Drug-Resistant Tuberculosis Clinical Trials: Proposed Core Research Definitions in Adults

Furin, J+., Alirol, E., Allen, E., Fielding, K., Merle, C., Abubakar, I., Andersen, J., Davies, G., Dheda, K., Diacon, A., Dooley, K.E., Dravnice, G., Eisenach, K., Everitt, D., Ferstenberg, D.,Goolam-Mahomed, A., Grobusch, M.P., , Gupta, R., Harausz, E., Harrington, M., Horsburgh, R., , Lienhardt, C.., McNeeley, D., Mitnick, C.D., Nachman, S., Nahid, P., Nunn, A.J., Phillips, P., Rodriguez, C., Shah, S., Wells, C., Thomas-Nyang'wa, B*, du Cros, P.*

Structured Summary

Drug-resistant tuberculosis (DR-TB) is a growing public health problem, and for the first time in decades there are new drugs for treatment of this disease. These new drugs have prompted strengthened efforts in DR-TB clinical trials research, and there are now multiple ongoing and planned DR-TB clinical trials. To facilitate comparability and maximize policy impact, a common set of core research definitions is needed, and this paper presents a core set of efficacy and safety definitions as well as other important considerations in DR-TB clinical trials work. In order to elaborate these definitions, a search of clinical trials registries, published manuscripts, and conference proceedings was undertaken to identify groups conducting trials of new regimens for the treatment of DR-TB. Individuals from these groups developed the core set of definitions presented here. Further work is needed to validate and assess the utility of these definitions but they represent an important first step to ensure there is comparability in MDR-TB clinical trials.

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* co-senior authors

+Corresponding author: Jennifer Furin, TB Research Unit, Case Western Reserve University School of Medicine, 2210 Circle Dr., Room E-202, Cleveland, OH 44149. Phone: + 1 440 855 1395. Email: jjf38@case.edu

Introduction

Drug-resistant tuberculosis (DR-TB) is a growing public health problem, with more than half a million new cases occurring each year[1]. For the first time in decades, there are several new and re-purposed drugs that show potential for improving treatment for persons with all forms of DR-TB[2]. Many of these drugs are being tested in combination regimens through clinical trials that are enrolling or planning to enroll participants in the next two years[3]. This is the first time there has been a core group of researchers, industry partners, policy makers and funders working collaboratively on DR-TB clinical trials[4]. Because multiple groups will be leading these trials, it is important to have a common set of core definitions that are used so that data can be shared and compared between the different trials and, ultimately, to generate a more robust evidence-base to guide policy. This paper expands upon regulatory guidance issued in 2013[5] and proposes core research definitions for DR-TB clinical trials in adults that were developed by a group of international experts currently involved in DR-TB clinical research.

Methods

In order to identify stakeholders, a search of clinical trials registries, published manuscripts, and conference proceedings was undertaken to identify groups conducting trials of new regimens for the treatment of DR-TB. A convenience and snowball sampling technique[6] was used to identify individuals from these groups who were then invited via email to participate in the development of the core research definitions. A total of 31 individuals were identified, of whom 30 agreed to participate in the development of the initial core definitions, for a response rate of 96.7% The core definitions that emerged from this process were further refined based on feedback provided at the Global MDR-TB Clinical Trials Landscape Meeting held by RESIST-TB and The Union's TREAT TB in Washington, D.C., in December 2014. In some areas, consensus could not be reached, and when this occurred options and the rationale for supporting each were documented.

Results

Proposed Core Research Definitions

The core definitions for participants with confirmed pulmonary DR-TB considered and discussed are presented in Table 1 below.

Specific Trial Considerations

Table 2 reviews detailed comments and suggestions on adapting the core definitions in specific clinical trials settings and protocols.

Additional Components of Trial Design

Table 3 presents recommendations from the group in other areas that are important in the design of DR-TB trials.

Discussion

In this paper, we suggest core research definitions for DR-TB clinical trials that can be used to harmonize existing and planned clinical trials. Of note, different trials may need to operationalize these definitions in ways that make the most sense for their trial in the context in which it will be conducted. For this reason, complete consensus was not always be possible, even between closely collaborating research groups; yet the aim in putting forth the recommended definitions is be to strive for the highest achievable level of transparency and data comparability. Lack of strict consensus was also due to differences in objectives and interpretation of existing data and genuine uncertainty in the absence of hard data. Areas in which consensus was not possible highlight gaps that could be addressed through future research, including meta-analyses. For example, the wide range of acceptable intervals between culture samples used for defining culture conversion is not based on hard evidence but rather on prevailing convention and trial logistics. Other areas in which it was difficult to reach consensus and further research is warranted in the use of liquid or solid media, the definition of treatment failure, especially when there is only one positive culture and clinical improvement, and the specified period of follow-up in trials that have arms of different lengths. The definitions we propose are meant to reflect the minimum standard that would allow cross-trial comparability. Indeed, there is flexibility to pursue more stringent criteria. Ultimately, based on further evidence and practical experience with implementation and use, revision of these definitions may be needed.

