Cluster randomized trial of a medication monitor in the treatment management of patients with pulmonary tuberculosis

Statistical Analysis Plan

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Review and edits incorporated over version 7.0:

Clarification of implementation of analyses. No analysis methods have been altered.

1. Table of Contents

2. Background

In this section, we will describe some background information about the trial.

Aims

The overall aim of the trial is to investigate whether drug-sensitive adult pulmonary TB patients managed using a novel treatment strategy, including a medication monitor for reminding daily drug dosing and monitoring adherence patterns, and targeted intensive management of patients with poor adherence patterns (intervention arm), have better clinical and adherence outcomes compared with patients managed according to standard of care (control arm).

Design

Open (unblinded) pragmatic cluster-randomised trial, with districts/counties as the unit of randomisation.

Intervention and control

National TB Control Programme guidelines in China require drug sensitive TB patients to take fixed-dose combination tablets daily for six months.

Patients in both the control and intervention arms will be asked to keep their medication in a medication monitor box, which records the date and time of each opening. Patients in the intervention arm will bring the box to each monthly follow-up visit, at which time the doctor will connect it to the computer and download the data.

Data from the box for patients in the control arm will be downloaded once, at the end of treatment or earlier if patient stops using the medication monitor before the end of treatment; the doctor will not be able to access these adherence data.

In the control arm, patients, in consultation with the doctor, choose whether to take their tablets under direct observation by a healthcare worker, direct observation by a family member, or self-administered. After each dose is taken, a mark is put on a TB treatment record card, which is shown to the doctor at the monthly follow-up visit as a way of determining adherence. During the treatment period the CDC, township & village doctors make visits to the patient as defined by current practice.

In the intervention arm, the medication monitor will beep to remind the patient (i) to take their daily medication and (ii) when their next monthly follow-up visit is due. In addition, the doctor will be able to see how often the medication monitor has been opened and can then use these data to determine whether the patient needs additional support. During the treatment period the CDC, township & village doctors make visits to the patient as defined by current practice.

Randomisation

Restricted randomisation was used with the following cluster level characteristics:

- Prefectures
- Hospital or TB dispensary
- Urban or Rural
- Number of SS+ TB cases notified by the TB clinic in 2015

Restriction reduced the number of possible allocations from 24!/(12!*12!) = 2,704,156 to approximately 33,531 possible allocations.

Sample size

Protocol sample size

Assuming 12 clusters per arm, 125 patients per cluster, 5% of individuals whose outcome at 18 months cannot be ascertained, composite poor outcome of a poor treatment outcome or recurrence unto 18 months after enrolemnt estimated to be 18% in the control arm and taking account of the clustered design, using a coefficient of variation of 0.3, there will be 97% and 85% power to assess 50% and 40% relative reduction in poor outcome, respectively.

If k=0.25 then assuming 12 clusters per arm, 125 patients per cluster and composite poor outcome estimated to be 18% in the control arm there is 92% and 82% power to assess 40% and 35% reduction in poor outcome, respectively.

We will allow some clusters to over or under-recruit as long as the overall harmonic mean is 125. The maximum number of TB patients enrolled per cluster will be around 150.

Recalculation of sample size

Following a site visit in April 2018, it was decided that two intervention sites in the same hospital should be considered one site. This reduction in the number of clusters reduced power by approximately 1% in all scenarios considered. Slower recruitment and the potential for higher lost to follow up were also a concern leading to the recalculations of sample size in Table 1.

Table 1: Updated sample size calculations

Coefficient of variation of cluster size	Effect size	Lost to follow-up	Power
Protocol calculations			
0.3	50%	5%	97%
0.3	40%	5%	85%
0.25	40%	5%	92%
0.25	30%	5%	82%

Updated calculations			
0.3	50%	5%	97%
0.3	40%	5%	83%
0.25	40%	5%	90%
0.25	30%	5%	80%
0.3	50%	10%	96%
0.3	40%	10%	83%
0.25	40%	10%	89%
0.25	30%	10%	79%
0.3	50%	15%	96%
0.3	40%	15%	82%
0.25	40%	15%	89%
0.25	30%	15%	78%

Post enrolment exclusion criteria

The following lists the limited reasons for post-enrolment exclusions were given in the trial protocol:

(i) Participants whose Xpert result was not known at enrolment and found to either be Xpert-negative or Xpert-positive and rifampicin resistant

(ii) Participants who stopped taking the FDC within the first 1 month due to an adverse reaction.

