VOT interim analysis plan

At an NIHR review of the programme grant in Dec 2015, the slower than expected recruitment rates in the VOT study were reviewed along with preliminary data on the acceptability of VOT vs DOT, uptake of either intervention following randomization and cross-over rates from DOT to VOT arms and vice versa.

These early indicators are suggestive that the primary outcome (the proportion achieving over 80% of doses that were planned to be observed being observed) is likely to be favourable for VOT. As a result of this meeting, NIHR asked for an interim analysis to be conducted that would examine whether there is evidence for interventional effectiveness at this stage potentially allowing the study to be stopped early or to inform recommendations about how long the trial needed to continue.

When writing the trial protocol for the study an interim analysis was not considered necessary due to the low risk of adverse outcomes in this trial. This document therefore sets out a plan for an interim analysis as requested by NIHR, the funders of the study. The results of this interim analysis will be reviewed by the trials independent monitoring committee who will advise NIHR about early termination of the trial. This document sets out an a-priori plan for the interim analysis.

The following primary and secondary outcomes will be examined:

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).

Secondary Outcome measure:

Proportion of doses observed over 2 months (continuous variable)

Primary and secondary analyses

It is proposed that the interim analysis be conducted in two parts. The first is based upon the full study protocol written before the study began, and the second is proposed as it will provide evidence of effectiveness more relevant to implementation of the intervention outside of the RCT setting.

- Primary analysis – as described above. Intention to treat (ITT) analysis of primary outcome. (i.e. considering all those who were randomized regardless of whether they ever took up either arm of the intervention).
- Secondary analysis including only those individuals who started the randomized intervention and have at least 1 week of outcome data for the primary outcome and secondary outcome (this is because a number of patients refused observation immediately following randomization).

Sensitivity analyses

VOT readings were classified in the following way:

1. All meds observed
2. Some meds observed
3. No meds observed
4. Unknown, unable to tell
5. Other
6. Probably took meds
7. Technical issues with clip

The Probably category includes instances when we have evidence that the patient sent a video clip but it could not be opened (patients have no control over whether or not a sent video clip can be opened)

DOT observations were classified in the following way:

1. All meds observed
2. Some meds observed
3. No meds observed
4. Unknown, unable to tell
5. Other

6. Probably took meds
7. Self-observed therapy

The self observed therapy indicates times when the case worker believes the patient took their medicine but did not observe this.

For each of the analytic strategies described above there will be one main analysis and two sensitivity analyses. The main analysis will consider VOT 1 or 6 and DOT 1 or 6 as positive outcomes (i.e comparing how often sessions were thought to have been definitely or probably successfully completed).

Sensitivity analysis A) VOT 1 and DOT 1 will be considered as positive outcomes i.e. comparing how often sessions were definitely completed successfully.

Sensitivity analysis B) VOT 1&2 and DOT 1 or 6 or 7 will be considered as positive outcomes i.e. considering self observed sessions in DOT patients to be considered as successful treatment.

Primary outcome analysis strategy:

For the primary outcome, the following combination of analyses will be conducted:

- Analysis 1: Primary ITT analysis (positive outcomes: VOT 1 or 6; DOT 1 or 6)
- Analysis 2: Primary ITT analysis (sensitivity analysis A - positive outcomes: VOT 1; DOT 1)
- Analysis 3: Primary ITT analysis (sensitivity analysis B - positive outcomes: VOT 1&2; DOT 1 or 6 or 7)
- Analysis 4: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (positive outcomes: VOT 1 or 6; DOT 1 or 6)
- Analysis 5: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (sensitivity analysis A - positive outcomes: VOT 1; DOT 1)
- Analysis 6: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (sensitivity analysis B - positive outcomes: VOT 1&2; DOT 1 or 6 or 7)

Descriptive analysis of the baseline characteristics of those randomised to intervention and control arms will be compared to check for balanced randomisation. Logistic regression will be used for all analyses of the primary outcome for analyses 1-3. All analyses will account for the balanced randomisation by inclusion of time since start of treatment variable (binary, less than two months or not). We will also adjust for treatment clinic, age and sex a-priori, as we believe these to be prognostic factors. If there is evidence of imbalance in randomisation a multivariable logistic regression analysis will be reported separately to account for this. As we are primarily examining the effect of social rather than biological factors within this study, we will not include disease, or microbiological factors. Instead any adjustment will consider social risk factors including, problem drug or alcohol use, no recourse to public funds, homelessness, imprisonment, mental health, and history of non-adherence or previous treatment, and immigration status. As analyses 4-6 are not being conducted on an ITT basis, we expect there to be imbalance within the study arms and are likely to require additional adjustment to control for these confounding factors.

Secondary outcome analysis strategy:

For the secondary outcome, the following combination of analyses will be conducted:

- Analysis 1: Primary ITT analysis (positive outcomes: VOT 1 or 6; DOT 1 or 6)
- Analysis 2: Primary ITT analysis (sensitivity analysis A - positive outcomes: VOT 1; DOT 1)
- Analysis 3: Primary ITT analysis (sensitivity analysis B - positive outcomes: VOT 1&2; DOT 1 or 6 or 7)
- Analysis 4: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (positive outcomes: VOT 1 or 6; DOT 1 or 6)
- Analysis 5: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (sensitivity analysis A - positive outcomes: VOT 1; DOT 1)

  Analysis 6: Secondary analysis restricted to only those individuals who started the randomized intervention and have at least 1 week of outcome (sensitivity analysis B - positive outcomes: VOT 1&2; DOT 1 or 6 or 7)

Descriptive analysis of the baseline characteristics of those randomised to intervention and control arms will be compared to check for balanced randomisation. Logistic regression will be used for all analyses of the primary outcome for analyses 1-3. All analyses will account for the balanced randomisation by inclusion of time since start of treatment variable (binary, less than two months or not). We will also adjust for treatment clinic, age and sex a-priori, as

we believe these to be prognostic factors. If there is evidence of imbalance in randomisation a multivariable logistic regression analysis will be reported separately to account for this. As we are primarily examining the effect of social rather than biological factors within this study, we will not include disease, or microbiological factors. Instead any adjustment will consider social risk factors including, problem drug or alcohol use, no recourse to public funds, homelessness, imprisonment, mental health, and history of non-adherence or previous treatment, and immigration status. As analyses 4-6 are not being conducted on an ITT basis, we expect there to be imbalance within the study arms and are likely to require additional adjustment to control for these confounding factors.

Stopping rules

We are planning one interim analysis and will therefore use the Haybittle–Peto boundary as a rule for deciding whether to stop the trial early. We will use a p-value threshold = 0.001 for this purpose.

The recommendation on whether to stop the trial early will be informed by this p-value threshold for analyses 1-6 of the primary and secondary outcomes. As we believe that many individuals did not take up the offer of DOT post-randomisation, for the purposes of early stopping we will place more emphasis on analyses 3-6 for the primary outcome when making a decision as to whether to terminate the trial early or not.

Analysis of possible harms

The interim analysis will include a descriptive analysis of the possible harms, including:

- Loss to follow up levels
- Deaths from tuberculosis
- Reported side effects

Additional notes on the classification of outcomes

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 described to highlight the potential value.