There were multiple limitations to the approach used. First, the group of researchers participating in this development process was not randomly selected and may not have included or be representative of all individuals working on DR-TB clinical trials. Attempts were made to be comprehensive in inclusion, but some individuals working on DR-TB trials may have been overlooked. Second, there was almost never complete consensus on the definitions, and it is possible that the majority or more active voices may have prevailed in the definitions we propose. Areas of debate are detailed in Table 2. Including the specifics of these debate in the results was felt to be important to illustrate the areas in which there was not complete agreement. At the same time the inclusion of a number of dissenting opinions may also weaken the recommendations of the core definitions. Finally, these definitions have yet to be validated in trials.

Conclusion

A set of core research definitions for DR-TB clinical trials were developed through a systematic process and are presented in this paper. In spite of the limitations mentioned above, it is recommended that these definitions be used as a minimum core set in all planned and future DR-TB trials. Clinical trialists, statisticians, microbiologists, government agencies, pharmaceutical companies, government-funded trials networks, and non-governmental organizations that are the most heavily engaged in DR-TB trial design, implementation, and analysis were all involved in the development of these definitions and thus they represent the current state-of-the-field. Ongoing and planned trials can help validate these core definitions and assess their utility. We are hopeful that these research definitions will be a useful tool that can help advance DR-TB research during this time of renewed interest in and availability of new drugs and potentially transformative new combination regimens for participants with this highly-morbid, often-fatal communicable disease.

Table1: Core Definitions

Measure	**Proposed Definition**
Sputum culture conversion	At least two consecutive negative sputum cultures taken between 7. to 30 days apart at a trial-defined time point after at least one initial positive sputum. One missing or contaminated culture may occur between the two negative cultures. Inability to produce sputum even with induction is considered to be a negative result. Sputum culture conversion is said to occur at the time of the first negative culture.
Favorable outcome	A participant's last two culture results at the end of treatment are negative and the participant has not been classified as having an unfavorable outcome by a study-defined time point.
Death	Death of a participant from any cause beginning at the time of randomization and extending through the specified follow-up period.
Treatment failure	The presence of a positive mycobacterial culture from at least one specimen beginning at a specified month.
Lost-to-Follow-up	Failure to complete the full duration of follow-up as specified in the trial protocol. .

Recurrence	Diagnosis of DR-TB during the pre-defined follow up period after previous documentation of successful treatment completion
Unfavorable outcome	Composite outcome that includes death, treatment failure, treatment discontinuation, and recurrence (see comment in Table 2).
Treatment discontinuation/modification	Discontinuation or modification of treatment, for any reason, based on a decision by the trial participant, trial investigator or trial safety monitoring body.
Multidrug Background Therapy/ Regimen (MBT/MBR)	A regimen that meets local standards for the treatment of DR TB.
Adequate adherence	Achievement of a targeted level of adherence (e.g. ≥ 90% of doses) within a trial-specified time period.
Unassessable	There is insufficient information for the participant to contribute to the assessment of the primary endpoint.
Safety	Proportion of participants experiencing a grade 3 or higher adverse event during treatment and follow-up AND any lower grade events that result in treatment modification/discontinuation

Table 2: Specific Trial Considerations

Variable	**Considerations for specific trials**
Sputum culture conversion	The precise number of days apart must take into account two issues. The number of days apart must be long enough to signify a meaningful biological change. Conventionally, this number is usually 30 days, although a longer period of time could be used depending on the trial design. The number of

