28/2014

VOT RCT - Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) Checklist

Contents

Administrative information

1) Title: A multicentre, analyst-blinded, randomised, superiority study to compare the efficacy of Video Observed Treatment (VOT) versus Directly Observed Treatment (DOT) in supporting adherence in patients with active tuberculosis.

2a) Trial identifier and registry name: ISRCTN26184967

2b) All items from trial registration dataset

3) Protocol Version: V3 - 28/07V2 - 14/05/2014

4) Funding: National Institute of Health Research (NIHR) Programme Grant

5) Roles and Responsibilities

5a) Names Affiliations and roles of protocol contributors

Dr Andrew Hayward, UCL Centre for Infectious Disease Epidemiology

Chief Investigator

Professor Ibrahim Abubakar, UCL Centre for Infectious Disease Epidemiology –

Co-lead & Trials advisor

Dr Alistair Story, University College London Hospitals, Advice VOT implementation and TB services liaison

Dr Marc Lipman – UCL, North Central London London TB Service – Clinical advisor

Dr Rob Aldridge – UCL Centre for Infectious Disease Epidemiology – Statistical Advisor

Prof Tim McHugh – UCL, Department of Infection and Immunity - Microbiology Advisor

Dr Peter White – Imperial College London – Health Economics and Modelling Lead

AH and AS conceived the study, IA, ML, RA, TM contributed to study design, RA is conducting the primary statistical analysis. PW will lead the economic analysis.

5b) Trial Sponsor:

University College London

UCL Sponsor Representative - David Wilson; david.wilson@ucl.ac.uk

5c) Role of Study Sponsor and Funders

The study sponsor has responsibility for the overall conduct and quality of the trial. The funder influenced study design through the peer review process but otherwise the funder and sponsor had and will have no role in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

5d) Additional roles and responsibilities.

Principal investigator (PI)

- Design and conduct of TB Reach VOT trial
- Preparation of protocol and revisions
- Preparation of investigators brochure (IB) and CRFs [case report forms]
- Organising steering committee meetings
- Publication of study reports
- Determining members of TMC [Trial Management Committee]

Steering committee (SC)

- (see section 5a for members) plus Study co-ordinator (Elizabeth Garber)
- Agreement of final protocol
- Liaising with study sites
- Arranging site quality control visits
- Reviewing progress of study and if necessary agreeing changes to the protocol and/or investigators brochure to facilitate the smooth running of the study.
- Budget administration and contractual issues with individual centres

External Trials Management Committee (TMC)

- Chair – Professor Andrew Nunn –UCL MRC Clinical Trials Unit
- Members – Professor Mark Woodhead, Consultant in Respiratory and General Medicine, Central Manchester University Hospitals, Dr Ann Chapman, Consultant in Infectious Diseases – Monklands Hospital, Airdrie, Scotland, Josie Mavromatis – Lay Representative
- Advising on study design
- External scrutiny of study procedures, implementation and recruitment

- Review of SUSAR [Serious unexpected suspected adverse events]

Data monitoring Committee

The study is a non-pharmaceutical intervention with no planned stopping rules or interim analyses. There will therefore be no formal data monitoring committee. However the trial statistician (Rob Aldridge) will prepare data reports for the TMC to be checked by an independent statistician from MRC CTU.

Data manager

- Maintenance of trial IT system and data entry
- Data verification
- Responsible for trial master file

Lead investigators

In each participating centre a lead investigator (senior nurse or clinician) will be identified, to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol and investigators brochure.

Introduction

6a & b) Background

In the United Kingdom, tuberculosis patients at high risk of poor adherence to tuberculosis treatment are recommended to have directly observed treatment (DOT) to minimise the risk of relapse, drug resistance and spread of infection. Groups eligible for DOT include patients with social risk factors (including alcohol or drug use, history of imprisonment, homelessness), mental health problems, evidence of poor adherence, previous TB treatment and clinically complex disease requiring extra support. Direct observation can be time and resource intensive for both patients and NHS services, requiring at least three visits per week. The three times weekly regime used for DOT may also be less satisfactory than a daily regime. In the UK, surveillance data suggest that a high proportion of patients who are recommended for DOT do not receive DOT. In the US DOT is the recommended mode of treatment for all TB patients. Recently the University of California San Diego (UCSD) has developed a smart phone “app” allowing patients to easily submit video recordings of themselves taking treatment to a secure server for reading by a health care worker (Video Observed Treatment – VOT). This has been shown to be feasible and highly acceptable in

non-socially complex cases in the US but has not been trialled in more socially complex patients such as those recommended for DOT in the UK. Our study team have pioneered the use of VOT with the pan London Find&Treat TB outreach service (but without the use of a dedicated smart phone app) in socially complex cases in London and again found it to be highly acceptable to patients. We have also modelled potential cost savings through using DOT rather than VOT and found VOT to be considerably cheaper to deliver than DOT. We are collaborating with UCSD to use their VOT "app" in a trial of effectiveness in UK patients eligible for DOT.

7) Research Hypothesis: In comparison to DOT, VOT increases the proportion of patients who have more than 80% of doses observed during a 2 months period.