(iii) Participants who permanently stopped the treatment management model within the first 1 month due to, for example, travel, hospitalisation, etc.

(iv) Participants subsequently found to be HIV-positive

(v) Participants who were subsequently required to extend their treatment for greater than 6 months due tuberculous pleuritis, diabetes, silicosis, extra-pulmonary TB, trachea or bronchus tuberculosis

Patients meeting these criteria will be excluded from all analyses.

3. Trial Outcomes

Here we will describe the trial outcomes that will be analysed by study arm. First we will give a brief description, then in the section “derivation of variables” we will describe these outcomes more fully.

Trial protocol study outcomes

In this section, we will describe the trial outcomes given in the trial protocol.

Primary endpoint:

The primary outcome is a composite poor outcome measured up to 18 months from start of TB treatment. The trial protocol defined this as

1) A poor outcome at the end of treatment because of:
    - Death

- treatment failure
- loss to follow-up

or

2) Subsequent recurrence up to 18 months after treatment initiation. This can be identified by any of
   - culture positive for TB
   - chest x-ray suggestive of new TB
   - (re-)starting TB treatment

After completion of treatment, patients will be followed with a phone call at 9 and 15 months, and should have cultures and chest x-ray at 12 and 18 months.

Secondary outcomes:

Clinical outcomes:

1. Composite poor outcome at the end of treatment (death, treatment failure or loss to follow-up)
2. Composite poor outcome measured over 12 months from start of TB treatment.
3. Lost to follow-up during treatment

Adherence to treatment outcomes:

1. The percentage of months in which the patient missed at least 20% of doses, measured using data from medication monitor box.
2. The percentage of doses missed, measured using data from the medication monitor box each month.

Exploratory outcomes:

Two-month smear conversion among patients smear positive at the start of treatment

Cost effectiveness outcomes:

These will be examined separately and are not covered by this document

Additional trial outcomes

Several *secondary* outcomes have been added before unblinding of trial data.

Clinical outcomes:

1. Time to recurrence of TB
2. Length of treatment
3. Unable to use FDC

Adherence to treatment outcomes:

1. Percentage of visits attended on schedule

4. Derivation of Trial Outcomes

Primary outcome: Poor outcome

Treatment outcomes recorded in the trial database are more finely categorises than the outcomes described in the trial protocol. These are matched as shown in table 2.

Table 2: *Mapping of protocol treatment outcomes to database treatment outcomes*

Trial protocol treatment outcomes	**Corresponding trial database treatment outcome**
Cured	Cured
Completed treatment	Completed treatment
Failed treatment	Failed treatment
Death	Death for TB
	Death for non-TB
Lost to follow up	Lost to follow up (discontinuation of 2 months or more)
	Refusing treatment (not as a result of adverse reaction)
Side effect	Adverse reaction (resulting in patient refusing treatment)
Transfer out	
	Change to MDR treatment (acquired)

The database also allows a treatment outcome of other. The final database will have these checked and reclassified into the appropriate category.

Patients will be classified as having a favourable outcome if:

- They have a treatment outcome at the end of treatment of
    - cured or
    - completed treatment
- And no recurrence defined by either
    - A negative culture at 18 months
    - At 18 months, culture is missing, or the patient was unable to produce sputum and they have no signs of new active TB meaning (1) no self-reported restart of treatment or (2) no sign of new active TB on x-ray

Patients will be classified as having a poor outcome if they have *either*:

- A treatment outcome at the end of treatment of
    - Failed treatment
    - Change to MDR TB
    - Death (TB or non-TB)
    - Lost to follow-up (discontinuation of 2 months or more)
    - Patient refused treatment (not as a result of an adverse event)

    - Stopped because of an adverse reaction
- Subsequent recurrence of TB identified by
    - Positive culture at 6, 12 or 18 months
    - CXR results satisfying case definition for new active TB at 6, 12 or 18 months
    - Self-reported restart of TB treatment at 9, 12, 15, or 18 months.

