BMJ Open

Capturing patient-reported outcomes and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods sub-study protocol, TB PRACTECAL-PRO

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043954
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2020
Complete List of Authors:	Stringer, Beverley; Médecins Sans Frontières, Manson Unit Lowton, Karen ; University of Sussex, Department of Sociology James, Nicola ; Médecins Sans Frontières, Manson Unit Nyang'wa, Bern-Thomas; Médecins Sans Frontières, Manson Unit; London School of Hygiene & Tropical Medicine, Clinical research Department
Keywords:	Tuberculosis < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protocol manuscript

Capturing patient-reported outcomes and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods sub-study protocol, TB PRACTECAL-PRO

Running title: Patient-reported outcomes in TB PRACTECAL-PRO

Authors: Beverly Stringer[1], Karen Lowton[2], Nicola James[1], Bern-Thomas Nyang'wa[1, 3]

Affiliations: 1. Manson Unit, Médecins Sans Frontières, London, UK

2. Department of Sociology, University of Sussex, Brighton, UK

3. Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author: Beverley Stringer; beverley.stringer@london.msf.org

Keywords: patient-reported outcomes, quality of life, qualitative, MDR-TB, clinical trial

Word count: 3831

Abstract

Introduction: People living with drug-resistant tuberculosis (TB) currently have few options for effective treatment and cure. Regimens that are available are toxic, may involve injections and take up to two years to complete treatment, with success rates as low as 50%. The TB-PRACTECAL trial is evaluating shorter, more tolerable regimens of oral drugs; we detail the sub-study within this trial, PRACTECAL-PRO, which aims to evaluate patient experiences and perspectives on treatment, to understand outcomes more fully.

Methods and analysis: We are conducting a mixed-methods evaluation within both investigational and standard-of-care arms within the TB-PRACTECAL trial, using sequential quality of life (QoL) surveys and in-depth interviews. Data collection involves the Short Form 12 (SF-12) and St Georges Respiratory Questionnaire (SGRQ), collected at up to four fixed timepoints, from baseline, to up to 12 months later. Healthy participants will be surveyed to establish locally-relevant controls. We will also purposively sample participants for qualitative data collection and analysis, to provide rich explanation of quality of life scores. The study will be implemented in all six TB-PRACTECAL study sites in Uzbekistan, South Africa and Belarus. QoL surveys will be scored and analysed according to SF-12 and SGRQ developers' manuals. Differences between scores at baseline and later timepoints will be evaluated as well as graphical exploration of group score trajectories of investigational and standard of care arms.

Ethics and dissemination: Ethics approval was obtained from the Médecins Sans Frontières (MSF) Ethics Review Board. Local ethics approval has been obtained in Uzbekistan, Belarus and South Africa. Results of the sub-study will be shared with local health authorities, the World Health Organisation and submitted for publication in a peer-reviewed journal.

Registration: Clinicaltrials.gov, NCT03942354 (https://clinicaltrials.gov/ct2/show/NCT03942354)

ARTICLE SUMMARY

Strengths and limitations of this study

- This study aims to be one of the first randomised TB trials to incorporate patient perspectives on their experience of investigational treatments, including standard of care and healthy controls.
- Analysis includes in-depth interviews alongside standardised quality of life surveys.
- The study will detail how a novel regimen is experienced in diverse populations and contexts, covering some of the most challenging scenarios for multidrug-resistant tuberculosis (MDR-TB) treatment.
- Our findings will enable evaluation of the utility of SF-12 and SGRQ survey tools in populations living with tuberculosis.
- Limitations of the mixed-methods sub-study include the relatively small sample size.

MAIN TEXT

Introduction

TB global epidemiology

Tuberculosis remains the deadliest infectious disease globally, with mortality estimates exceeding those for both HIV and malaria. The emergence of MDR-TB, defined as disease caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, has complicated global efforts to control the epidemic. Approximately 500,000 cases of MDR-TB occur globally each year, representing nearly 5% of the world's annual TB burden [1]. Currently, around 20% of patients diagnosed with MDR-TB are on treatment, and there is an urgent need to scale up treatment programmes [2]. Scale-up is being severely hampered by financial, political, logistical, and technical obstacles, with one of the most important challenges being the nature of current standard of care regimens [3]. Current regimens used to treat MDR-TB have poor efficacy; the most recent meta-analysis of treatment outcomes for pulmonary MDR TB suggested that only 61% of patients had successful outcomes, 8% had failure or relapse, and 14% died [4]. Low treatment effectiveness, combined with high costs, and implementation difficulties are preventing many national TB programmes from offering treatment for MDR-TB [5]. This in turn fuels the spread of further MDR-TB infections [6]. There is a global need for an improved treatment regimen for MDR-TB that is efficacious, safe, tolerable, and that can be implemented in a variety of epidemiological settings. Given the high rates of HIV co-infection among certain populations of patients with MDR-TB [7], it is imperative that patients with HIV be included in any evaluations of new treatment regimens.

Patient reported outcome measures

Patient-reported outcomes (PROs) are useful in evaluating the effectiveness of many medical interventions from the patient's perspective, which then can help fulfill critical considerations, such as shared decision-making, and ensuring greater user satisfaction with services [8]. For example, in child diabetes services, PROs are being used to measure changes in general wellbeing following treatment [9]. PROs can be beneficial for assessing treatment needs, monitoring patient progress, evaluating clinical outcomes, and helping to understand mechanisms of behavior change [8]. Routine use of patient-reported outcomes to inform healthcare policy for a range of long-term conditions shows that use of both qualitative and quantitative methods of capturing PROs is preferable [10].

Collection of patient reported outcome measures (PROMs), using tools such as questionnaires or surveys embedded within clinical trials, can help to understand the effects of healthcare decisions made by patients and their clinicians. PROMs are also used to support licensing claims for new medicines and to influence the development of health policy, including decisions about the cost-effectiveness of treatment, [11]. The past three decades have seen increasing recognition that clinical trials should capture the patient's perspective, and that this should be given as much emphasis in making treatment decisions as more "objectively" reported biomedical outcome measures. However, despite this, a recent systematic evaluation showed that collection of patient-reported outcomes is frequently absent from clinical trial protocols [12].

PROMs are also useful in assessing experiences and perspectives from the patient's standpoint, since individuals commonly report their QoL status differently from clinicians who report on their behalf. Currently, although clinician-reported adverse events (AEs) are typically collected within clinical trials, evidence suggests that this form of data collection may underestimate symptom onset and severity when compared to patients' own reports of their experience [13,14].

Most PROMs used in clinical trials currently use quantitative measures. Questionnaire-style PROMs, or QoL measures, can be generically focused, (e.g. the Short-Form (SF) 36, SF-12, and SF-6) [15] or condition/disease-specific (e.g. the St George's Respiratory Questionnaire, SGRQ), [16] a respiratory QoL instrument formulated for use in chronic obstructive pulmonary disease (COPD) [17].

When value is only placed on a PROM's level of validity, inconsistency in its use across trial sites may ultimately lead to biased results. Sometimes quantitative measures using standardised questions may be interpreted ambiguously or unclearly for some groups of individuals, which then deters completion or generates unreliable results [10]. Therefore, PROMs used alongside qualitative methods may offer a fuller understanding of patient perspectives [18], especially when used in countries outside of the settings where they were originally developed.

Quality of life measures in tuberculosis

Currently, work on developing QoL measures specific to TB is in its infancy. However, some meaningful data has been collected, and this has informed proposals that at least one PROM used must capture all health-related physical impairment (e.g. not be organ- or system-specific); that PROM's should be able to evaluate psychological morbidity, an issue especially pertinent for patients with MDR-TB; and that PROM's should be culturally and linguistically appropriate for the study population and to include evaluation of social role limitations and stigma [19].

A systematic review of the impact of TB and the effects of treatment on patients' QoL showed that the SF-36 was the most commonly-used measure to capture patient-reported outcomes [20]. In China, SF-36 scores of patients diagnosed with TB indicated poor quality of life before treatment, but these significantly improved during treatment [21]. A systematic review summarising the impact of TB on patient-reported health-related QoL reported meaningful improvement in QoL scores after treatment start [5]. TB treatment therefore appears to have a positive effect on QoL, with improvements in physical rather than mental health tending to be noted more often [21].