Primary Objective: To assess the effectiveness of VOT in comparison to DOT on adherence to treatment

Additional Objectives

- To measure the impact on adherence over 6 months
- To measure impact on loss to follow up and treatment completion
- To measure effect on culture conversion and development of resistance
- To measure impact on transmission
- To measure impact on quality of life and patient satisfaction
- To assess cost effectiveness of VOT

8) Description of trial design.

The TB Reach VOT trial is designed as a randomised, controlled, analyst blinded multicenter superiority trial with two parallel groups (VOT and DOT) with a 1:1 allocation and a primary endpoint of 80% of doses being observed over a 2 month period.

Methods: Participants, interventions, and outcomes

9) Description of study settings: Tuberculosis outpatient clinics in London and Birmingham and the London TB outreach service: Find&Treat.

10) Inclusion criteria: Any patient 16 years of age or older eligible for DOT at participating clinics regardless of whether the patients have previously agreed to treatment observation.

Exclusion criteria

1) Patients who are eligible for DOT but not suitable for VOT due to:

a) Need for injectable treatment regime

b) No access to the facilities to charge a smart phone.

2) Patients in whom the primary outcome cannot be measured because they have less than 2 months of treatment remaining.

3) MDRTB patients requiring twice daily treatment who will be recruited into a non-randomised arm of the study where VOT is offered, with the same follow up as the other study arms. This represents small numbers of patients and is planned because DOT is highly difficult to organise in this group and VOT is therefore already considered the optimal arrangement. Also due to the small number of MDRTB patients, it would be difficult to randomly assign participants to these treatment groups.

11a) Interventions for each group

VOT: Daily submission of VOT clip using dedicated smartphone with pre-loaded app allowing upload to a secure server. Participants will be trained on how to lay out each drug on a labelled laminated medication sheet with a space for each drug and take each drug type individually saying either the name of the drug or the colour of the pills, size, and the number taken. Participants will be asked to show their mouth is empty by opening their mouth and sticking out their tongue and finally be asked to report any symptoms from a list of key side effects (which will be printed on the reverse of the laminated medication sheet – Appendix 1 & 2). Any reported or observed side effects will be addressed by study nurses as indicated in Appendix 3.

Training will include submission of test videos.
VOT clips will be submitted automatically as soon as the phone is connected to a cellular data network (data plan provided with phone) or wireless network.
VOT clips will be read by a study nurse/VOT observer daily during weekdays with weekend clips read on Mondays.
No incentives or travel costs will be provided but participants will be able to make use of study smartphone for e-mails, domestic telephone calls and internet searches (limited data downloads apply).

After any missed dose of VOT the observer will attempt to contact the patient by telephone to find out what the problem is and encourage submission of further video clips. If this is a technical problem that cannot be resolved over the phone a visit will be arranged to resolve this. If they are unable to contact them within 24 hours of a missed dose they will contact the case manager to discuss.

DOT: A trained health professional, or responsible lay person supported by a trained health professional, provides the prescribed medication and observes the patient swallowing every tablet prescribed (or for some schedules observing doses during weekdays with self-administered therapy at weekends). Organised by clinic according to usual practice – may be

a) clinic based
b) community based working with a responsible professional such as a hostel worker or pharmacist
c) through a DOT worker outreaching DOT.

Clinics may choose to use incentives and provide travel costs as per normal practice
After each missed dose of DOT the case manager will attempt to contact the patient by telephone to find out what the problem is and encourage re-engagement.

11b) Criteria for discontinuing or modifying allocated interventions for a given trial participant.

If participants have repeated episodes of non-adherence in either DOT or VOT arms they will crossover to the other arm of the trial.

If participants fail to take up the offer of VOT or DOT after randomisation they will be considered VOT/DOT failure and returned to clinic for them to organise treatment.