Appendix A and B give flow diagrams for deriving patient outcomes. Appendix A describes derivation when no outcomes are missing. Appendix B additionally describes derivation when some components are missing.

18 month follow up visits will be included if they occur within 24 months from enrolment.

Detection of NTM sensitivity analysis

Where possible, species identification has been performed on positive cultures. In a sensitivity analysis, we will recode positive cultures to negative where species identification confirms no mTB. Where species identification confirms mTB or no species identification is available, a positive culture results will be assumed to be positive for mTB.

Endpoint review committee

Details of this are described in a separate document. In brief, patients will have their outcome status reviewed if they have signs of TB recurrence on an x-ray or they self-report treatment restart, but they have no positive culture to confirm recurrence.

When the endpoint review committee decide that the patient should be classified as poor outcome, the data is used as entered on the database.

When the endpoint review committee decide that the patient should be classified as a favourable outcome, the data on treatment restart and x-ray results are recoded to no treatment restart and no sign of active TB before the statistical analysis is conducted.

If the endpoint review committee determine that they do not have enough information to determine whether recurrence has occurred or the experts disagree, the variables indicating recurrence will be set to missing before the statistical analysis is conducted.

Secondary outcomes

Clinical outcomes

End of treatment

A poor treatment outcome will be defined in the same way as the first component of the primary outcome, incorporating x-ray and culture results at the end of treatment.

12 months

Poor outcomes at 12 months will be derived as for 18 months, with follow up after 12 months omitted.

Lost to follow up during treatment

Patients will be counted as lost to follow up if their treatment outcome is recorded as missed (lost to follow up), stopped due to an adverse reaction, or refused treatment. This requires patients to have stopped treatment for 2 months or more.

Patients will be counted as not lost to follow up during treatment if they have any other treatment outcome.

Time to recurrence

Patients will be followed from treatment completion to their last contact date. This analysis will only include those who successfully completed treatment (treatment outcome of cured or completed treatment). Recurrence is any of:

- positive culture
- chest x-ray satisfying case definition for new active TB
- self-report of restarting treatment

Length of treatment

Length of treatment will be measured at the time from initiation of treatment to the date of end of treatment and will be analysed as a continuous outcome.

Unable to use FDC

Patients will be counted as unable to use FDC if they stopped using the MERM box with this reasoning recorded on the early withdrawal form.

Adherence to treatment outcomes:

Percentage of months in which the patient missed at least 20% of doses

Using data collected from the MERM, missed doses will be measured from the start of treatment until the treatment completion date. Days when the box was known to not be in use (missed heartbeat or non-use recorded on the MERM usage form) will be excluded. Otherwise, treatment is expected once daily, a missed dose is defined as a calendar day with no record of the medication monitor box being opened.

A percentage of days where a dose was missed in each 30 day period following treatment initiation will be calculated. From this, months with a percentage greater than 20% will be calculated.

A sensitivity analysis will use data collected from the MERM only excluding days where the heartbeat was missed (i.e. ignoring non-use recorded on the MERM usage form).

Percentage of doses missed

This will use the same data as above, summarising each patient's adherence over the whole course of their treatment.

The sensitivity analysis described above will be repeated for this outcome.

Percentage of visits attended on schedule

This will use the monthly visit form. A visit will be considered late if there are more days between visits than the number of doses given to the patient at their previous visit. This will be summarised across the patient's whole course of treatment.

5. Process measures

From the medication monitors the following will be measured in both arms:

- Rate of medication monitor "errors" reported including missed heartbeats
- Reason for medication monitor "errors"
- Number of short openings
- % of patients withdrawn and no longer using the MERM box, and reasons for withdrawal

In the intervention arm, we will also calculate:

- Number of times alarm sounds before box opening
- % of patients requiring intense management; and of these % who received intense management
- % of patients requiring DOT; and of these % who received DOT

Other process measures calculated for both arms are:

- Median number of visits per month from township/village doctor to patient excluding any intensive management or DOT phases as result of missed doses.
- Percentage patients who receive >1 month of drugs with agreement from Doctor.
- Percentage patients who travel away from area, with agreement from Doctor.