The SGRQ appears to be an effective tool to assess morbidity-related QoL during treatment for people who live with TB, alongside measures of lung function, clinical improvements, chest X-ray findings, and adverse events [22]. QoL measures have also been used specifically to test impairment after microbiological cure, showing the importance of such measures in assessing health outcomes that are not apparent through biological measurement [23]. Both physical and QoL measures demonstrate that TB appears to lead to residual disability among ambulatory patients in whom treatment outcomes may have been considered successful [19, 23].

Qualitative PRO measures in Tuberculosis

Using qualitative methods to assess QoL for people who live with TB include examining areas such as general health perceptions, somatic sensation or pain, psychological health, spiritual well-being, and physical, social and role functioning [19]. One such study, conducted in the USA, identified domains of QoL most prominently affected by TB [24], using focus groups and individual interviews with patients with a history of active TB, and their clinicians. Pill burden, duration of treatment, loss of income, and fear were cited alongside the domains already captured by quantitative measures. Importantly, benefits of TB as an illness were described, such as its effect on increasing spirituality and improving life perspectives. Social relationships for patients receiving TB treatment have been reported as important, not only as a means of acknowledging the patient's rights and dignity, but also as a way of understanding the individual interests of the patient, stigma and discrimination versus the collective interests of the practitioner and scientific community [24]. Other published qualitative work in relation to patient perspectives has examined perceptions of self-administered TB treatment and adherence [25,26].

Design of the TB-PRACTECAL trial

TB-PRACTECAL is a multicentre, open-label, phase II-III randomised trial evaluating exclusively oral six-month long regimens containing bedaquiline, pretomanid, linezolid only, with moxifloxacin

or with clofazimine, or the treatment of microbiologically-confirmed pulmonary MDR-TB and extensively drug resistant (XDR)-TB.

PRACTECAL-PRO is a sub-study of the TB-PRACTECAL trial and aims to answer questions relating to the perceptions, expectations and experiences of novel TB treatment for adult patients participating in these six-month treatment regimens in Uzbekistan, South Africa and Belarus.

Objectives of PRACTECAL-PRO

The TB-PRACTECAL trial assumes that even if the investigational arms show non-inferior efficacy and safety, as compared to standard of care, patients will likely prefer shorter, exclusively oral regimens with a lower pill count. In the sub-study we will therefore explore these assumptions through the following objectives:

Primary objectives

1. To assess quantitatively QoL measures for patients within the trial, from baseline to 12 months, including those treated in investigational arms as well as the standard of care arm.
2. To describe qualitatively patient satisfaction and experience with trial treatments in the investigational arms.

Secondary objectives

1. To understand what factors enable a novel treatment regimen to be tolerated or rejected by patients.
2. To evaluate utility of the SGRQ and SF-12 questionnaires, and qualitative methods within TB clinical trials.

Methods and Analysis

Overall study design

PRACTECAL-PRO uses a mixed-methods approach, with QoL surveys and in-depth interviews being employed at different time points over the twelve-month intervention period. It is expected that the qualitative interviews will allow for a more in-depth explanation of the quantitative survey data. QoL is assessed quantitatively within all trial arms, from baseline to twelve months with selected participants being interviewed at baseline, three to six and at twelve months. In addition to these main objectives, we aim to understand what factors enable novel treatment regimens to be tolerated or rejected by patients, and to report on utility of the SGRQ, SF-12, and qualitative methods in TB clinical trials.

Patient and public involvement

Patients and, where feasible, the wider community have been engaged in setup and implementation stages of the main TB-PRACTECAL trial [27,28,29]. Tools not available in the local languages are not only translated but also undergo cognitive debriefing by the teams and patients locally.

Settings

TB-PRACTECAL, and the PRACTECAL-PRO sub-study is being conducted in six sites, in three countries; Uzbekistan, South Africa and Belarus. In Uzbekistan, the trial is taking place in Tashkent City and six rayons (districts) in Karakalpakstan, Western Uzbekistan, specifically Nukus City,

Nukus, Takhiatash, Chimbay, Kegeily and Xodjeli rayons. Implementation of the trial in Uzbekistan is being conducted by the Republican Specialised Scientific-Practical Medical Centre for Phthisiology and Pulmonology of the Republic of Uzbekistan. In South Africa, the trial is being conducted in Doris Goodwin and Don McKenzie Hospitals through the Tuberculosis and HIV Investigative Network (THINK), and Helen Joseph Hospital through the University of Witwatersrand's Clinical HIV Research Unit. In Belarus, the trial is taking place in Minsk City and Oblast, implemented by the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis of the Republic of Belarus.

Implementation timelines

The study started recruitment in Belarus in October 2019, is currently recruiting in Karakalpakstan, Uzbekistan and THINK, South Africa. Recruitment completion is expected in mid-2021 and final follow up and results are expected at the end of 2022.

Sampling

With the increasing use of QoL measures in research, historical datasets are now becoming more readily available to help guide sample size estimation and timing of surveys [30,31,32,33,34]. Although there are published studies examining QoL changes for people with TB, most do not inform power calculations. We recognize that it is likely that there will not be adequate power to formally detect any differences between the SGRQ in those receiving investigational treatments, and those receiving standard of care over time, however we aim to carry out a graphical exploration of group trajectories, plotting means and 95% confidence intervals by group at each timepoint. This will enable us to explore whether there is any suggestion that QoL improves more quickly in patients who complete treatment earlier. From a review of the literature on QoL measures for tuberculosis, it appears that sample sizes are often based on a prospective cohort design, giving a projected sample size of around 100-200 patients, we are confident that the TB PRACTECAL-PRO will recruit this number.

For survey completion, we aim to recruit 54 patients in the investigational arms and 54 patients in the standard of care arm, across the three countries; 108 patients in total. All patients (interventional arm and standard therapy) will complete measures at baseline, three months, six months, and twelve months. Where a recruited patient is discontinued from the trial, we will recruit an additional participant to achieve our intended sample at baseline of at least 54 investigational-arm patients and 54 standard of care patients across all sites. If numbers are likely to exceed this, we aim to keep recruiting to build a larger cohort.

Survey data from 108 healthy controls from the general population in the three study countries will be collected at one timepoint only, matched as closely as possible to the age and sex profile of trial patients. Each healthy control will be screened for TB symptoms using a symptom screening tool outlined in trial standard operating procedures; only those screen-negative will participate. For those screen-positive, we will offer further investigation and treatment using established programmatic protocols. Additionally, we will ask each potential healthy control to tell the investigator if they consider themselves generally healthy and with no significant illnesses. Prospective participants reporting any health problems will also be excluded from the sub-study.

To explore more thoroughly patient experiences across the full range of QoL scores and understand the effects of and tolerance to novel TB treatments, we will use purposive sampling to invite intervention arm participants to take part in an in-depth interview. We aim to complete up to 54 interviews across the three countries (i.e. 18 per country). Selection will be based on the responses to baseline survey questionnaires; we will select patients with scores indicating a very poor QoL, those with QoL scores in the mid-range, and those with scores indicating a very high QoL.

We will seek to interview a balance of men and women, with a range of ages across all trial sites, and aim for equal numbers of patients across the different intervention arms. We aim to select an equal

number of participants from each of the three trial treatment regimens at each time point while also allowing some flexibility should one of the investigational arms close early. Previous experience of similar studies has established sample size as around 12 interviews as a working figure for homogenous group selection [35]. All in-depth interviews will be conducted in the local language, audio recorded and transcribed verbatim, with voluntary informed consent, in a private setting within outpatient clinics during scheduled visits. All interviews will be translated into English by local translators.

Participants

Sub-study participants all have MDR-TB and will have been recruited from the main PRACTECAL study. As part of existing trial procedures, participants will be invited to take part voluntarily using an information sheet and consent form about the purpose of the study in their native language. Participants will be informed of their right to withdraw from the study at any time and the limits of confidentiality will be made explicit in the information sheet. We will conduct in-depth interviews at three timepoints during participation in the trial: 1) at or around baseline; 2) 3-6 months after therapy in the trial; and 3) 12 months into the programme, i.e. after treatment has been completed. Recruitment to in-depth interviews will close when data saturation occurs; that is when no new information is being generated from subsequent interviews [36].

Instruments

Surveys

The SGRQ, a disease specific 50-item questionnaire scored in three domains, has been shown to be an effective tool for measuring the impact of airway-obstructing disease on QoL, and has been used to evaluate QoL for TB as well as for other respiratory diseases [34]. A generic health related QoL tool, the SF-12, is shorter than the SGRQ and was originally designed to reduce respondent burden when completing QoL surveys for people with chronic conditions, while still achieving minimum standards of precision for purposes of group comparisons involving multiple health dimensions [37]. Previously translated SGRQ are available for use in Belarus and South Africa, with two translated questionnaires for Karakalpak and Uzbek required. We will also carry out quantitative data collection using the SGRQ and SF-12 questionnaires in Karakalpakstan, Uzbekistan, by translating questionnaires into Karakalpak. The SF-12 is already available in English, Russian, Sesotho, and Zulu, with two translated questionnaires for Karakalpak and Uzbek.