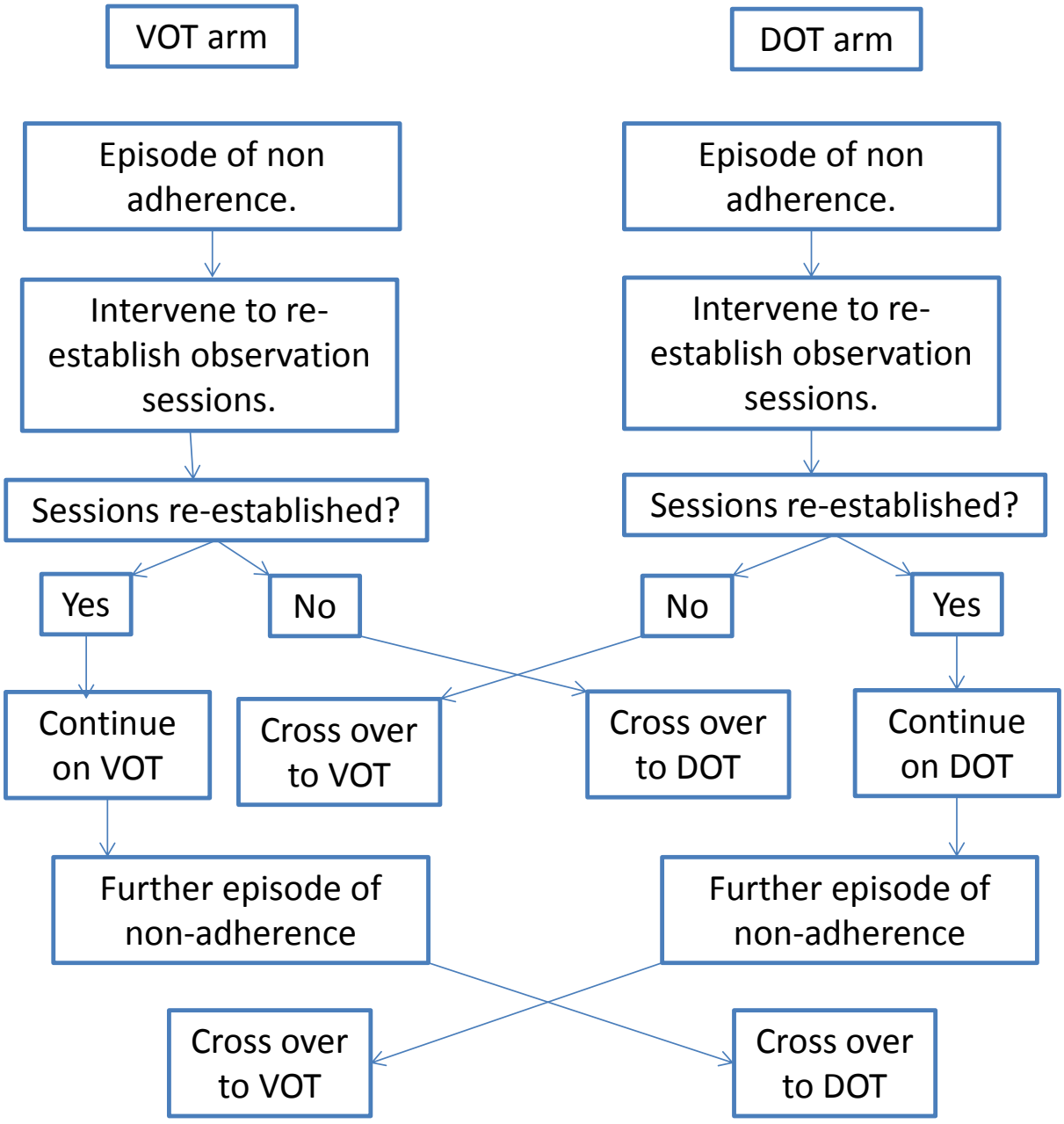
Non-adherence is defined as follows:
Patients on daily therapy are considered non-adherent after missing three daily doses within one week or two doses per week in two consecutive weeks.
Patients on three times per week therapy are considered non-adherent after two or more doses are missed within two weeks.
(Taken from - Tuberculosis case management and cohort review – Guidance for health professionals. Royal College of Nursing).

If, a VOT arm participant meets the above definition of non-adherence, the VOT observer will arrange face-to-face re-training to re-engage the participant with VOT. If retraining

cannot be arranged they will be referred back to the clinic for DOT and enter the DOT arm of the study. If the patient agrees to retraining, but has a subsequent episode of non-adherence (see definition above) they will be referred back to the clinic for DOT and enter the DOT arm of the study.

If a DOT arm participant meets the above definition of non-adherence, the case manager will arrange a face-to-face meeting to re-engage the participant with DOT. If this does not lead to agreement to recommence DOT the participant will be offered to swap to the VOT arm of the trial. If the patient does agree to attend DOT but has a subsequent episode of non-adherence (see definition above) they will be offered VOT and enter the VOT arm of the study.

Changeover of study arm will only be made after a case discussion between a senior member of the study team (AH, AS or ML and the clinic case manager) to review the evidence that they meet the criteria above. Principal Investigators at each site will also be included in such decision.



Patients switching from VOT to DOT during the first 2 months of follow up will be considered as VOT failures for the primary outcome. Patients switching from DOT to VOT during the first 2 months of follow up will be considered as DOT failures for the primary outcome.

For patients who have already crossed over study arms and continue to be non-adherent the clinic responsible for their care will determine the preferred mode of continuing to support adherence for the remainder of their care.

11c) Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g, drug tablet return, laboratory tests)

Participants will receive training in how to submit VOT clips during a household or clinic visit (according to participant preference) with additional training provided if participants fail to return clips or send unsatisfactory clips.

Adherence is primary outcome – see section 12.

11d) Relevant concomitant care and interventions that are permitted or prohibited during the trial.

In the DOT arm clinics may use incentives and enablers (mainly travel expenses) as per usual practice.

VOT arm patients are able to make use of study smartphone for e-mails, domestic telephone calls and internet searches (limited data downloads apply). However on enrolment they will be asked to sign a form (Mobile Phone Sign Out Form – Appendix 4) agreeing to the appropriate use of the mobile phone and the understanding that they may be returned to the DOT arm if the phone is lost or stolen. A copy will be retained by the study and the participant. Similarly, a release form (Mobile Phone Return Form – Appendix 5) will be completed and a copy given to the patient when the patient returns the phone to a team member.