6. Analysis

Patient flow

A CONSORT diagram for CRTs will be constructed to indicate (i) clusters and patients enrolled, (ii) patients not enrolled and reasons why, (iii) follow-up of clusters and patients (iv) analysis of clusters and patients. [1]

Baseline characteristics

Cluster level characteristics

The baseline characteristics of clusters in the intervention and control arms will be described as follows:

- Prefecture
- Hospital or dispensary
- Urban or Rural (using randomisation definition, urban if more than 50% of population in Urban setting)
- Number of SS+ TB cases notified by the TB clinic in 2015
- Number of townships and villages in county/district
- Number of doctors delivering TB care
- Per capita net income
- Population size
- Laboratory onsite
- X-ray onsite
- Months of TB medication dispensed during intensive phase (1 month, other)
- Months of TB medication dispensed during continuation phase (1 month, other)
- Are incentives offered

These will be tabulated by intervention status at the cluster level using either number and percentage or the median and interquartile range as appropriate.

Individual level characteristics

The baseline characteristics of TB patients recruited into the study in the intervention and control arms will be described as follows:

Socio-demographics

- age
- gender
- marital status
- employment status and category
- education level
- place of residence (house of registration vs other)
- number of household members
- own home
- sufficient money to cover costs
- monthly expenditure

TB diagnosis variables

- smear status

- distance to local TB clinic
- distance to supervision facility

Characteristics will be tabulated by intervention status at the cluster level using either number and percentage or the median and interquartile range as appropriate.

Populations

Intention to treat

Intention to treat analyses will be conducted including all participants enrolled in the study, excluding only the post-enrolment exclusions and patients with a change of diagnosis confirmed by endpoint review committee [2]. This will be the primary comparison.

Per-protocol

Per-protocol analyses will also be conducted, excluding all patients described above as well as patients who withdrew early from use of the MERM regardless of the reason given.

Statistical methods

The analysis is based on a total of 23 clusters, 12 in the control arm and 11 in the intervention arm using cluster level analysis due to the s small number of clusters per intervention arm [3]. Further details are described below.

Summary measures

For all outcomes, the geometric mean of the cluster-level outcomes will be reported by intervention arm. This will use cluster-level risk for binary outcomes, means for quantitative outcomes, and rates for time to event outcomes.

Unadjusted analysis

The analysis will be performed at the cluster level and will give each cluster equal weight [4].

For all outcome types, the mean difference of the cluster level outcomes will be calculated. The 95% CI and p-value will be calculated from a t-test with 21= 23 - 2 degrees of freedom.

For quantitative outcomes the mean for each cluster will be analysed in the t-test. For binary outcomes the risk and log-risk (for ratio measures) for each cluster will be analysed where log-risk will be the primary measure of the two. For time to event outcomes the rate and log-rate for each cluster will be analysed. Comparisons on the log scale will be primary for risks and rates.

Log risks and log rates are not defined for clusters with no events. For outcomes where this occurs, we use a heuristic of adding 0.5 to the number of events in each cluster.

Adjusted analysis

Potential confounding factors will be adjusted for. The adjusted analysis will be the primary analysis. A priori adjustment factors are:

- Age
- Sex
- Occupation (farmer or other)
- Local residency
- Distance to nearest TB clinic
- Level of education
- Household expenditure
- Smear result at start of treatment

We will adjust for these using a two-stage approach.

In the first stage, the regression model will include terms for all covariates but not study arm. For binary outcomes, a logistic model will be used. For time to event outcomes, a Poisson model will be used, and for quantitative outcomes a linear model will be used.

For binary and time to event outcomes we will calculate (1) the log of the ratio of observed to expected (O/E) events (ratio residuals) and (2) the difference between the observed and the expected event rates $(O-E)/m_i$ where m_i is the cluster size of cluster *i* (difference residual).

For quantitative outcomes, we will calculate the difference residual as the difference between the expected and observed cluster means.