By using the SGRQ and SF12 we aim to evaluate whether both disease-specific and general health related QoL scores improve in investigational arm patients, from baseline to successful completion of treatment. We hypothesise that QoL scores in both investigational arm and standard-of-care patients will be worse than those of healthy controls at baseline. By using these measures, we will be adding to the available data on QoL in patients being treated for TB and will contribute data to their utility in TB clinical trials.

For survey tools not available in the local language, certified translations will be obtained by working in collaboration with survey developers using an agreed cognitive debriefing protocol with a small number of patients receiving TB therapy. Local clinic workers will be trained to use questionnaires prior to the study, allowing for pretesting of tools. Data quality control and cleaning will be done in real time and feedback and follow up supervision will take place weekly.

Interviews

Topic guides have been developed from the results of a previously conducted literature review [5,6 18,19,20], also including questions arising from survey results. Topic areas include general health perceptions, physical health, somatic sensation or pain, side effects of drugs, benefits of treatment, hassles of therapy etc. Topic guides will be pretested [38].

In-depth interviews will be undertaken by the trial Principal Investigator and a locally trained researcher. Where possible interviews will be conducted in participants' own native languages, but where this is not feasible, interviews will be done in English, with simultaneous translation. Interpreters will be trained and checked for proficiencies to support the Principal Investigator and locally-trained researchers. All researchers will document field notes during fieldwork, detailing insights and observations that develop over time and through repeated analysis of events, activities, and interactions. This aims to enhance understanding of data collected through in-depth interviews, increasing the strength of results [39].

Data analysis

In analysing our data, objectives include:

- comparing baseline scores between trial patients (all investigational arm patients, plus standard-of-care patients) with healthy controls.
- assessing changes in scores over time in patients in intervention arms and patients in the standard-of-care arm.
- assessing the utility of SGRQ and SF-12 instruments in a TB clinical trial.
- Using qualitative data to more fully understand patient experiences of a shortened trial treatment regimen.

Quantitative data

Data will be scored using the developers' scoring manuals. We recognise that it is likely there will not be adequate power to formally detect any differences in SGRQ and SF12 scores between those receiving investigational treatments and those receiving standard of care overtime, however we aim to carry out a graphical exploration of group trajectories, plotting means and 95% confidence intervals by group at each time point. This will enable us to explore whether there is any suggestion that QoL improves more quickly in patients who complete treatment earlier.

Qualitative data

Transcripts will be analysed thematically, aiming to identify and explain patterns in the data [40]. Field notes made throughout the fieldwork period will be used to guide data analysis. Transcribed interview data will be broken into units of meaning (i.e. a word, phrase, sentence or paragraph) and open or tentative codes will be applied to those units. Axial coding will be used to compare codes across the dataset to identify the relationships between them and to derive core codes. Selective coding will then be undertaken whereby the core codes will be repeatedly applied to transcripts leading to identification and development of latent patterns and themes. Negative cases (i.e. data that challenges the emerging analysis) will be examined in order to test emerging themes and to explain why these cases are different [39].

A coding dictionary and analytic memos will be developed and scrutinized by a minimum of two team members to enhance analytic credibility. Selected anonymised interview excerpts or case studies will be drawn out to ensure the individual 'stories' are not lost and to explore how the themes inter-relate between and within cases [41].

Discussion

Effective treatment for MDR/XDR-TB is urgently needed, to address the epidemic in countries participating in this trial and sub-study as well as elsewhere. It is also critical to understanding patient perspectives on treatment tolerability and the impact treatments can have on QoL, in order to assess the potential of new treatments on offer. There is increasing recognition that clinical trials should capture patients' perspectives, and that this should be given as much emphasis as biomedical evidence

in guiding treatment decisions [9,10,13,18]. The results of our sub-study will also give insights about the benefits and risks of treatment through greater understanding of participant opinions and experience, which might otherwise be overlooked. The methods used here will help assess patient perspectives, potentially demonstrating how patient priorities can be evaluated in complex trial intervention. Adding patient perspectives is beneficial to supporting licensing claims for new medicines and to influence the development of health policy, including decisions about the cost-effectiveness of treatment, [11]. Finally, results of this study will add evidence helping to better understand the validity of survey tools used to measure QoL for people living with and treated for tuberculosis.

Ethics and dissemination

The study will be conducted according to the ethical principles as defined in the Declaration of Helsinki. The protocol and corresponding documents were reviewed and approved by the MSF Ethics Review Board, reference number 1541b. Local ethical approval has been obtained from relevant agencies in each study setting. In South Africa, this includes PharmaEthics, University of Witwatersrand Human Research Ethics Committee; in Uzbekistan, the Ethical Committee of the Ministry of Health of the Republic of Uzbekistan; in Belarus, the Ethics Committee of the State Institution Republican Scientific and Practical Centre of Pulmonology and Tuberculosis, and the Centre of Expertise for Testing in Healthcare.

Request for consent for participants to join the sub-study will follow their agreement to join the wider TB-PRACTECAL trial. Information given, and informed consent processes will be similar across study sites. Participation in PRACTECAL-PRO is optional for patients who have already consented to the main TB-PRACTECAL trial, and consent for the sub-study is obtained in addition to that for the main trial.

Printed and electronic versions of the final report will be provided to all partners involved in this project. A meeting will be held with participants to discuss the emergent findings and to gain their feedback and thoughts on these. A study manuscript will be produced and submitted for publication in a peer reviewed scientific journal, and authorship of any publication will be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as defined by the International Committee of Medical Journal Editors (ICMJE).

Discussions will be held with national ministries of health, MSF trial team contacts and coordination teams regarding the influence of study findings on future programme activities. Research methodology and results will also be presented at scientific conferences.

Author Contributions

B. E. Stringer is the Principal Investigator of the study, has contributed to concept and protocol development and is responsible for its implementation. Professor K Lowton is Co-Investigator, and has contributed to conceptualisation and protocol development with responsibility for supervision of quantitative data collection and analysis of the PRO sub-study. Dr Bern-Thomas Nyang'wa is Chief Investigator and the sponsor's representative for the TB-PRACTECAL trial, and defined study scope, contributed to protocol development and sign-off. N. James is a Research Associate for the TB-PRACTECAL trial and contributed to review and finalisation of the manuscript.

Funding statement

This work was supported by Médecins sans Frontières.

Data Statement

Data will be made available in line with MSF data sharing policy.

Competing interests statement

There are no known conflicts of interest.

Acknowledgements

Emma Veitch, freelance medical editor for MSF, UK, provided editorial assistance and her work was funded by MSF UK.

Professor Kevin Schwartzman, Director, Respiratory Division, McGill University and McGill University Health Centre peer reviewed the study protocol.

Dr Heidi Lempp, Reader in Medical Sociology, Faculty of Life Sciences & Medicine, Kings College London, peer reviewed the study protocol

Professor Elizabeth Allen, Head of Medical Statistic Department, London School of Hygiene and Tropical Medicine contributed to the statistical analysis component of the study protocol.

Paul W. Jones, Frances H. Quirk, Chloë M. Baveystock, Department of Medicine, St. George's Hospital Medical School, London, United Kingdom, developed the SGRQ.

We would like to thank Principal Investigators at each site for overseeing implementation:
Dr Varvara Solodovnikova, Republican Research and Practical Centre for Pulmonology and Tuberculosis, Belarus
Professor Parpieva Nargiza, Country Principal Investigator, Republican Specialised Scientific-Practical Medical Centre of Tuberculosis And Pulmonology, Tashkent, Uzbekistan
Dr Liverko Irinve, Republican Specialised Scientific-Practical Medical Centre for Phthisiology and Pulmonology of the Republic of Uzbekistan, Tashkent, Uzbekistan
Dr Tigay Zinaida, Republican TB Hospital 2, Nukus, Uzbekistan
Dr Mohammed Rassool, Wits Health Consortium CHRU, Helen Joseph Hospital, South Africa
Dr Ronelle Moodliar, THINK: Tuberculosis & HIV Investigative Network, Doris Goodwin and Don McKenzie Hospitals, South Africa

We would also like to thank those involved in the cognitive debriefing work towards the SGRQ translations.

