

Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults

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SUMMARY

Drug-resistant tuberculosis (DR-TB) is a growing public health problem, and for the first time in decades, new drugs for the treatment of this disease have been developed. 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 maximise 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. 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 clinical trials on multidrug-resistant TB.

KEY WORDS: drug-resistant tuberculosis; research; definitions

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 repurposed 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 enrol participants in the next 2 years.³ This is the first time that a core group of researchers, industry partners, policy makers and funders has worked collaboratively on DR-TB clinical trials.⁴ Because multiple groups will be leading these trials, it is important to use a common set of core definitions so that data can be shared and compared between the

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Table 1 Core definitions

Measure	Proposed definition
Sputum culture conversion	At least two consecutive negative sputum cultures taken between 7 and 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.
Favourable 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 unfavourable outcome by a study-defined time point.
Death	Death of a participant from any cause beginning from the time of randomisation and extending through the specified follow-up period.
Treatment failure	The presence of a positive mycobacterial culture from <i>at least one</i> specimen beginning at a specified month.
Loss 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.
Unfavourable outcome	Composite outcome that includes death, treatment failure, treatment discontinuation and recurrence (see 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., $\geq 90\%$ of doses) within a trial-specified time period.
Unassessable	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.

DR-TB = drug-resistant tuberculosis.

different trials and, ultimately, 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

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 was used to identify individuals from these groups,⁶ who were then invited via e-mail to participate in the development of the core research definitions. A total of 31 individuals were identified, 30 of whom agreed to participate in the development of the initial core definitions, at 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 International Union Against Tuberculosis and Lung Disease's TREAT TB in Washington, DC, USA, 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.

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 harmonise existing and planned clinical trials. Of note, different trials may need to operationalise 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

Table 2 Specific trial considerations

Variable	Considerations for specific trials
Sputum culture conversion	<p>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. This number is generally 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. This number is generally 7 days although the period of time could be as short as 1 day.</p> <p>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 (D Everitt, Global Alliance for TB Drug Development; personal communication). Logistical issues faced in trial execution may also determine the precise definition in each clinical trial.</p> <p>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.</p> <p>Secondary/sensitivity analyses that investigate stricter and more inclusive alternate definitions can be important in trial interpretation.</p> <p>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 than in superiority trials.</p> <p>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 treatment to increase the likelihood that those subsequent cultures will stay negative.</p>
Favourable outcome	Trials could include clinical indicators of favourable outcomes as well, although such clinical indicators have not necessarily been shown to correlate with microbiological outcomes. ⁷
Death	<p>The cause of death should also be determined and reported and might be incorporated in secondary/sensitivity analyses.</p> <p>In some trials, all deaths are counted as unfavourable, while in others, only certain types of deaths (i.e., traumatic deaths, deaths during childbirth) are counted as 'unassessable'.</p>
Treatment failure	<p>The specified month will depend on trial objectives and the length of the regimen being assessed. In general, this should be in the final third of the expected treatment period.</p> <p>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.</p> <p>Trial designers will need to decide what to do if culture is not 'positive' but only have a few colonies.</p>
Loss to follow-up	<p>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.</p> <p>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.</p> <p>This could also include individuals who withdraw consent, individuals who require the use of prohibited medications or individuals who do not return for trial visits.</p> <p>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 give details on how these conditions will be handled in the statistical analysis plan.</p>
Recurrence	<p>This could be due to <i>re-infection</i> where there is evidence that recurrence is due to a different strain of <i>Mycobacterium tuberculosis</i>. This could also be due to <i>relapse</i> where there is evidence that recurrence is due to the same strain recorded in the baseline specimen.</p> <p>Some trials consider both to be an unfavourable outcome, although others do not consider re-infection to be an unfavourable outcome. Re-infection is often included as an unfavourable outcome in trials, as it may be a censoring endpoint and thus the final endpoint may be unassessable.</p> <p>To determine if 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.</p>
Unfavourable outcome	<p>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.</p> <p>Trials could include clinical indicators of unfavourable outcomes as well.</p>
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 'optimised 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 recognised national or international expert group.
Adequate adherence	<p>More detailed definitions will depend on the goal of the trial and should be specified within the trial protocol/manual of operating procedures.</p> <p>90% was chosen based on a recent study of treatment interruptions that found that patients who missed >10% of doses had worse clinical outcomes.⁹</p>
Unassessable	<p>This could be due to a number of reasons, and trial protocols will need to specify what the criteria for 'unassessable' are and how such participants will be handled in the primary and secondary analyses.</p> <p>In the past, most unassessable participants were classified as unfavourable outcomes. However in tuberculosis trials, not all unassessable outcomes may be unfavourable.¹⁰ Determining whether or not an unassessable outcome is unfavourable will depend on the trial design and the goals of the trial.</p>
Safety	Continued assessment and grading of adverse events during the follow-up period is especially important for drugs with a long terminal half-life.

