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Totality of outcomes: A different paradigm in assessing interventions for treatment of tuberculosis

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ABSTRACT

Conventional analytic methods used for tuberculosis (TB) outcomes research use standardized outcomes definitions and assess safety and efficacy separately. These methods are subject to important limitations. Conventionally utilized outcome definitions fail to capture important aspects of patients' treatment experience and obscure meaningful differences between patients. Assessing safety and efficacy separately fails to yield an objective risk–benefit comparison to guide clinical practice. We propose to address these issues through an analytic approach based on prioritized outcomes. This approach enables a more comprehensive and integrated assessment of TB interventions. It simultaneously considers a "totality of outcomes", including clinical benefit, adverse events, and quality of life. These composite outcomes are ranked terms of overall desirability and compared using statistical methods for ordinal outcomes. Here we discuss the application of this approach to TB research, the considerations involved with prioritizing TB treatment outcomes, and the statistical methods involved in comparing prioritized outcomes.

1. Introduction

Studies assessing different treatment strategies for tuberculosis (TB) typically use binary outcomes (e.g., successful versus unsuccessful treatment, death versus survival) based on a standardized set of outcome definitions that were established to report TB program data to the World Health Organization. Five mutually exclusive outcomes are defined: cured, treatment completed, treatment failed, died, and lost to follow-up [1] (Table 1).[1] Treatment success is typically defined as either cured or treatment completed, which may poorly reflect how well a treatment works and how it contributes to patient well-being. Moreover, these classifications are subject to several limitations when used for TB treatment research, as they obscure meaningful differences between individual patient outcomes.

Firstly, these definitions do not consider side effects during treatment, so patients who complete treatment without any major side effects and patients who complete treatment but suffer irreparable hearing loss are equivalently classified. Secondly, the definitions do not consider the condition of a patient at the end of the observation period. Patients who complete treatment are classified as *treatment successes* even if they are faring poorly clinically with worsening radiographic findings at the end of treatment. Thirdly, the definitions do not capture risk of relapse, which occurs after the end of the prescribed treatment period but is arguably integral to the definition of cure. Fourthly, for patients who are classified as failing treatment, the definitions do not capture the possibility for retreatment. Because the first event that occurs is used to define the treatment outcome [2], patients in the "treatment failed" category may include those who ultimately died during the observation period and those who were ultimately cured [3]. And finally, because the definitions only describe patients' status at a single endpoint, they are ill-suited for incorporating indicators related to the treatment experience, such as the length of treatment, the pill burden, the dosing schedule, or the mode of administration (i.e., injectable versus oral).

An alternative analytic approach that could address the challenge of differentiating patient outcomes based on all meaningful

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[1] This list excludes the categories of "Not evaluated," which means that no treatment outcome has been assigned, and "Treatment success," which is the sum of "Cured" and "Treatment completed."

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Table 1
World Health Organization reporting definitions for tuberculosis (TB) treatment outcomes.

Outcome	Definition for patients treated for TB susceptible to rifampin	Definition for patients treated for TB resistant to at least rifampin (including multidrug-resistant TB)
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase of treatment
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least on previous occasion were negative, either because tests were not done or because results are unavailable	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive culture taken at least 30 days apart are negative after the intensive phase of treatment
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment	Treatment terminated or need for permanent regimen change of at least two antituberculosis drugs because of one of four reasons (fully described in guidelines), which are related to lack of bacteriologic response, development of additional drug resistance, or adverse reactions to drug(s)
Died	A patient who dies for any reason before starting or during the course of treatment	A patient who dies for any reason during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more	A patient whose treatment was interrupted for 2 consecutive months or more

Table adapted from World Health Organization, "Definitions and reporting framework for tuberculosis – 2013 revision" [1].

comparisons is one based on prioritized outcomes. Prioritized outcomes approaches consider each individual patient's treatment experience with respect to multiple types of clinical outcomes during the entire period of observation (i.e., a "totality of outcomes") and then rank patients according to their overall treatment experience. Formal statistical comparisons are used to compare groups of patients based on the ranks of their totality of outcomes. This idea was first proposed in the statistical literature by Chuang-Stein in the context of clinical trials of antihypertensive drugs [4]. Since then, a body of methodological work has been produced in different disease areas [5–14]. More recently, Evans et al described an adaptation of this approach in the context of antibiotic stewardship trials [15]. In this concept paper, we describe how prioritized outcome approaches can be used to assess a totality of outcomes for TB treatment.

2. Example 1: a prioritized outcomes approach to risk–benefit analysis of TB treatments

To illustrate the advantage of a prioritized outcome approach, we present an example using a highly simplified scheme for ranking outcomes of patients treated for multidrug-resistant (MDR) TB. Many of the drugs available for treatment of MDR-TB are known to have substantial toxicity, and MDR-TB treatment regimens are poorly tolerated by patients. Clinicians are forced to subjectively weight the risks and benefits of using a regimen that may offer a greater chance of cure but results in a higher risk of adverse events.

Let us consider two regimens, A and B, each used to treat 300 patients, and producing the simplified outcome distributions shown in Fig. 1. Regimen B is associated with a significantly higher treatment success rate compared to regimen A (73% versus 65%, relative risk [RR] for treatment success = 1.31, 95% confidence interval [CI] 1.03–1.67), but also a significantly higher prevalence of serious adverse events (50% versus 40%, RR for serious adverse events = 1.20, 95% CI 1.04–1.39). Thus, a comparison based purely on clinical benefit would favor Regimen B, while a comparison based purely on toxicity would favor Regimen A. The question arises: Does the clinical benefit derived from choosing Regimen B outweigh the higher risk of serious adverse events associated with it?

A prioritized outcomes approach allows comparison of both indicators simultaneously and, thereby, directly addresses this risk–benefit question. One must first rank the desirability of

Regimen A

	Treatment success	No treatment success
No serious adverse event	85	95
Serious adverse event(s)	110	10

Treatment success rate: 65%
Serious adverse event rate: 40%

Regimen B

	Treatment success	No treatment success
No serious adverse event	140	10
Serious adverse event(s)	80	70

Treatment success rate: 73%
Serious adverse event rate: 50%

Fig. 1. Hypothetical distribution of outcomes and serious adverse events among patients treated with two regimens.

patient outcomes. In this case, let us consider: Treatment success without adverse event > treatment success with adverse event > lack of treatment success without adverse event > lack of treatment success with adverse event. Categorizing the 300 patients in each group into these four categories, then comparing the ranks in the two groups using the Wilcoxon rank sum tests, favors Regimen B with a p-value of 0.018. The estimated probability that a randomly selected patient taking Regimen B will have a better score than a patient from Regimen A is 55.4% (95% confidence interval [CI]: 52.8–57.9%) when all pairwise comparisons are included in the estimation, with half a point added to the numerator of the estimate whenever a tie occurs.

Thus, while comparing clinical benefit and toxicity separately yields contradictory information about which regimen may be preferable, a prioritized outcome approach suggests that Regimen B may be better overall, given these outcome distributions.

3. Prioritizing outcomes for TB research

The example above presented a simplistic outcome ranking scheme for illustrative purposes, but in actuality, the outcome ranking scheme could be much more complex. Developing this ranking scheme is the first and most important step in applying a prioritized outcome approach. It is important to acknowledge from the outset that the act of ranking is inherently subjective and different aspects of the treatment experience may be more important to consider depending on the research question and study context. Therefore, it is critical to achieve consensus in creating this ranking scheme before proceeding with analysis.

A method that has been used to validate prioritized outcome rankings for HIV [8] and cardiovascular disease [5] is to use consensus ranking to inform development of rule-based ranking