References

[1] World Health Organization, Global Tuberculosis Report 2019. 2019.
[2] WHO, “Drug resistant- TB, surveillance and response,” J. Chem. Inf. Model., vol. 53, no. 9, pp. 1689–1699, 2013.
[3] J. Hughes, G. Brigden, B. Nyang’wa, F. Varaine, J. Hughes, and M. Rich, “Principles for designing future regimens for multidrug-resistant tuberculosis Principles for designing future regimens for multidrug- resistant tuberculosis,” Bull. WHO. 2014, 92(1), 68–74. doi:10.2471/BLT.13.122028.
[4] Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF *et al*. Lancet. 2018 Sep 8;392(10150):821-834. doi:10.1016/S0140-6736(18)31644-1
[5] M. Bauer, A. Leavens, and K. Schwartzman, “A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life,” Qual. Life Res., vol. 22, no. 8, pp. 2213–2235, 2013.
[6] C. “Fitzpatrick Floyd, K.,” C. Fitzpatrick, and K. Floyd, “A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis,” Pharmacoeconomics, vol. 30, no. 1, p. 63–80. doi: 10.2165/11595340–000000000–00000., 2012.

[7] E. Pontali, A. Matteelli, and G. B. Migliori, "Drug-resistant tuberculosis," Curr. Opin. Pulm. Med., vol. 19, no. 3, pp. 266–272, 2013.
[8] M. Wolpert, J. Jacob, E. Napoleone, A. Whale, A. Calderon, and J. Edbrooke-Childs, Child-and Parent-reported Outcomes and Experience from Child and Young People's Mental Health Services 2011–2015, no. December. 2016.
[9] M. Monaghan, R. E. Sanders, K. P. Kelly, F. R. Cogen, and R. Streisand, "Using Qualitative Methods to Guide Clinical Trial Design: Parent Recommendations for Intervention Modification in Type 1 Diabetes," J. Fam. Psychol., 2011.
[10] J. Neale and J. Strang, "Blending qualitative and quantitative research methods to optimize patient reported outcome measures (PROMs)," Addiction, vol. 110, no. 8, pp. 1215–1216, 2015.
[11] Fallowfield, L. (1990). Human horizons series. The quality of life: The missing measurement in health care. Souvenir Press.
[12] D. Kyte et al., "Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols," PLoS One, 2014. 15;9(10):e110229. doi: 10.1371/journal.pone.0110229.
[13] C. Sjödahl Hammarlund, M. H. Nilsson, M. Idvall, S. R. Rosas, and P. Hagell, "Conceptualizing and prioritizing clinical trial outcomes from the perspectives of people with Parkinson's disease versus health care professionals: A concept mapping study," Qual. Life Res., 2014. 23(6):1687-700. doi: 10.1007/s11136-013-0614-3.
[14] R. D. McLeod, L. D, Coon, C. D. Martin, S. A, Fehnel, S. E & Hays, "and Emerging Methods," Pharmacoeconomics Outcomes Res. - Expert Rev., vol. 11, no. 2, pp. 163–169, 2012.
[15] RAND, "36, 12 and 6 -Item Short Form Survey Scoring Instructions | RAND," 2012.
[16] Jones. P.W., "Patients original English version." St. Georges. Questionnaire, vol. 44, no. July, pp. 1–10, 2010.
[17] L. Daudey et al., "Health status in COPD cannot be measured by the St George's Respiratory Questionnaire alone: An evaluation of the underlying concepts of this questionnaire," Respir. Res., vol. 11, pp. 1–7, 2010.
[18] C. Holmberg, J. J. Karner, J. Rappenecker, and C. M. Witt, "Clinical trial participants' experiences of completing questionnaires: A qualitative study," BMJ Open, 2014. 24;4(3):e004363. doi: 10.1136/bmjopen-2013-004363.
[19] J. Brown, S. Capocci, C. Smith, S. Morris, I. Abubakar, and M. Lipman, "Health status and quality of life in tuberculosis," Int J Infect Dis, vol. 32, pp. 68–75, 2015.
[20] N. Guo, F. Marra, and C. A. Marra, "Measuring health-related quality of life in tuberculosis: A systematic review," Health Qual. Life Outcomes, vol. 7, pp. 1–10, 2009.
[21] D. Chamla, "The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China.," Int. J. Tuberc. Lung Dis., vol. 8, no. 9, pp. 1100–1106, 2004.
[22] N. N. Hansel, A. W. Wu, B. Chang, and G. B. Diette, "Quality of life in tuberculosis: Patient and provider perspectives," Qual. Life Res., vol. 13, no. 3, pp. 639–652, 2004.
[23] G. P. Maguire et al., "Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting," Int. J. Tuberc. Lung Dis., vol. 13, no. 12, pp. 1500–1506, 2009.
[24] J. Bieberly and J. Ali, "Treatment adherence of the latently infected tuberculosis population (Post-Katrina) at Wetmore TB Clinic, New Orleans, USA," Int. J. Tuberc. Lung Dis., 2008. Oct;12(10):1134-8.
[25] Stringer, B et al. (2016). 'They prefer hidden treatment': anti-tuberculosis drug-taking practices and drug regulation in Karakalpakstan. *The International Journal of Tuberculosis and Lung Disease*, Volume 20, Number 8, 1 August 2016, pp. 1084-1090(7).
[26] Horter, S et al. (2016). Where there is hope: a qualitative study examining patients' adherence to multi-drug resistant tuberculosis treatment in Karakalpakstan, Uzbekistan. *BMC Infect Dis*.16:362.
[27] Engaging communities in tuberculosis research: The experience of the TB-PRACTECAL trial - The BMJ. https://blogs.bmj.com/bmj/2018/11/09/engaging-communities-tuberculosisresearch-experience-practecal-trial/ (accessed 16 Dec 2019).
[28] Babaniyazov A, Nyang'wa BT, Pardington N, et al. 'Trial and Error' operational reflections on the set-up of a community engagement programme for a phase ii/iii clinical trial to identify new MDR-TB treatments in Uzbekistan. In: Médecins Sans Frontières Scientific Day South Asia (not peer reviewed). 2016. (doi:10.7490/F1000RESEARCH.1112000.1)

[29] Wharton-Smith A, Gray N, Stringer B et al. Optimising recruitment to a TB clinical trial in Uzbekistan [version 1; not peer reviewed]. F1000Research 2020, 9:466 (poster) (doi:10.7490/f1000research.1117924.1)
[30] B. Gandek, J. E. Ware, and N. K. Aaronson et al., "Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries:\rresults from the IQOLA Project. International Quality of Life Assessment.," J. Clin. Epidemiol., vol. 51, no. 11, pp. 1171–1178, 1998.
[31] A. R. Patel et al., "The validity of the SF-12 and SF-6D instruments in people living with HIV/AIDS in Kenya," Health Qual. Life Outcomes, vol. 15, no. 1, pp. 1–9, 2017.
[32] C. Hayes, N. Bhandari, N. Kathe, and N. Payakachat, "Reliability and Validity of the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2) in Adults with Non-Cancer Pain," Healthcare, vol. 5, no. 2, p. 22, 2017.
[33] B. Roberts, J. Browne, K. F. Ocaka, T. Oyok, and E. Sondorp, "The reliability and validity of the SF-8 with a conflict-affected population in northern Uganda," Health Qual. Life Outcomes, vol. 6, pp. 1–10, 2008.
[34] J. G. Pasipanodya et al., "Using the St. George Respiratory Questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis," Chest, vol. 132, no. 5, pp. 1591– 1598, 2007.
[35] G. Guest, A. Bunce, and L. Johnson, "How Many Interviews Are Enough?," Field methods, vol. 18, no. 1, pp. 59–82, 2006.
[36] J. Green and N. Thorogood, Principles and approaches in qualitative research. 3rd ed. Sage, 2014.
[37] J. E. Ware, M. Kosinski, S. D. Keller, I. QualityMetric, H. New England Medical Center, and L. Health Assessment, "SF-12 : how to score the SF-12 physical and mental health summary scales," no. April, 2002.
[38] Hurst, S et al. (2015). Pretesting Qualitative Data Collection Procedures to Facilitate Methodological Adherence and Team Building in Nigeria. *Int J Qual Methods*.14:53-64.
[39] K. Charmaz, Constructing Grounded Theory: A Practical Guide Through Qualitative Analysis, 1st ed. Sage, 2006.
[40] E. H. Bradley, L. A. Curry, and K. J. Devers, "Qualitative Data Analysis for Health Services Research: Developing Taxonomy , Themes , and Theory," pp. 1758–1772, 2007.
[41] Braun, V. and Clarke, V. (2006) Using thematic analysis in psychology. Qualitative Research in Psychology, 3 (2). pp. 77-101. ISSN 1478-0887.