When phones are returned to the study team they will be thoroughly cleaned with Sani-Cloth CHG 2% wipes. All areas of the phone will be wiped and made damp with the cloth. The phone will then be left on a clean paper towel until dry. Once dry it can be stored in the usual manner.

Dosset boxes are allowed in either arm.

VOT arm participants living outside of mobile phone signal coverage areas will receive help in identifying a local wireless network they can log onto.

VOT observers may contact participant via email, text or telephone to encourage them to continue to submit videos.

Patients in VOT or DOT arms may be referred to relevant agencies to address social /addiction issues. The responsibility for this referral rests with the treating clinic.

12) Outcomes

Primary Outcome Measure:

Proportion of participants having more than 80% of scheduled VOT/DOT sessions successfully completed in the 2 months following randomisation (binary aggregation) in participants with a minimum of 6 weeks follow up data.

Secondary Outcome measures:

Collected continuously:

- Proportion of doses observed over 2 months (continuous variable – comparison of means)
- Proportion of doses observed over 6 months (continuous variable – comparison of means)
- Reported side effects

Collected directly by study at baseline and through telephone interview of participant at 2 and 6 months:

- Quality of Life (EQ5D)
- Participant satisfaction (Likert scale)
- Participant resource use for DOT/VOT (Participant time, missed work)
- Employment
- Hospitalisation

Collected directly by study through questionnaire for VOT/DOT observer at 2 and 6 months:

- Time spent observing each dose over the previous week (including travel time where relevant) – staff band and employer
- Time spent re-engaging patients with DOT/VOT
- Travel costs to meet with patients for re-engagement
- Any major side effects requiring a change in treatment regime

Collected by treating clinic - Sputum culture at 2 months after start of treatment. If required, additional testing will be performed until conversion.

Collected from national surveillance data

- Treatment outcome at 12 months (Completed, loss to follow up, transferred out, died)
- Acquisition of new resistance
- Membership of a transmission cluster (based on data from national strain typing service)

13) Participant timeline

In patients who are eligible for DOT there is concern about adherence and potential loss to follow up. In a clinic setting DOT is therefore generally set up and arranged during the clinic appointment during which it is first discussed. We wish to mirror this rapid service in the trial and therefore will aim to complete recruitment during the clinic session at which DOT is first discussed with the patient. This will also minimise loss to follow up prior to being able to establish the intervention. Randomisation into the treatment groups is balanced on the stage of treatment at enrolment, thus the length of time on DOT prior to enrolment should not differ between groups, but should there be any imbalances this will be controlled for in the analysis.
In order to meet the needs of participating clinics and allow this rapid recruitment over multiple sites there are three options for recruitment:

A) When clinics first join the study, study nurses will attend outpatient clinics and be able to recruit patients referred by the clinic nurse through a face to face meeting. Clinic nurses will be encouraged to observe as part of their training in recruitment. Study nurses may also attend clinic if they are given advance warning that a patient who is eligible for DOT (or already on DOT) will be at clinic.
B) When study nurses are not available on site, and clinic resources permit, clinic nurses will: explain the study; provide study information; seek consent; randomise the patient; complete the baseline questionnaire with the patient (largely populated from existing data collected during the course of routine care) and liaise with the study team to organise follow up.
C) When study nurses are not available on site and there are insufficient clinic resources to recruit patients directly, the clinic nurse will arrange a video conference with the study team who will: discuss the study with the patient; seek written consent; randomise and arrange onward follow up. The clinic nurse will complete the baseline questionnaire (largely populated from existing data collected during the course of routine care).

Day zero. Time zero – Clinic identifies patient eligible for DOT during outpatient or inpatient episode. (A, B, C)

Day zero. Time 0-5 mins – Clinic nurse discusses the recommendation that the patient be treated with DOT and the possibility of being involved in a study of how best to observe treatment (face to face) or using video observed therapy. (A, B, C)

Day zero – Time 5-25 minutes - Clinic nurse provides patient information sheet to patient and allows them to assess whether they wish to receive further information. (A, B, C)

Day zero – Time 25-50 minutes –Clinic nurse (A) or study nurse (B or C) explain the study, seek written consent, randomise and arrange onward care.

Day zero – Time 50-60 minutes - study nurse (A) or clinic nurse (B, C) collect baseline data largely populated from existing clinical data/care records.

Day zero Time 60 minutes -120 minutes (A & B) – Training in use of VOT and provision of smart phone.

Day one (or first working day after day zero) – (C) VOT training up to 1 hour at patients home or at clinic depending on patient preference.

Day one (A & B) or two (C) – VOT arm – patient attempt to submit VOT clip unaided, study team liaises and arranges further training if necessary.

Day one (or first scheduled DOT appointment) – patient begins attending for DOT.