	days apart must also ensure that the two samples are taken on different days. Conventionally, this number is 7 days although the period of time could be as short as 1 day. Time periods between the cultures will differ depending on the goal of the trial. Regulatory agencies have accepted a minimum of 7 days apart in some treatment shortening trials[7]. Logistical issues faced in trial execution may also determine the precise definition in each clinical trial. Trials will also need to decide what to do if a participant has one negative culture and then dies or if the confirmatory culture at the specified endpoint is contaminated or lost. Secondary/sensitivity analyses that investigate stricter and more inclusive alternate definitions can be important in trial interpretation. Future trials with more robust regimens may want to increase the number of cultures during the specified time period (i.e. 3 or 4 negative cultures within a 30 day period). This may be more important in non-inferiority trials compared with superiority trials. A maximum time period is given to avoid a situation in which a participant has one negative culture and subsequent cultures are assessed at longer intervals after longer durations of therapy to increase the likelihood that those subsequent cultures will stay negative
Favorable outcome	Trials could include clinical indicators of favorable outcomes as well, although such clinical indicators have not necessarily been shown to correlate with microbiologic outcomes[8].
Death	The cause of death should also be determined and reported and might be incorporated in secondary/sensitivity analyses In some trials, all deaths are counted as unfavorable, while in others, certain types of deaths (i.e. traumatic deaths, deaths during childbirth) are counted as "unassessable".
Treatment failure	The specified month will depend on the trial objectives and the length of the regimen being assessed. In general, this should be in the final third of the expected treatment period. Of note, there is limited evidence that a single positive culture during a trial necessarily indicates failure, and it is recommended that clinical considerations be taken into account when assessing the significance of a single positive culture[9]. The trial protocol will need to specify the clinical indicators to be assessed. Trials will need to decide what to do if the cultures are not "positive" but only have a few colonies.

Lost-to-Follow-up	Classification of these individuals in the analysis will vary depending on the trial protocol. In general, a participant is considered to be lost to follow-up if he or she does not contribute data to the primary endpoint. Trials should allow for such participants to contribute data to secondary/sensitivity analysis. For example, if a participant is lost to follow up late into the trial but does contribute data to a secondary objective (i.e. culture data at 6 months), the participant could be included in the analysis of 6 month endpoints. This could also include individuals who withdraw consent, individuals who required the use of prohibited medications, or individuals who did not return for trial visits. Another situation to be considered in each trial is how to handle data from participants that may be available outside of the trial. For example, if a participant does not come for trial visits but does show up for routine care. Each trial should detail how they will handle these conditions in the statistical analysis plan.
Recurrence	This could be due to re-infection in which there is evidence that the recurrence is with a different strain of *Mycobacterium tuberculosis*. This could also be due to relapse for which there is evidence that the recurrence is due to the same strain recorded in the baseline specimen. Some trials consider both to be an unfavorable outcome, although others do not consider re-infection to be an unfavorable outcome. Reinfection is often included as an unfavorable outcomes in trials because it may be a censoring endpoint and thus the final endpoint may be unassessable. In order to determine if the recurrence is due to relapse or re-infection, genotyping analyses of the mycobacterial DNA strain are needed. Resources for doing these analyses should be built into trial budgets whenever possible.
Unfavorable outcome	Although this composite endpoint has been used in many TB clinical trials, each of the separate outcomes included in the composite endpoint likely represents a qualitatively different outcome which may be obscured when they are all grouped together. For this reason, it is recommended that each of the specific endpoints included in the composite outcome be assessed separately. Trials could include clinical indicators of unfavorable outcomes as well.

Treatment discontinuation/modification	Some potential reasons for this could be protocol-defined toxicity, withdrawal of consent, or non-adherence to trial procedures.
Multidrug Background Therapy/ Regimen (MBT/MBR)	Also referred to as "appropriate combination regimen" or "optimized backbone regimen" These standards could include a WHO-recommended regimen, the contents of which are consistent with WHO guidelines, or a regimen recommended by another recognized national or international expert group.
Adequate adherence	More detailed definitions will depend on the goal of the trial and should be specified within the trial protocol/manual of operating procedures. 90% was chosen based on a recent study of treatment interruptions that found patient who missed more than 10% of doses had worse clinical outcomes[10].
Unassessable	This could be due to a number of reasons, and trial protocols will need to specify what the criteria for "unassessble" are and how such participants will be handled in the primary and secondary analyses. In the past, most unassessable participants were classified as unfavorable outcomes. However in TB trials, not all unassessable outcomes may be unfavorable[11]. Determining if an unassessable outcome is unfavorable will depend on the trial design and goals of the trial.
Safety	Continued assessment and grading of adverse events during the follow-up period is especially important for drugs with a long terminal half- life. Targeted safety endpoints should include drug-specific concerns, such as QT prolongation Trial protocols will need to specify the grading scales to be used (see point 6 below). Causality relatedness should also be assessed following CIOMS guidelines[12].