BMJ Open

Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods sub-study protocol, TB PRACTECAL-PRO

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043954.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Dec-2020
Complete List of Authors:	Stringer, Beverley; Médecins Sans Frontières, Manson Unit Lowton, Karen ; University of Sussex, Department of Sociology James, Nicola ; Médecins Sans Frontières, Manson Unit Nyang'wa, Bern-Thomas; Médecins Sans Frontières, Manson Unit; London School of Hygiene & Tropical Medicine, Clinical research Department
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Research methods, Public health
Keywords:	Tuberculosis < INFECTIOUS DISEASES, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protocol manuscript

Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods sub-study protocol, TB PRACTECAL-PRO

Running title: Patient-reported outcomes in TB PRACTECAL-PRO

Authors: Beverley Stringer[1], Karen Lowton[2], Nicola James[1], Bern-Thomas Nyang'wa[1, 3]

Affiliations: 1. Manson Unit, Médecins Sans Frontières, London, UK

2. Department of Sociology, University of Sussex, Brighton, UK

3. Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK

Corresponding author: Beverley Stringer; beverley.stringer@london.msf.org

Keywords: patient-reported outcomes, quality of life, qualitative, MDR-TB, clinical trial

Word count: 3258

Abstract

Introduction: People living with multidrug-resistant tuberculosis (MDR-TB) currently have few options for effective treatment and cure. Regimens that are available are toxic, may involve injections and take up to two years to complete treatment, with success rates as low as 50%. The TB-PRACTECAL trial is evaluating shorter, more tolerable regimens of oral drugs; we detail the sub-study within this trial, PRACTECAL-PRO, which aims to evaluate patient experiences and perspectives on treatment, to understand outcomes more fully.

Methods and analysis: We are conducting a mixed-methods evaluation within both investigational and standard-of-care arms within the TB-PRACTECAL trial, using sequential quality of life (QoL) surveys and in-depth interviews. Data collection involves the Short Form 12 (SF-12) and St George's Respiratory Questionnaire (SGRQ), collected at up to four fixed timepoints, from baseline, to up to 12 months later. Healthy volunteers will be surveyed to establish locally-relevant controls. We will also purposively sample participants for qualitative data collection and analysis, to provide rich explanation of quality of life scores. The study will be implemented in all six TB-PRACTECAL study sites in Uzbekistan, South Africa and Belarus. QoL surveys will be scored and analysed according to SF-12 and SGRQ developers' manuals. Differences between scores at baseline and later timepoints will be evaluated as well as graphical exploration of group score trajectories of investigational and standard of care arms.

Ethics and dissemination: Ethics approval was obtained from the Médecins Sans Frontières (MSF) Ethics Review Board. Local ethics approval has been obtained in Uzbekistan, Belarus and South Africa. Results of the sub-study will be shared with local health authorities, the World Health Organisation and submitted for publication in a peer-reviewed journal.

Protocol version 2.0 of 1st June 2019
Registration: Clinicaltrials.gov, NCT03942354

ARTICLE SUMMARY

Strengths and limitations of this study

- This study aims to be one of the first randomised TB trials to incorporate patient perspectives on their experience of investigational treatments and compare QoL scores with standard of care participants and healthy controls.
- Analysis includes in-depth interviews alongside standardised quality of life surveys.
  The study will detail how a novel regimen is experienced in diverse populations and contexts, covering some of the most challenging scenarios for multidrug-resistant tuberculosis (MDR-TB) treatment.
- Our findings will enable description of the utility of SF-12 and SGRQ survey tools in populations living with tuberculosis.
- Limitations of the mixed-methods sub-study include the relatively small sample size

MAIN TEXT

Introduction

TB global epidemiology

Tuberculosis remains the deadliest infectious disease globally, with mortality estimates exceeding those for both HIV and malaria. The emergence of MDR-TB, defined as disease caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, has complicated global efforts to control the epidemic. Approximately 500,000 cases of MDR-TB occur globally each year, representing nearly 5% of the world's annual TB burden [1]. Currently, around 20% of patients diagnosed with MDR-TB are on treatment, and there is an urgent need to scale up treatment programmes [2]. Scale-up is being severely hampered by financial, political, logistical, and technical obstacles, with one of the most important challenges being the nature of current standard of care regimens [3]. Current regimens used to treat MDR-TB have poor efficacy; the most recent meta-analysis of treatment outcomes for pulmonary MDR-TB suggested that only 61% of patients had successful outcomes, 8% had failure or relapse, and 14% died [4]. Low treatment effectiveness, combined with high costs and implementation difficulties are preventing many national TB programmes from offering treatment for MDR-TB [5]. This in turn fuels the spread of further MDR-TB infections [6]. There is a global need for an improved treatment regimen for MDR-TB that is efficacious, safe, tolerable, and that can be implemented in a variety of epidemiological settings. Given the high rates of HIV co-infection among certain populations of patients with MDR-TB [7], it is imperative that patients with HIV be included in any evaluations of new treatment regimens.

Patient reported outcome measures

Patient-reported outcomes (PROs) are useful in evaluating the effectiveness of many medical interventions from the patient's perspective, which then can help fulfill critical considerations, such as shared decision-making, and ensuring greater user satisfaction with services [8]. By using PROs in the PRACTECAL study we will be able to assess participant progress and clinical outcomes with regards to quality of life. Most PROMs used in clinical trials currently use quantitative measures only. Questionnaire-style PROMs, or QoL measures, can be generically focused, (e.g. the Short-Form (SF) 36, SF-12, and SF-6) [9] or condition/disease-specific (e.g. the St George's Respiratory Questionnaire, SGRQ), [10] a respiratory QoL instrument formulated for use in chronic obstructive pulmonary disease (COPD) [11]. Routine use of patient-reported outcomes to inform healthcare policy for a range of long-term conditions shows that use of both qualitative and quantitative methods of capturing PROs is preferable [12]. We anticipate that adding participant in-depth interviews to QoL surveys will enrich our understanding from a patient perspective on the acceptability of this novel treatment and will offer detail at a country specific level.

Quality of life measures in tuberculosis

Currently, work on developing QoL measures specific to TB is in its infancy. However, some meaningful data has been collected, and this has informed proposals that at least one PROM used must capture all health-related physical impairment (e.g. not be organ- or system-specific); that PROM's should be able to evaluate psychological morbidity, an issue especially pertinent for patients with MDR-TB; and that PROM's should be culturally and linguistically appropriate for the study population and to include evaluation of social role limitations and stigma [13].

A systematic review of the impact of TB and the effects of treatment on patients' QoL showed that the SF-36 was the most commonly-used measure to capture patient-reported outcomes [14]. In China, SF-36 scores of patients diagnosed with TB indicated poor quality of life before treatment, but these significantly improved during treatment [15]. Being mindful of participant burden we chose to use the

SF12 which accurately reproduces the two summary component scores (I.e. physical and mental health) of the SF36 [16]. Additionally, the qualitative interviews will explore further these domains.

The SGRQ appears to be an effective tool to assess morbidity-related QoL during treatment for people who live with TB, alongside measures of lung function, clinical improvements, chest X-ray findings, and adverse events [17]. QoL measures have also been used specifically to test impairment after microbiological cure, showing the importance of such measures in assessing health outcomes that are not apparent through biological measurement [18]. Both physical and QoL measures demonstrate that TB appears to lead to residual disability among ambulatory patients in whom treatment outcomes may have been considered successful [13,18].

Qualitative PRO measures in Tuberculosis

Using qualitative methods to assess QoL for people who live with TB will include examining areas such as general health perceptions, somatic sensation or pain, psychological health, spiritual well-being, and physical, social and role functioning [13]. Other published qualitative work in relation to patient perspectives has examined perceptions of self-administered TB treatment and adherence [19,20]. However, there is less known about trial participant experiences and quality of life using qualitative data for a new TB regimen. We hope this adds to emerging work, for example on children and their care givers acceptance of a fixed dose regimen for TB in South Africa [21].