Table 2 (continued)

Variable	Considerations for specific trials
	Targeted safety endpoints should include drug-specific concerns, such as QT prolongation Trial protocols will need to specify the grading scales to be used Causality relatedness should also be assessed following CIOMS guidelines. ¹¹

WHO = World Health Organization; CIOMS = Council for International Organizations of Medical Sciences.

not always possible, even between closely collaborating research groups; nevertheless, the aim in putting forth the recommended definitions is to strive for the highest achievable level of transpar-

ency 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

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; however, liquid medium is becoming the more accepted type. Liquid medium is more sensitive than solid medium for culture, especially when numbers of bacilli are low or if the bacilli have been exposed to medication. Furthermore, liquid culture systems are commercially manufactured and widely marketed, thus providing a standardised product (culture media) and facilitating harmonisation (same method and product used by all) among the laboratories participating in multinational trials.	Studies have shown different results in solid vs. liquid media, and for this reason it would be ideal to use both medium types.
Length of follow-up	All participants should be followed for the same overall period of time, beginning at the time of randomisation.	The number of months from randomisation 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 the majority (80%) of relapses will occur in the first 6 months after treatment has been completed. ¹² Some trials may elect to follow all participants for a defined period of time after completion of treatment. Both approaches introduce some forms of bias, but following from the time of randomisation seems to favour 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 or Hain MTBDRplus (version 2.0) but a negative culture should be excluded from efficacy analyses based on trial endpoints and at the discretion of the investigator; those positive for drug-resistant TB by a new method should be confirmed by a standard method.
Predictor variables	It is recommended that information about variables commonly associated with response to anti-tuberculosis treatment be collected.	Could include: 1) HIV status, 2) CD4 count if HIV-positive, 3) body mass index, 4) presence of diabetes mellitus, 5) anaemia, 6) extra-pulmonary TB, 7) socio-economic 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), as the drug may persist in the serum or tissues long after treatment is stopped.

DST = drug-susceptibility testing; HIV = human immunodeficiency virus; TB = tuberculosis.

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 required is 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. There is, however, flexibility to pursue more stringent criteria. Based on further evidence and practical experience with implementation and use, revision of these definitions may ultimately 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 prevailed in the definitions we propose. Areas of debate are detailed in Table 2. Including the specifics of these debates in the results was felt to be important to illustrate the areas in which there was lack of complete agreement. However, the inclusion of a number of dissenting opinions may also have weakened the recommendations of the core definitions. Finally, these definitions have yet to be validated in trials.

CONCLUSION

This paper presents a set of core research definitions for DR-TB clinical trials that was developed through a systematic process. 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 organisations that are the most heavily engaged in DR-TB trial design, implementation and analysis were all involved in the development of these definitions, and they thus

represent the current state of the field. Ongoing and planned trials can help validate these core definitions and assess their utility. We are optimistic 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.

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RESUME

La tuberculose pharmacorésistante (TB-DR) est un problème de santé publique croissant, et pour la première fois en plusieurs décennies, il y a de nouveaux médicaments pour le traitement de cette maladie. Ces nouveaux médicaments ont suscité une accélération des efforts en matière de recherche en essais cliniques et il y a actuellement de nombreux essais cliniques relatifs à la TB-DR en cours ou planifiés. Pour faciliter les comparaisons et maximiser l'impact des politiques, un ensemble commun de définitions majeures en matière de recherche est nécessaire, et cet article présente une série des principales définitions en matière de sécurité et d'efficacité ainsi que d'autres

considérations importantes relatives aux essais cliniques de la TB-DR. Pour élaborer ces définitions, on a entrepris une recherche de registres d'essais cliniques, de manuscrits publiés et d'actes de conférence afin d'identifier les groupes réalisant des essais de nouveaux protocoles de traitement de la TB-DR. Les membres de ces groupes ont élaboré l'ensemble des définitions majeures présentées ici. D'autres travaux sont requis afin de valider et d'évaluer l'utilité de ces définitions, mais elles représentent déjà une première étape importante pour assurer la comparabilité entre les essais cliniques dans la TB-MDR.

RESUMEN

La tuberculosis farmacorresistente (TB-DR) constituye un problema de salud pública cada vez mayor y por primera vez en varios decenios, existen nuevos medicamentos para el tratamiento de la enfermedad. Estos nuevos medicamentos han motivado la intensificación de las iniciativas de ensayos clínicos sobre la TB-DR y en la actualidad múltiples investigaciones están en curso o en etapa de planificación. Con el propósito de facilitar la comparabilidad y lograr una máxima repercusión en las políticas, es preciso contar con un conjunto común de definiciones básicas de investigación. En el presente artículo se propone un conjunto de definiciones básicas de eficacia y seguridad toxicológica, además de otros

aspectos importantes en el trabajo de los ensayos clínicos sobre la TB-DR. Con el fin de elaborar estas definiciones se emprendió una búsqueda de grupos que realizan ensayos clínicos de nuevas pautas terapéuticas para el tratamiento de la TB-DR, en los registros de ensayos clínicos, los artículos publicados y las actas de las conferencias científicas. Personas integrantes de estos grupos formularon el grupo básico de definiciones que se presentan a continuación. Es necesario continuar el trabajo, con el fin de validar y evaluar la utilidad de estas definiciones, pero el conjunto ya representa una etapa importante en favor de la comparabilidad de los ensayos clínicos sobre la TB-MDR.