Table 3: Unresolved Issues in Clinical Trials

Issue	**Recommendation**	**Comment**

Type of culture media used	Both solid and liquid media should be used in planned trials, but liquid media is becoming the more accepted type. Liquid media is more sensitive than solid media for culture, especially with numbers of bacilli are low or if the bacilli have been exposed to medications. Furthermore, liquid culture systems are commercially manufactured and widely marketed thus providing a standardized product (culture media) and facilitating harmonization (same method and product used by all) among the labs participating in multi-national trials.	Studies have shown different results in solid media versus liquid media, and for this reason it would be ideal to use both media types.
Length of follow up	All participants should be followed for the same overall period of time, beginning at the time of randomization.	The number of months from randomization will depend on the goals of the trial, but the period should include a minimum of 6 months after treatment completion for all participants; a maximum of 12 months is likely to be sufficient. A minimum of 6 months is recommended because a majority (80%) of relapses will occur in the first six months after treatment has been completed[13]. Some trials may elect to follow all participants for a defined period of time AFTER completion of treatment. Both approaches introduce some forms of biases, but following from the time of randomization seems to favor the control regimen and may be more robust in the design of non-inferiority trials.

Role of molecular tests (i.e. Xpert MTB/RIF®, Hain Lineprobe version 2.0®)	Acceptable to define eligibility for inclusion, provided the result is confirmed by a phenotypic DST method specified in the protocol	Participants with a positive Xpert MTB/RIF® or HAIN MTBdr plus (version 2.0) but a negative culture be excluded from efficacy analyses based on the trial endpoints and discretion of the investigator and that those positive for DR-TB by a new method be confirmed by a standard method.
Predictor variables	It is recommended that information about variables commonly associated with response to TB treatment be collected.	Could include: 1) HIV status; 2) CD4 count if HIV positive; 3) body mass index; 4) presence of diabetes mellitus; 5) anemia; 6) extrapulmonary TB; 7) socioeconomic status; 8) tobacco use; 9) radiographic extent of disease; 10) other concomitant immunosuppressing conditions; 11) history of liver disease; 12) other concomitant infectious diseases such as malaria or other parasitic diseases, in endemic settings; and 13) smear grade
Monitoring for resistance development	Samples should be stored and tested for resistance at baseline and over the course of treatment, with an emphasis on testing samples collected from participants with treatment failure or relapse.	This may be especially important for drugs that have long terminal half-lives (or that have metabolites with long half-lives), given that drug may persist in the serum or tissues long after therapy is stopped.

[1] World Health Organization*: Global Tuberculosis Report 2014 (WHO/HTM/TB/2014.08).* Geneva: World Health Organization; 2014.

[2] Zumla, A., Schito, M., and Maeurer, M. Advancing the portfolio of tuberculosis diagnostics, drugs, biomarkers and vaccines. The Lancet Infectious Diseases 14(4): 267-9. 2014.

[3] Zumla, A., Gillespie, S., Hoelscher, M., et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances and future prospects. The Lancet Infectious Diseases March 24 :49-62. 2014. http://dx.doi.org/10.1016/.

[4] Brigden, G., Thomas-Nyanga, B., duCross, P., et al. Principles for designing future regimens for multidrug-resistant tuberculosis. Bulletin of the World Health Organization 92: 68-74. 2013

[5] U.S. Food and Drug Administration. Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment. Draft Guidance. November, 2013. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm373580.pdf

[6] Vaismoradi, M., Turunen, H. and Bondas, T. Content analysis and thematic analysis: implications for conducting a qualitative descriptive trial. Nursing Health Sciences.15(3): 398-405, 2013.

[7] The U.S. Food and Drug Administration allowed for this in TB Alliance's planned protocols for the STAND trial. http://www.tballiance.org/pipeline/developing-regimens-novel.php.

[8] Donomae, I. and Yamamoto K. Clinical evaluation of ethambutol in pulmonary tuberculosis. Ann N Y Acad Sci 1966;135 (2):849-81.

[9] Mitchison DA, Keyes AB, Edwards EA, Ayuma P, Byfield SP, Nunn AJ: Quality control in tuberculosis bacteriology. 2. The origin of isolated positive cultures from the sputum of patients in four studies of short course chemotherapy in Africa. *Tubercle* 1980, 61:135.

[10] Podewils LJ, Gler MTS, Quelapio MI, Chen MP (2013) Patterns of Treatment Interruption among Patients with Multidrug-Resistant TB (MDR TB) and Association with Interim and Final Treatment Outcomes. PLoS ONE 8(7): e70064. doi:10.1371/journal.pone.0070064

[11] Phillips, P., Crook, A., and Nunn, A. The evolution of and challenges in defining the clinical endpoint in tuberculosis treatment trials with non-inferiority designs. Trials 12(S1): A31, 2011.

[12] Council for International Organization the Medical Science. Management of Safety Information from Clinical Trials, report of CIOMS working group 4, Geneva 2005.

[13] Johnson, J., and Thiel, B. Time until relapse in tuberculosis treatment trials: implications for phase 3 trial design. American Journal of Respiratory and Critical Care Medicine 186(5): 464, 212.