Design of the TB-PRACTECAL trial

TB-PRACTECAL is a multicentre, open-label, phase II-III randomised trial evaluating exclusively oral six-month long regimens containing bedaquiline, pretomanid, linezolid only, with moxifloxacin or with clofazimine, for the treatment of microbiologically-confirmed pulmonary MDR-TB and extensively drug resistant (XDR)-TB.

PRACTECAL-PRO is a sub-study of the TB-PRACTECAL trial and aims to answer questions relating to adult patients' quality of life while taking novel TB treatment in Uzbekistan, South Africa and Belarus.

Objectives of PRACTECAL-PRO

The TB-PRACTECAL trial assumes that even if the investigational arms show non-inferior efficacy and safety, as compared to standard of care, patients will likely prefer shorter, exclusively oral regimens with a lower pill count. We hypothesise that QoL scores in both investigational arm and standard-of-care patients will be worse than those of healthy controls at baseline. By using these measures, we will be adding to the available data on QoL in patients being treated for TB and will contribute data to their utility in TB clinical trials.

In the sub-study we will therefore explore these assumptions through the following objectives:

Primary objectives

1. To assess quantitatively QoL measures for patients within the trial, from baseline to 12 months, including those treated in investigational arms as well as the standard of care arm.
2. To describe qualitatively patient satisfaction and experience with trial treatments in the investigational arms.

Secondary objective

1. To understand what factors enable a novel treatment regimen to be tolerated or rejected by patients.
2. To evaluate utility of the SGRQ and SF-12 questionnaires, and qualitative methods within TB clinical trials.

Methods and Analysis

Overall study design

PRACTECAL-PRO uses a mixed-methods approach, with QoL surveys and in-depth interviews being employed at different time points over the twelve-month intervention period. It is expected that the qualitative interviews will allow for a more in-depth explanation of the quantitative survey data. QoL is assessed quantitatively within all trial arms, from baseline to twelve months with selected participants being interviewed at baseline, three to six and at twelve months.

Patient and public involvement

Patients and, where feasible, the wider community have been engaged in setup and implementation stages of the main TB-PRACTECAL trial [22,23,24]. Tools not available in the local languages are not only translated but also undergo cognitive debriefing by the teams and patients locally.

Settings

TB-PRACTECAL, and the PRACTECAL-PRO sub-study is being conducted in six sites, in three countries; Uzbekistan, South Africa and Belarus. In Uzbekistan, the trial is taking place in Tashkent City and six rayons (districts) in Karakalpakstan, Western Uzbekistan, specifically Nukus City, Nukus, Takhiatash, Chimbay, Kegeily and Xodjeli rayons. Implementation of the trial in Uzbekistan is being conducted by the Republican Specialised Scientific-Practical Medical Centre for Phthisiology and Pulmonology of the Republic of Uzbekistan. In South Africa, the trial is being conducted in Doris Goodwin and Don McKenzie Hospitals through the Tuberculosis and HIV Investigative Network (THINK), and Helen Joseph Hospital through the University of Witwatersrand's Clinical HIV Research Unit. In Belarus, the trial is taking place in Minsk City and Oblast, implemented by the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis of the Republic of Belarus.

Implementation timelines

The study started recruitment in Belarus in October 2019, is currently recruiting in Karakalpakstan, Uzbekistan and THINK, South Africa. Recruitment completion is expected in mid-2021 and final follow up and results are expected at the end of 2022.

Sampling

With the increasing use of QoL measures in research, historical datasets are now becoming more readily available to help guide sample size estimation and timing of surveys [25,26,27,28,29]. Although there are published studies examining QoL changes for people with TB, most do not inform power calculations. We recognize that it is likely that there will not be adequate power to formally

detect any differences between the SGRQ in those receiving investigational treatments, and those receiving standard of care over time, however we aim to carry out a graphical exploration of group trajectories, plotting means and 95% confidence intervals by group at each timepoint. This will enable us to explore whether there is any suggestion that QoL improves more quickly in patients who complete treatment earlier. From a review of the literature on QoL measures for tuberculosis, it appears that sample sizes are often based on a prospective cohort design, giving a projected sample size of around 100-200 patients, we are confident that the TB PRACTECAL-PRO will recruit this number.

For survey completion, we aim to recruit 54 patients in the investigational arms and 54 patients in the standard of care arm, across the three countries; 108 patients in total. All patients (interventional arm and standard therapy) will complete measures at baseline, three months, six months, and twelve months. Where a recruited patient is discontinued from the trial, we will recruit an additional participant to achieve our intended sample at baseline of at least 54 investigational-arm patients and 54 standard of care patients across all sites. If numbers are likely to exceed this, we aim to keep recruiting to build a larger cohort.

Survey data from 108 healthy controls from the general population in the three study countries will be collected at one timepoint only, matched as closely as possible to the age and sex profile of trial patients. Each site will opportunistically identify participants from the community setting which may include personal contacts and colleagues not working on the PRACTECAL study. The healthy control will be screened for TB symptoms using a symptom screening tool outlined in trial standard operating procedures; only those who screen-negative will participate. For those who screen-positive, we will offer further investigation and treatment using established programmatic protocols. Additionally, we will ask each potential healthy control to tell the investigator if they consider themselves generally healthy and with no significant illnesses. Prospective participants reporting any health problems will also be excluded from the sub-study.

To explore more thoroughly patient experiences across the full range of QoL scores and understand the effects of and tolerance to novel TB treatments, we will use purposive sampling to invite intervention arm participants to take part in an in-depth interview. We aim to complete up to 54 interviews across the three countries (i.e. 18 per country). Selection will be based on the responses to baseline survey questionnaires; we will select patients with scores indicating a very poor QoL, those with QoL scores in the mid-range, and those with scores indicating a very high QoL.

We will seek to interview a balance of men and women, with a range of ages across all trial sites, and aim for equal numbers of patients across the different intervention arms. We aim to select an equal number of participants from each of the three trial treatment regimens at each time point while also allowing some flexibility should one of the investigational arms close early. Previous experience of similar studies has established sample size as around 12 interviews as a working figure for homogenous group selection [30]. All in-depth interviews will be conducted in the local language, audio recorded and transcribed verbatim, with voluntary informed consent, in a private setting within outpatient clinics during scheduled visits. All interviews will be translated into English by local translators.

Participants

Sub-study participants all have MDR-TB and will have been recruited from the main PRACTECAL study. As part of existing trial procedures, participants will be invited to take part voluntarily using an information sheet and consent form about the purpose of the study in their native language. Participants will be informed of their right to withdraw from the study at any time and the limits of confidentiality will be made explicit in the information sheet. We will conduct in-depth interviews at

three timepoints during participation in the trial: 1) at or around baseline; 2) 3-6 months after therapy in the trial; and 3) 12 months into the programme, i.e. after treatment has been completed. Recruitment to in-depth interviews will close when data saturation occurs; that is when no new information is being generated from subsequent interviews [31].

Instruments

Surveys

The SGRQ, a disease specific 50-item questionnaire scored in three domains, has been shown to be an effective tool for measuring the impact of airway-obstructing disease on QoL, and has been used to evaluate QoL for TB as well as for other respiratory diseases [29]. A generic health related QoL tool, the SF-12, is shorter than the SGRQ and was originally designed to reduce respondent burden when completing QoL surveys for people with chronic conditions, while still achieving minimum standards of precision for purposes of group comparisons involving multiple health dimensions [32]. Previously translated SGRQ are available for use in Belarus and South Africa, with two translated questionnaires for Karakalpak and Uzbek required. We will also carry out quantitative data collection using the SGRQ and SF-12 questionnaires in Karakalpakstan, Uzbekistan, by translating questionnaires into Karakalpak. The SF-12 is already available in English, Russian, Sesotho, and Zulu, with two translated questionnaires for Karakalpak and Uzbek.

For survey tools not available in the local language, certified translations will be obtained by working in collaboration with survey developers using an agreed cognitive debriefing protocol with a small number of patients receiving TB therapy. Local clinic workers will be trained to use questionnaires prior to the study, allowing for pretesting of tools. Data quality control and cleaning will be done in real time and feedback and follow up supervision will take place weekly.

Interviews

Topic guides have been developed from the results of a previously conducted literature review [5,6,13,14,33], also including questions arising from survey results. Topic areas include general health perceptions, physical health, somatic sensation or pain, side effects of drugs, benefits of treatment, hassles of therapy etc. Topic guides will be pretested [34].