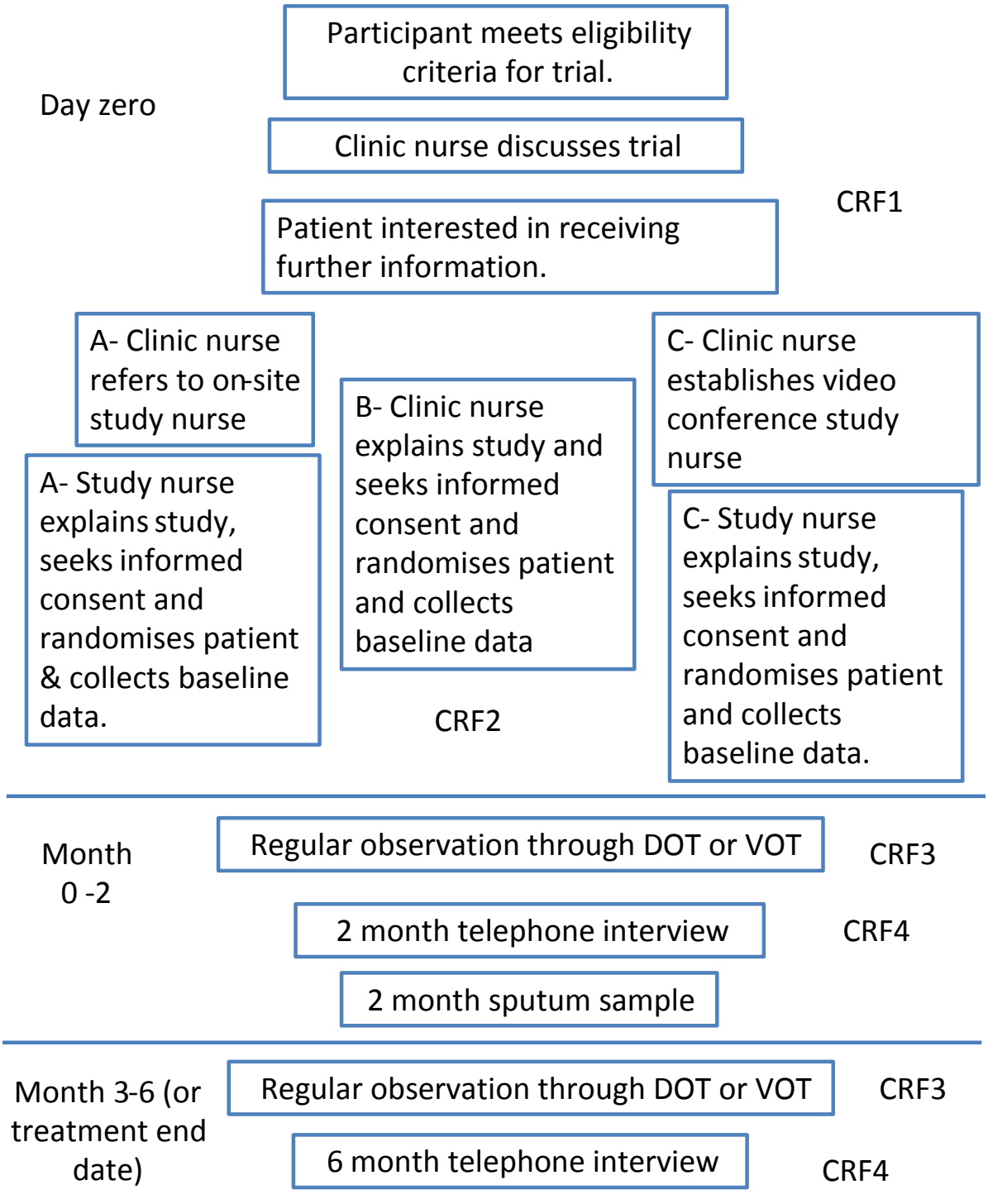
0-2 months – regular DOT/VOT with adherence data collection and monitoring of side effects.

2 months – Study team contact participant by telephone to complete follow up questionnaire covering satisfaction with DOT or VOT, Time spent on DOT or VOT, Employment and quality of life, periods of time spent away from home.

Regular out-patient appointment closest to 2 months clinic nurse requests sputum sample to test for culture conversion at local laboratory.

6 months or end of treatment - Study team contact participant by telephone to complete end of follow up questionnaire covering satisfaction with DOT or VOT, Time spent on DOT or VOT, Employment and quality of life, periods of time spent away from home. For patients still requiring onward care the study will liaise with the clinic and Find&Treat to organise continuing DOT or VOT.

Schematic of participant timeline



Final outcome from national surveillance dataset at 12 months

14) Sample size:

A widely used programmatic measure of acceptable adherence is that patients are known to have taken at least 80% of their scheduled doses. This is particularly important early in treatment. We therefore define an adherent patient as one who is observed to take over 80% of their treatment and will compare the proportion of patients who are adherent in each arm over the first 2 months from randomisation as the primary outcome.

We have examined the power implications of a range of realistic differences in the primary outcome with 90% power at the 5% significance level (2 sided) with equal numbers in intervention and control arms of a superiority trial (table 1).

We have reviewed adherence data from Cohort review of TB patients and the VOT pilot and this suggests the 3rd or 4th scenarios are realistic.

Table 1 – Sample size needed at differing estimates of adherence and effect size.

	50% vs 70%	**40% vs 60%**	**65% vs 80%**	**60% vs 75%**
Intervention	**121**	**126**	**181**	**200**
Control	**121**	**126**	**181**	**200**
Total	**242**	**252**	**362**	**400**

We will aim to recruit 400 participants into the trial over a two year period.