In the second stage of analysis, differences between these residual values between the arms will be calculated in a similar way to the unadjusted anlaysis. The p-value and 95% CI is calculated from a t-test with 21 = 23 – 2 degrees of freedom.

Missing data

For the primary outcome, the composite outcome will be missing if a patient meets neither definition of a favourable or poor outcome, for example if a patient has become lost to follow up after treatment completion, with no sign of a relapse at last follow up. Our primary analysis will use multiple imputation to enable us to include all patients regardless of this missing data and allow us to utilise all information available to us for such a patient.

A secondary complete case analysis will include only those with a defined primary outcome, using the patient flow in appendix B to determine the outcome.

All secondary outcomes will be analysed using complete cases only.

Multiple imputation

Multiple imputation with chained equations will be used to account for missing data in the components of the primary composite outcome.

25 imputed dataset will be created, based on the assumption that 25% of patients will have one or more components missing [5]. If perfect prediction is an issue, regression with augmented data will be used to rectify the problem [6]. If the problem remains, problematic covariate/s will be removed from the imputation. If these methods are unable to solve the issue, a complete case analysis will be used as the primary analysis.

Each of the following components will be imputed as binary [7]:

- Treatment outcome (Y_0)
- Recurrence by 12 months (Y_{12})
- Recurrence by 18 months (Y_{18})

Treatment outcome will be taken directly from the data with a favourable or poor outcome as described in section 4.

Recurrence by 12 months will be calculated from the data as follows: if the patient has a negative culture at 12 or 18 months then there is no recurrence. If the patient has a poor treatment outcome, a positive culture or x-ray results suggestive of active TB at 12 months, or self-reported restart of treatment at 9 or 12 months this will be counted as a recurrence. Otherwise, recurrence at 12 months will be missing.

Recurrence by 18 months will be be calculated from the data as follows: if the patient has a negative culture at 18 months then there is no recurrence. If the patient has recurrence by 12 months, a positive culture or x-ray results suggestive of active TB at 18 months, or self-reported restart of treatment at 15 or 18 months this will be counted as a recurrence. Otherwise, recurrence at 18 months will be missing.

We impute data for missing components Y_k using logistic regression adjusting for the *a priori* adjustment factors listed above, cluster (i.e. treating clusters as fixed effects), and the two other components of the outcome [8].

From this imputed dataset, the composite primary outcome will be 1 if the patient has a poor treatment outcome or recurrence as 12 or 18 month, and 0 if the patient has a favourable treatment outcome and does not have recurrence at either 12 or 18 months.

Each imputed dataset will be analysed as described above and results combined using Rubin's rules [9].

In addition, a complete case sensitivity analysis will be performed with treatment outcomes determined with the flow chart in appendix B.

Subgroup analyses

For the primary outcome, subgroup analyses by the following factors will be performed [10]:

- Age group (<40, ≥40 same cut off as first trial)
- Literacy - low/high literacy (based on “education-level” recorded at enrolment, and defined as “illiterate” vs “any schooling”)
- Gender
- Monthly household expenditure (≤3000 CNY, <3000 CNY)
- Urban/rural
- Type of health care provider (hospital or dispensary)

The first 4 of these are individual level characteristics and will be calculated as follows. First calculate the risk of a poor outcome in each subgroup and cluster. Calculate the mean of these risks with in subgroup to estimate the risk of a poor outcome in control and intervention arms. To test for a difference, calculate the difference between the two subgroups within each cluster. A t-test is performed on these differences to test for effect modification.

The last two factors are cluster level characteristics. For these subgroup analyses, a linear regression will be used with trial arm, subgroup, and an interaction between the two as independent variables. A likelihood ratio test will be used to estimate a p-value for the interaction. The risk of a poor outcome and it’s confidence interval in each arm will be calculated from the relevant coefficients from the regression.

Estimating between cluster variability

The coefficient of variation will be estimated separately for each arm for the primary outcome using the methods described in Hayes and Moulton page 147 [4].

Calculate the between cluster variance as:

$$\sigma_B^2 = s^2 - \frac{p(1-p)}{\bar{m}_H}$$

Where s^2 is the variance between the observed cluster summaries, p is the overall proportion with a poor outcome from all clusters combined, and m_H is the harmonic mean of the number of observations in each cluster.