In-depth interviews will be undertaken by the trial Principal Investigator and a locally trained researcher. Where possible interviews will be conducted in participants' own native languages, but where this is not feasible, interviews will be done in English, with simultaneous translation. Interpreters will be trained and checked for proficiencies to support the Principal Investigator and locally-trained researchers. All researchers will document field notes during fieldwork, detailing insights and observations that develop over time and through repeated analysis of events, activities, and interactions. This aims to enhance understanding of data collected through in-depth interviews, increasing the strength of results [35].

Data analysis

In analysing our data, we will:

- compare baseline scores between trial patients (all investigational arm patients, plus standard-of-care patients) with healthy controls.
- assess changes in scores over time in patients in intervention arms and patients in the standard-of-care arm.
- assess the utility of SGRQ and SF-12 instruments in a TB clinical trial.

- Use qualitative data to more fully understand patient experiences of a shortened trial treatment regimen.

Quantitative data

Data will be scored using the developers' scoring manuals.

Qualitative data

Transcripts will be analysed thematically, aiming to identify and explain patterns in the data [36]. Field notes made throughout the fieldwork period will be used to guide data analysis. Transcribed interview data will be broken into units of meaning (i.e. a word, phrase, sentence or paragraph) and open or tentative codes will be applied to those units. Axial coding will be used to compare codes across the dataset to identify the relationships between them and to derive core codes. Selective coding will then be undertaken whereby the core codes will be repeatedly applied to transcripts leading to identification and development of latent patterns and themes. Negative cases (i.e. data that challenges the emerging analysis) will be examined in order to test emerging themes and to explain why these cases are different [35].

A coding dictionary and analytic memos will be developed and scrutinized by a minimum of two team members to enhance analytic credibility. Selected anonymised interview excerpts or case studies will be drawn out to ensure the individual 'stories' are not lost and to explore how the themes inter-relate between and within cases [37].

The results of our sub-study will give insights about the benefits and risks of treatment through greater understanding of participant opinions and experience, which might otherwise be overlooked. The methods used here will help assess patient perspectives, potentially demonstrating how patient priorities can be evaluated in complex trial intervention. Adding patient perspectives is beneficial to supporting licensing claims for new medicines and to influence the development of health policy, including decisions about the cost-effectiveness of treatment [38].

Ethics and dissemination

The study will be conducted according to the ethical principles as defined in the Declaration of Helsinki. The protocol and corresponding documents were reviewed and approved by the MSF Ethics Review Board, reference number 1541b. Local ethical approval has been obtained from relevant agencies in each study setting. In South Africa, this includes PharmaEthics, University of Witwatersrand Human Research Ethics Committee; in Uzbekistan, the Ethical Committee of the Ministry of Health of the Republic of Uzbekistan; in Belarus, the Ethics Committee of the State Institution Republican Scientific and Practical Centre of Pulmonology and Tuberculosis, and the Centre of Expertise for Testing in Healthcare.

Request for consent for participants to join the sub-study will follow their agreement to join the wider TB-PRACTECAL trial. Information given, and informed consent processes will be similar across study sites. Participation in PRACTECAL-PRO is optional for patients who have already consented to the main TB-PRACTECAL trial, and consent for the sub-study is obtained in addition to that for the main trial.

Printed and electronic versions of the final report will be provided to all partners involved in this project. A meeting will be held with participants to discuss the emergent findings and to gain their feedback and thoughts on these. A study manuscript will be produced and submitted for publication in a peer reviewed scientific journal, and authorship of any publication will be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as defined by the International Committee of Medical Journal Editors (ICMJE).

Discussions will be held with national ministries of health, MSF trial team contacts and coordination teams regarding the influence of study findings on future programme activities. Research methodology and results will also be presented at scientific conferences.

Author Contributions
B. E. Stringer is the Principal Investigator of the study, has contributed to concept and protocol development and is responsible for its implementation. Professor K Lowton is Co-Investigator, and has contributed to conceptualisation and protocol development with responsibility for supervision of quantitative data collection and analysis of the PRO sub-study. Dr Bern-Thomas Nyang'wa is Chief Investigator and the sponsor's representative for the TB-PRACTECAL trial, and defined study scope, contributed to protocol development and sign-off. N. James is a Research Associate for the TB-PRACTECAL trial and contributed to review and finalisation of the manuscript.

Funding statement
This work was supported by Médecins sans Frontières.

Data Statement
Data will be made available in line with MSF data sharing policy.

Competing interests statement
There are no known conflicts of interest.

Acknowledgements

Emma Veitch, freelance medical editor for MSF, UK, provided editorial assistance and her work was funded by MSF UK.

Professor Kevin Schwartzman, Director, Respiratory Division, McGill University and McGill University Health Centre peer reviewed the study protocol.

Dr Heidi Lempp, Reader in Medical Sociology, Faculty of Life Sciences & Medicine, Kings College London, peer reviewed the study protocol

Professor Elizabeth Allen, Head of Medical Statistic Department, London School of Hygiene and Tropical Medicine contributed to the statistical analysis component of the study protocol.

Paul W. Jones, Frances H. Quirk, Chloë M. Baveystock, Department of Medicine, St. George's Hospital Medical School, London, United Kingdom, developed the SGRQ.

We would like to thank Principal Investigators at each site for overseeing implementation:
Dr Varvara Solodovnikova, Republican Research and Practical Centre for Pulmonology and Tuberculosis, Belarus
Professor Parpieva Nargiza, Country Principal Investigator, Republican Specialised Scientific-Practical Medical Centre of Tuberculosis And Pulmonology, Tashkent, Uzbekistan
Dr Liverko Irinve, Republican Specialised Scientific-Practical Medical Centre for Phthisiology and Pulmonology of the Republic of Uzbekistan, Tashkent, Uzbekistan
Dr Tigay Zinaida, Republican TB Hospital 2, Nukus, Uzbekistan
Dr Mohammed Rassool, Wits Health Consortium CHRU, Helen Joseph Hospital, South Africa
Dr Ronelle Moodliar, THINK: Tuberculosis & HIV Investigative Network, Doris Goodwin and Don McKenzie Hospitals, South Africa

We would also like to thank those involved in the cognitive debriefing work towards the SGRQ translations.

References

[1] World Health Organization, Global Tuberculosis Report 2019. 2019.
[2] WHO, "Drug resistant- TB, surveillance and response," J. Chem. Inf. Model., vol. 53, no. 9, pp. 1689–1699, 2013.
[3] J. Hughes, G. Brigden, B. Nyang'wa, F. Varaine, J. Hughes, and M. Rich, "Principles for designing future regimens for multidrug-resistant tuberculosis Principles for designing future regimens for multidrug- resistant tuberculosis," Bull. WHO. 2014, 92(1), 68–74. doi:10.2471/BLT.13.122028.
[4] Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF et al. Lancet. 2018 Sep 8;392(10150):821-834. doi:10.1016/S0140-6736(18)31644-1
[5] M. Bauer, A. Leavens, and K. Schwartzman, "A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life," Qual. Life Res., vol. 22, no. 8, pp. 2213–2235, 2013.
[6] C. "Fitzpatrick Floyd, K.," C. Fitzpatrick, and K. Floyd, "A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis," Pharmacoeconomics, vol. 30, no. 1, p. 63–80. doi: 10.2165/11595340–000000000–00000., 2012.
[7] E. Pontali, A. Matteelli, and G. B. Migliori, "Drug-resistant tuberculosis," Curr. Opin. Pulm. Med., vol. 19, no. 3, pp. 266–272, 2013.
[8] M. Wolpert, J. Jacob, E. Napoleone, A. Whale, A. Calderon, and J. Edbrooke-Childs, Child-and Parent-reported Outcomes and Experience from Child and Young People's Mental Health Services 2011–2015, no. December. 2016.
[9] RAND, "36, 12 and 6 -Item Short Form Survey Scoring Instructions | RAND," 2012.
[10] Jones. P.W., "Patients original English version." St. Georges. Questionnaire, vol. 44, no. July, pp. 1–10, 2010.
[11] L. Daudey et al., "Health status in COPD cannot be measured by the St George's Respiratory Questionnaire alone: An evaluation of the underlying concepts of this questionnaire," Respir. Res., vol. 11, pp. 1–7, 2010.
[12] J. Neale and J. Strang, "Blending qualitative and quantitative research methods to optimize patient reported outcome measures (PROMs)," Addiction, vol. 110, no. 8, pp. 1215–1216, 2015.
[13] J. Brown, S. Capocci, C. Smith, S. Morris, I. Abubakar, and M. Lipman, "Health status and quality of life in tuberculosis," Int J Infect Dis, vol. 32, pp. 68–75, 2015.
[14] N. Guo, F. Marra, and C. A. Marra, "Measuring health-related quality of life in tuberculosis: A systematic review," Health Qual. Life Outcomes, vol. 7, pp. 1–10, 2009.
[15] D. Chamla, "The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China.," Int. J. Tuberc. Lung Dis., vol. 8, no. 9, pp. 1100–1106, 2004.
[16] Jenkinson et al. (1997) 'A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies?' Journal of Public Health, Volume 19, Issue 2, June 1997, Pages 179–186.
[17] N. N. Hansel, A. W. Wu, B. Chang, and G. B. Diette, "Quality of life in tuberculosis: Patient and provider perspectives," Qual. Life Res., vol. 13, no. 3, pp. 639–652, 2004.
[18] G. P. Maguire et al., "Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting," Int. J. Tuberc. Lung Dis., vol. 13, no. 12, pp. 1500–1506, 2009.
[19] Stringer, B et al. (2016). 'They prefer hidden treatment': anti-tuberculosis drug-taking practices and drug regulation in Karakalpakstan. The International Journal of Tuberculosis and Lung Disease, Volume 20, Number 8, 1 August 2016, pp. 1084-1090(7).
[20] Horter, S et al. (2016). Where there is hope: a qualitative study examining patients' adherence to multi-drug resistant tuberculosis treatment in Karakalpakstan, Uzbekistan. BMC Infect Dis.16:362.
[21] Wademan, D. T. et al. (2019) 'Acceptability of a first-line anti-tuberculosis formulation for children: qualitative data from the SHINE trial,' The International Journal of Tuberculosis and Lung Disease, Volume 23, Number 12, 1 December 2019, pp. 1263-1268(6).