15) Recruitment Strategies for achieving adequate participant enrolment to reach target sample size.

Recruitment relies on conducting the study in multiple centres. We have focussed recruitment of clinics based on existing good relationships and high numbers of cases eligible for DOT. We are also approaching Birmingham clinics to increase numbers.

Based on the following assumptions we expect to be able to recruit 400 patients over a 2 year period.

Assumptions:

The annual number of eligible patients at each clinic will be similar to the annual number of patients reported to national enhanced surveillance in 2010 and 2011 as having social risk factors (homelessness, problem drug or alcohol use or history of imprisonment) but not on DOT, plus the number of patients already on DOT. This averaged at 420 eligible per annum.

It was also assumed that:
95% of those eligible for DOT are also eligible for the trial
Clinics attempt to recruit 75% of those eligible
2/3 of those who are approached agree to participate (based on pilot data VOT acceptance rates)

Note – As MDRTB patients with twice daily treatment are now not included in the randomisation we have not included MDRTB in the estimates. The true numbers of eligibles will be higher as we have ignored, previous history of TB and history of poor adherence, also this is based on incident eligible cases whereas we will also be recruiting patients who are currently on DOT.

We will initially attend outpatient appointments to induct clinics and promote the trial. We will visit clinics monthly for quality control visits.

Another strategy for achieving good recruitment is an emphasis on recruiting patients on the day the study is first introduced to them. As this is a hard – to – engage group delaying this could lead to substantial drop-out.

Methods: Assignment of interventions (for controlled trials)

Allocation:

16a) Sequence generation

We will use computer generated randomisation by minimisation to ensure balance across study sites and stage of treatment at which recruitment took place 1) at start of treatment; 2) after start but within first 2 months of treatment; 3) After first 2 months of treatment.

This will ensure that treatments are balanced within the two strata.

16b - Allocation concealment mechanism

Randomisation will be commissioned from SealedEnvelopeTM (http://www.sealedenvelope.com/) and conducted centrally using an integrated internet/telephone randomisation service. Clinics will randomise using the internet or telephone service, or contact the study centre who will randomise and pass on the allocation to the clinics. The systems also check for consent, study inclusion and exclusion criteria before allowing randomisation (Randomisation Form - Appendix 6).

16c) Implementation

The allocation sequence will be generated by SealedEnvelopeTM. Participant enrolment and assignment to intervention will be done by the study nurse or clinic nurse (see Participant timeline – section 13)

17a) Blinding (masking)

It is not possible to blind participants or care providers to the intervention.
It is also not possible to blind those undertaking interviews at 2 and 6 months, as these questions include information on participant time taken to have DOT or VOT which will make the allocation obvious.
Data analysis will be blinded to the allocation for the primary outcome by ensuring the statistical files for analysis are prepared blind to the intervention.

17b) If blinded, circumstances under which unblinding is permissible – not applicable.

Methods: Data collection, management, and analysis

18a) Data collection methods

Recruitment data (CRF 1 - Appendix 7): Recruiting clinics will collect anonymous data on the characteristics of patients who were approached for the trial but declined to participate using a study recruitment log sheet. This will include age, sex and factors that make them eligible for DOT.

Baseline Data (CRF 2 – Appendix 8): Study or clinic nurses will collect baseline data at the time of initial recruitment. This mainly consists of data already routinely collected by clinics, covering patient demographics, disease categorisation and factors that make them eligible for DOT. It will also include the validated EQ-5D quality of life scale and information on employment status and approximate weekly salary

VOT/DOT diary (CRF 3 – Appendix 9):

This will be recorded by the DOT observer at the time of the scheduled session and by the VOT observer at the time of reading scheduled video clips. DOT/VOT observers will be trained to complete (CRF 3 – see section 18a) consistently. CRF3 will be faxed/emailed on a weekly basis to the study centre with the study centre following up with DOT observers when weekly forms are not returned. CRF3 will be completed directly at the study centre on the VOT reading system.

The VOT reading system includes: fields to identify when doses are scheduled; when clips are submitted and read and the following categorisation of clips:

Patient took meds?

- Y (Yes, all meds)
- P (Probably)
- S (Yes, some meds)
- N (No meds taken)
- U (Unable to tell)
- DNA / Did not send clip

This data will be used for the primary outcome and secondary adherence outcome measures.

The system also collects additional data on video and audio quality. The system collects data on geo-location at the time of recording. This will be collected if the participant provides separate consent for this.

DOT: A DOT diary will be completed by DOT observers showing when doses are scheduled to be observed, whether or not the participant attended, when they attended and whether they took the medicines categorised as above.

Patient 2 and 6 month follow up (CRF 4a & 4b – Appendix 10): The study team will contact the participant by telephone to complete a 5 minute questionnaire covering

- Quality of Life (EQ5D)
- Participant satisfaction (Likert scale)
- Participant resource use for DOT/VOT (Participant time, missed work)
- Employment
- Hospitalisation

VOT/DOT observer 2 and 6 month follow up (CRF 5a & 5b – Appendix 11): This will be completed by the VOT/DOT observer and contain the following information.