7. References

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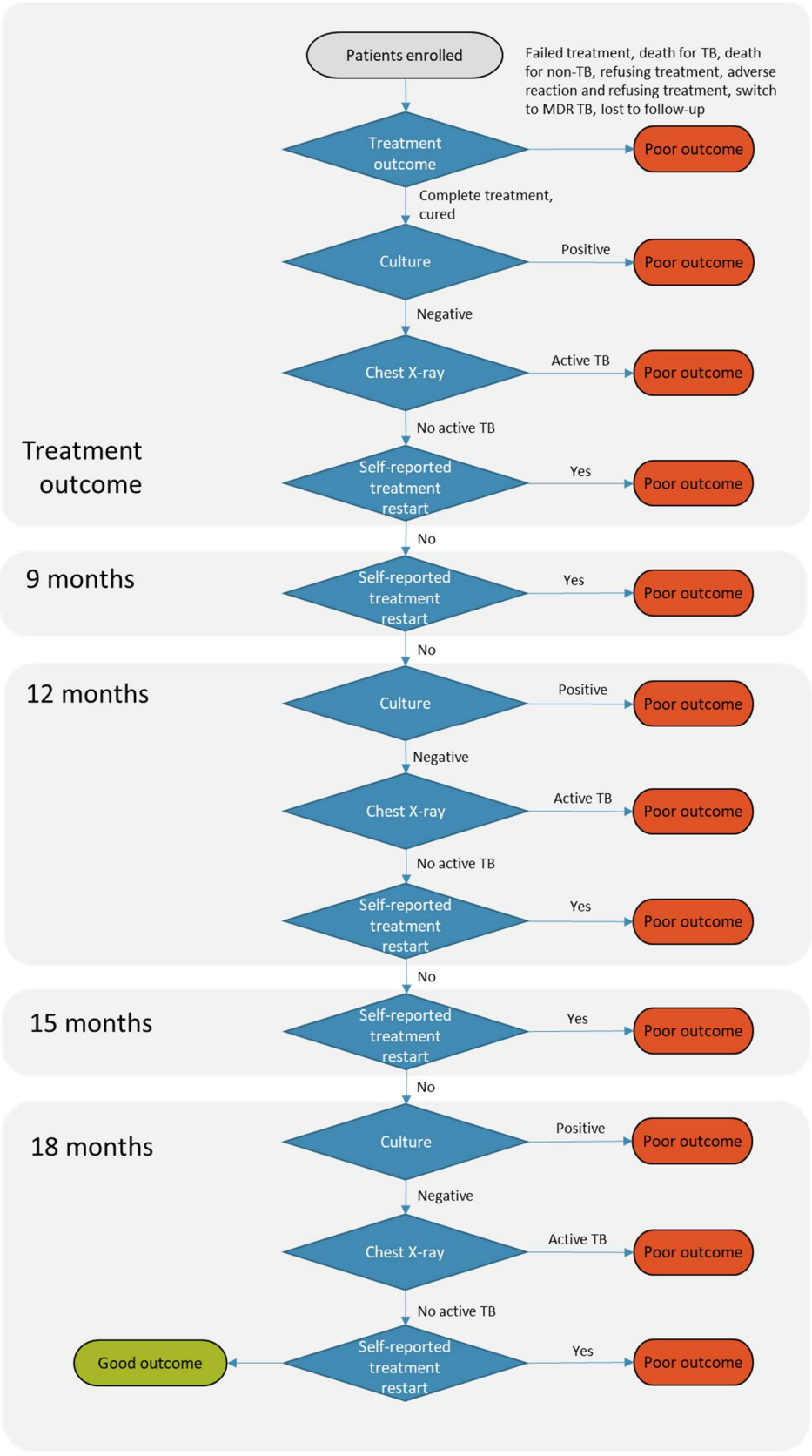
Appendix A treatment outcome flow diagram for primary outcome with no missing components after endpoint review



Appendix B: Treatment outcome flow diagram for primary outcome with complete case analysis