[22] Engaging communities in tuberculosis research: The experience of the TB-PRACTECAL trial - The BMJ. https://blogs.bmj.com/bmj/2018/11/09/engaging-communities-tuberculosisresearch-experience-practecal-trial/ (accessed 16 Dec 2019).
[23] Babaniyazov A, Nyang'wa BT, Pardington N, et al. 'Trial and Error' operational reflections on the set-up of a community engagement programme for a phase ii/iii clinical trial to identify new MDR-TB treatments in Uzbekistan. In: Médecins Sans Frontières Scientific Day South Asia (not peer reviewed). 2016. (doi:10.7490/F1000RESEARCH.1112000.1)
[24] Wharton-Smith A, Gray N, Stringer B et al. Optimising recruitment to a TB clinical trial in Uzbekistan [version 1; not peer reviewed]. F1000Research 2020, 9:466 (poster) (doi:10.7490/f1000research.1117924.1)
[25] B. Gandek, J. E. Ware, and N. K. Aaronson et al., "Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries:\rresults from the IQOLA Project. International Quality of Life Assessment.," J. Clin. Epidemiol., vol. 51, no. 11, pp. 1171–1178, 1998.
[26] A. R. Patel et al., "The validity of the SF-12 and SF-6D instruments in people living with HIV/AIDS in Kenya," Health Qual. Life Outcomes, vol. 15, no. 1, pp. 1–9, 2017.
[27] C. Hayes, N. Bhandari, N. Kathe, and N. Payakachat, "Reliability and Validity of the Medical Outcomes Study Short Form-12 Version 2 (SF-12v2) in Adults with Non-Cancer Pain," Healthcare, vol. 5, no. 2, p. 22, 2017.
[28] B. Roberts, J. Browne, K. F. Ocaka, T. Oyok, and E. Sondorp, "The reliability and validity of the SF-8 with a conflict-affected population in northern Uganda," Health Qual. Life Outcomes, vol. 6, pp. 1–10, 2008.
[29] J. G. Pasipanodya et al., "Using the St. George Respiratory Questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis," Chest, vol. 132, no. 5, pp. 1591– 1598, 2007.
[30] G. Guest, A. Bunce, and L. Johnson, "How Many Interviews Are Enough?," Field methods, vol. 18, no. 1, pp. 59–82, 2006.
[31] J. Green and N. Thorogood, Principles and approaches in qualitative research. 3rd ed. Sage, 2014.
[32] J. E. Ware, M. Kosinski, S. D. Keller, I. QualityMetric, H. New England Medical Center, and L. Health Assessment, "SF-12 : how to score the SF-12 physical and mental health summary scales," no. April, 2002.
[33] C. Holmberg, J. J. Karner, J. Rappenecker, and C. M. Witt, "Clinical trial participants' experiences of completing questionnaires: A qualitative study," BMJ Open, 2014. 24;4(3):e004363. doi: 10.1136/bmjopen-2013-004363.
[34] Hurst, S et al. (2015). Pretesting Qualitative Data Collection Procedures to Facilitate Methodological Adherence and Team Building in Nigeria. Int J Qual Methods.14:53-64.
[35] K. Charmaz, Constructing Grounded Theory: A Practical Guide Through Qualitative Analysis, 1st ed. Sage, 2006.
[36] E. H. Bradley, L. A. Curry, and K. J. Devers, "Qualitative Data Analysis for Health Services Research: Developing Taxonomy , Themes , and Theory," pp. 1758–1772, 2007.
[37] Braun, V. and Clarke, V. (2006) Using thematic analysis in psychology. Qualitative Research in Psychology, 3 (2). pp. 77-101. ISSN 1478-0887.
[38] Fallowfield, L. (1990). Human horizons series. The quality of life: The missing measurement in health care. Souvenir Press.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___2_____
	2b	All items from the World Health Organization Trial Registration Data Set	___Supplementary document ____
Protocol version	3	Date and version identifier	___1 ____
Funding	4	Sources and types of financial, material, and other support	___2_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 9_____
	5b	Name and contact information for the trial sponsor	___2_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___9_____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___NA_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___3-4_____
	6b	Explanation for choice of comparators	___5, 6_____
Objectives	7	Specific objectives or hypotheses	___4-5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___4_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___5_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___2, 6_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___7_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___6_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____NA_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__ NA_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___2, 4-5____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____6_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__6_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__6_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___NA_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__NA_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__NA_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__7-8_____
	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	_NA_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_8_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__8_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__7-8_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__NA_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___NA_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__NA_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_ NA_____
Ethics and dissemination			

Clinicaltrials.gov, NCT03942354

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__NA_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__8_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__9_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__NA_____
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	__NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__9_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__9_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	'PRO Informed Consent Forms_Minsk _v2.0__01June2019'

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

SPIRIT 2013 checklist

Table 1: World Health Organization Trial Registration Data Set

Registry and trial identifying number	Clinicaltrials.gov, NCT03942354, May 8, 2019 (https://clinicaltrials.gov/ct2/show/NCT03942354)
Secondary identifying numbers	MSF 1541a, PE 191022845, WitsHREC 190812, UBZ 8/6 - 1227
Source of monetary or material support	Médecins sans Frontières
Trial Sponsor	Médecins sans Frontières
Contact for public queries	Nicola James, MSF UK; nicola.james@london.msf.org,
Contact for scientific queries	Beverley Stringer, MSF UK; beverley.stringer@london.msf.org,
Public/Scientific title	Patient-reported Experiences and Quality of Life Outcomes in the TB-PRACTECAL Clinical Trial (PRACTECAL-PRO)
Countries of recruitment	Belarus, Uzbekistan, South Africa
Health condition(s) or problem(s) studied	multidrug-resistant tuberculosis
Key inclusion and exclusion criteria	Inclusion Criteria: Adult patients recruited into the TB-PRACTECAL trial in the approved sites OR Local healthy-controls of a similar profile in terms of age and gender aged ≥18 years AND Literate in the study questionnaire languages Able to sign the sub-study informed consent form after agreeing to the additional interviews and completion of questionnaires. Exclusion Criteria: TB patients excluded from TB-PRACTECAL clinical trial Healthy volunteers who self-asses as having significant illnesses Healthy volunteers positive to a TB symptom screening
Study type	Observational
Date of first enrolment	September 1, 2019
Target sample size	216 minimum
Recruitment status	Recruiting
Primary outcome(s)	1. To assess quantitatively QoL measures for patients within the trial, from baseline to 12 months, including those treated in investigational arms as well as the standard of care arm. 2. To describe qualitatively patient satisfaction and experience with trial treatments in the investigational arms.
Key secondary outcomes	1. To understand what factors enable a novel treatment regimen to be tolerated or rejected by patients. 2. To evaluate utility of the SGRQ and SF-12 questionnaires, and qualitative methods within TB clinical trials.