- Time spent on average observing doses over 2 or 4 month period (including travel time where relevant) – staff band and employer.
- Time spent re-engaging patients with DOT/VOT.
- Travel costs to meet with patients for re-engagement

sputum sample: At the outpatient appointment closest to 2 months after randomisation the clinic nurse will request a sputum sample and submit this to the local microbiology laboratory for smear and culture.

End of VOT/DOT participant engagement (CRF 6 – Appendix 12):

Semi-structured interviews will be performed with a purposively sampled subset of DOT and VOT participants to understand issues related to provision of DOT/VOT.

12 month follow up (CRF 7 – Appendix 13): The study data manager will work with PHE to link the participant register with national surveillance data to ascertain the following routinely recorded variables.

- Treatment outcome at 12 months (Completed, loss to follow up, transferred out, died)
- Acquisition of new resistance
- Membership of a transmission cluster (based on data from national strain typing service recorded in Enhanced surveillance)

Processes to promote data quality include:

- Training of study and clinic nurses
- Training of DOT and VOT providers
- Weekly submission of DOT diaries + Weekly VOT summary report
- Chase up of DOT provider if weekly forms not submitted
- Quality control visits to clinics every 3 months
- Double data entry for all paper-based CRFs

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

The study is predicated on maintaining regular contact with participants to monitor adherence.

Participants who are lost to follow up but have not withdrawn from the study, scheduled observations after loss to follow up will be recorded as not having been completed. It will also remain possible to obtain their final outcome data from national tuberculosis surveillance. For participants in the DOT arm who clinics decide to step-down care from DOT to self-administered therapy data will be collected on outpatient clinic attendance and collection of medications.

19) Data management

All data entered onto paper questionnaires will be double entered into the master data base with automatic range checks where appropriate. VOT data from the VOT reading system will be held on a secure NHS compliant server which hosts the VOT system which will be

backed up nightly. Weekly data integrity reports will be run on the system using automated routine. Monthly data exports will be made and data merged into the master data file. The master data file will be stored on a UCL password protected network with access restricted to study personnel. This will be backed up automatically on a daily basis. The master data file will use the unique study number allocated at the time of randomisation but will not include personal identifier information. This identifiable information will be held in a separate password protected file on the same network drive in the form of a look up table.

Statistical methods

20a) Statistical methods for analysing primary and secondary outcomes.
Characteristics of those randomised and those not randomised due to refusal or exclusion criteria will be compared. Baseline characteristics of those randomised to intervention and control arms will be compared to check for balanced randomisation. An intention to treat analyses will be used. Categorical outcomes will be compared across groups using the chi-square test or Fisher's exact test as appropriate. Continuous variables will be compared across groups using the Wilcoxon rank-sum test.

For some DOT schedules weekend doses are planned to be self-observed due to difficulty in providing DOT at the weekend. For the primary outcome these doses will not be considered in the denominator of scheduled doses, however, as this is a valuable advantage of VOT, secondary analyses will include these weekend doses as part of the treatment schedule). When participants are in hospital their dose will be considered to have been observed. When participants are in prison or custody the dose will be considered to have been observed if it can be verified with offender health that they were aware of the treatment regime. When patients are out of the country VOT participants will be encouraged to continue to take VOT clips which can either be submitted via a wifi connection or will automatically submit on return to the UK. Doses due during time abroad will not be considered as part of the primary outcome for either arm, but will be included in the secondary analyses to explore the potential value.

Patients who cross-over trial arms (see section 11b) prior to the end of 2 month follow up will be considered a failure for the primary outcome.

20b) Methods for any additional analyses (eg, subgroup and adjusted analyses)

Where there is evidence of unbalanced randomisation, secondary analysis of unbalanced variables will be adjusted for in analyses, if they are associated with outcome, using multivariable regression models as appropriate. An assessment of potential effect modifiers will be performed using interaction terms in the statistical models. If there is evidence of interaction effects will be reported in subgroup analyses.

20c) Definition of analysis relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Approaches such as the sensitivity analysis described in Carpenter et al will be explored to assess whether the data are not "missing at random" before using multiple imputation to infer missing data points.

Carpenter , J., Pocock, S. and Lamm, C. J. (2002) Coping with missing data in clinical trials: a model based approach applied to asthma trials. *Statistics in Medicine*, 21, 1043-1066

Patients who cross-over trial arms (see section 11b) prior to the end of 2 month follow up will be considered a failure for the primary outcome. Data post cross over will be considered in a separate analysis comparing adherence during periods of VOT with adherence during periods of DOT.

Monitoring

21a) Data monitoring

There is no formal DMC but the trial statistician will work with an independent MRC CTU statistician to prepare data reports for the DMC.

21b) Description of any interim analyses and stopping guidelines.

As this is a non-pharmaceutical behavioural intervention no interim analyses or stopping guidelines are proposed.

22) Harms

The following will considered as potential serious adverse events

- Loss to follow up.
- Death from tuberculosis.
- Breaches of data security.
- Violence to study personnel during the course of participant interaction.
- Complaints about the study from participants or participating centres.

These will be reported to the study coordinator and the study chief investigator who will investigate these, including discussion with affected patient's case managers and findings will be reported to the steering committee and data monitoring committee. Summary reports of adverse events and actions taken will be presented to the independent trial steering committee (TSC).

23) Auditing: As part of the NHS R&D approval process the project and individual study sites may be independently audited as part of their quality control processes. No separate auditing is planned.

Ethics and dissemination

24) Research ethics approval

The study has previously been approved by the Essex Multicentre Research Ethics committee. A substantial amendment reflecting the content of this protocol will be submitted for consideration in March 2014.

Study site R&D approval will also be obtained for all recruiting sites.

25) Protocol amendments

The study steering group will agree any protocol amendments and where these are major amendments discuss them with the chair of the TSC. The project manager will ensure substantial amendments are: approved by the ethics committee and site R&D committees; reported to the trial registry and communicated to study sites. Changes in the protocol will be highlighted in supplementary appendixes of publications.

26a) Written consent will be obtained for participation in the study by study team or clinic nurses (section 11).

26b) Additional consent provisions for collection and use of participant data.

Videos are automatically encoded with time, date and geo-location information when the video is made. Time and date information allow the study nurse to document which doses were taken. Participants in the VOT arm of the study will be asked whether they will allow the study access to geo-location information from the video for the purpose of studying flexibility in where patients take their treatment.
Participants in the VOT arm will also be asked whether they will allow the study to keep video clips for the following purposes.

- Behavioural analysis of VOT.
- Assessment of physical correlates of response to treatment.
- Development of training materials to use with patients and staff involved in VOT or for teaching of healthcare students.
- Development of materials to be used in conference presentations.
- Development of materials to be made publically available on web sites or other media.

Separate written consent will be sought by the study nurse at the time of VOT training so the participant can indicate which (if any) of these additional data uses they agree to.
Willingness to make this data available is not a pre-condition for enrolment in the main study.

27) Confidentiality

Information on potential trial participants will be collected in anonymous form.(CRF1)
All other CRFs will be identified using the unique participant id allocated at randomisation. The master data file will be stored on a UCL password protected network with access restricted to study personnel. This will be backed up automatically on a daily basis. The master data file will use the unique study number allocated at the time of randomisation but will not include personal identifier information. This identifiable information will be held in a separate password protected file on the same network drive in the form of a look up table.

Study sites will also maintain separate look up tables on NHS password protected computers.

All data analyses will be conducted on anonymised data with no identifiable data leaving the study site. Analyses will be reported at a level preventing deductive disclosure.

28) Declaration of interests

Study investigators and principal investigators have no financial or other competing interests.

29) Access to data

The Data manager will oversee the intra-study data sharing process, with input from the TSC.
The principle investigator, study statistician and independent statistician will be given access to the cleaned data sets. Project data sets will be kept as described in section 19 and confidentiality will be protected as described in section 27.

Ancillary and post-trial care

30) Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Care of patients at the end of the trial will remain the ultimate responsibility of the clinicians looking after them. Patients that are enrolled into the study are covered by indemnity for negligent harm through the standard NHS [National Health Service] Indemnity arrangements. The trial sponsor (UCL) has insurance to cover for non-negligent harm associated with the protocol.

31a) Dissemination policy

The primary outcome papers of this study will be approved by the Steering Committee as will any other analyses presented as a result of this work.

31b) Authorship eligibility guidelines and any intended use of professional writers.

The authors of VOT publications will be listed as….Disputes regarding authorship will be settled by the Principal investigator after consultation with the TMC.

31c) Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

No later than 3 years after the collection of the 12 month follow up data we will deliver a completely de-identified data set to an appropriate data archive for sharing purposes.

Appendices

Appendix 1 & 2: Laminated

Appendix 1 - Medication sheet also referred to as “Pill Form”

Appendix 2 – List of side effects

Appendix 3: Study nurses actions if participants demonstrate side effects to anti-TB Medication

Appendix 4: Mobile Phone Sign Out Form –

Appendix 5: Mobile Phone Return Form –

Appendix 6: Randomisation Form -

Appendix 7: CRF 1 - Recruitment / Eligibility data

Appendix 8: CRF 2 - Baseline Form & EQ5D

Appendix 9: CRF 3 - VOT / DOT diary

Appendix 10: CRF 4a & 4b - 2 month versus 6 month participant follow-up survey

Appendix 11: CRF 5a & 5b - 2 month versus 6 month VOT/ DOT observer survey

Appendix 12: CRF 6 - End of VOT/DOT participant engagement

Appendix 13: CRF 7 - 12 month follow-up

Informed consent materials

32) Model consent form and other related documentation given to participants and authorised surrogates

Appendix 14: Informed consent materials for the randomised and non-randomised arm

- PIS 1 & 2 - Full
- PIS Credit Card Size 1 & 2
- Consent form 1 & 2
- Supplementary Consent Form 1 & 2
- VOT participant recording procedure booklet
- Initial script 1 & 2 for clinic nurse
- Letter to GPs

33) Biological specimens. Clinics will be asked to submit a sputum sample for smear and culture testing at the sites local microbiology laboratory (recommended good practice). The results of this will be reported to the study but the sample or subsequent culture will not be made available to the study. No other biological specimens will be collected.