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Justifying Research Risks in a Clinical Trial for Treatment of Multidrug-Resistant Tuberculosis

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Investigators and ethics review committees must ensure the proper justification of risks to participants in clinical trials.[1] Despite the existence of a systematic framework for analyzing the ethical evaluation of research risks,[2] the literature contains few worked examples of such an analysis.[3] This paper demonstrates a step-by-step component analysis of the LiMiT Study, a phase I–II randomized controlled trial designed to evaluate once-daily (600 mg.) linezolid plus optimized background therapy versus placebo plus optimized background therapy for the first 16 weeks of study therapy for multidrug-resistant tuberculosis (TB).[4] This example represents a fairly complex, early-stage trial that we, as investigators, wanted to ensure met criteria for appropriate justification of research risks. Our analytic framework helped to isolate and clarify a few subtle issues that arise from using placebo in combination therapy among persons with difficult-to-treat tuberculosis.

Multidrug-Resistant Tuberculosis

Treatment of multidrug-resistant TB is lengthy, complex, toxic, and suboptimally effective. An estimated half million cases of multidrug-resistant TB were reported worldwide in 2006.[5] Treatment regimens are based on expert opinion and anecdotal experience, last at least 18 months, generally require a combination of five or more medications, and yield relatively poor results, with only 60–70% favorable outcomes for many programs (as compared to favorable outcomes of well over 90% for drug-susceptible TB). Resistance of multidrug-resistant isolates to additional drugs, as found in extensively drug-resistant TB, further complicates treatment.

HIV infection greatly increases TB morbidity[6] and mortality.[7] South Africa has 17% of the global burden of HIV infection and a severe TB epidemic, compounded by rising TB drug resistance and HIV coinfection.[8] In rural South Africa, a highly fatal epidemic of extensively drug-resistant TB occurred primarily among persons with HIV.[9]

Clinical trials are needed to evaluate the safety, tolerability, and efficacy of new drugs to treat multidrug- and extensively drug-resistant TB to improve outcomes and to shorten the duration of therapy. The antibiotic linezolid—used to treat drug-resistant bacterial infections, including methicillin-resistant *Staphylococcus aureus*[10]—has been used off-label to treat drug-resistant TB without benefit of a randomized controlled trial. In case series studies of patients treated with linezolid for multidrug-resistant TB, common toxicities included reversible bone marrow suppression, reversible optic neuropathy, and irreversible peripheral neuropathy. Adverse effects have occurred more frequently at higher doses or longer durations of treatment.[11]

The LiMiT Study will provide information regarding the tolerability and safety of 600 mg. linezolid administered daily for 16 weeks to treat multidrug- and extensively drug-resistant TB. Every participant in the trial received optimized background therapy, defined as treatment with four or more drugs with activity against TB to which the patient's isolate is believed to be sensitive by history or drug-susceptibility testing. In addition, each participant received either linezolid or placebo. (A third party removed markings from linezolid pills, prepared a placebo of the same size, shape, and color as the linezolid pills, and overencapsulated the linezolid and placebo pills to further mask their identity.) The LiMiT Study will also assess the feasibility of conducting complex studies involving multidrug-resistant TB. The trial setting is the multidrug-resistant TB treatment program supervised by physicians

at King George V Hospital in Durban, Republic of South Africa. Ethics committees at the University of KwaZulu-Natal, Columbia University Medical Center, Boston University School of Medicine, and the U.S. Centers for Disease Control and Prevention approved the study.

The statistical design is relevant to the trial's prospects for shifting expert opinion and potentially improving or expanding standards of care. The designed sample of 64 participants has 56% power to detect a difference in completion of initial-phase therapy (90% in the placebo group and 65% in the linezolid group) and 75% power to detect a difference in serious adverse events (20% in the placebo group and 50% in the linezolid group); both hypotheses are one-sided with type one error rate of 10%.

Component Analysis: A Unified Framework for Analyzing Risk

This clinical trial contains a mixture of interventions carried out for different purposes, described as therapeutic warrant and nontherapeutic warrant. Component analysis provides a principled framework for applying separate moral standards to therapeutic and nontherapeutic procedures. The analytic framework proceeds in four steps (**Figure 1**):

1. Distinguish therapeutic and nontherapeutic procedures.

2. Analyze risk in therapeutic procedures.

3. Analyze risk in nontherapeutic procedures.

4. Combine results of both analyses. Both tests must be passed in order for research risks to be ethically acceptable.

Step 1: Distinguish Therapeutic and Nontherapeutic Procedures. The first step in component analysis is to classify study procedures as therapeutic or nontherapeutic.[12] Therapeutic procedures are those used to diagnose, treat, or prevent a health-related state "on the basis of evidence sufficient to justify the belief that they may benefit research subjects."[13] They derive their justification from the benefit they potentially provide to the study participant. Nontherapeutic procedures are those used in the attempt to answer a research question and derive their justification from the importance of the scientific knowledge potentially gained.

Table 1 outlines the standard procedures for multidrug- and extensively drug-resistant TB at King George V Hospital in Durban, South Africa, and the procedures in the LiMiT Study protocol. The local standard of care is consistent with several international guidelines.[14] Each procedure in the LiMiT Study protocol that corresponds to a similar procedure in the local standard of care is classified as therapeutic, since it would have been performed regardless of study participation. For example, most procedures carried out during screening for study eligibility would be conducted during an initial evaluation for multidrug- and extensively drug-resistant TB. Therapeutic procedures in the LiMiT Study include medical history, physical examination, neurological evaluation, vision testing, HIV testing, blood chemistry and hematology, and TB sputum smears, cultures, and susceptibility testing.

Some procedures in the LiMiT Study are not a part of the local standard of care for the treatment and management of multidrug- and extensively drug-resistant TB, but they could provide information that might assist in managing treatment within this study. An example is evaluation of fasting blood sugar, which is a useful screening tool for diabetes. This condition has been shown to be associated with increased risk for TB disease, increased risk of adverse blood sugar levels seen with some anti-TB medications, and delayed time to culture conversion.[15] Although the standard of care does not regularly include screening for diabetes, this screening can be regarded as a component of optimal care. Clinically valuable information obtained in connection with optimal care might also have important research value, but the procedures are regarded as therapeutic only because they are geared toward individual care.

The experimental procedure of the LiMiT Study—linezolid plus optimized background therapy—is therapeutic because it is tailored for individual treatment and there is early evidence that linezolid might be effective against drug-resistant TB. In addition, placebo plus optimized background therapy is administered with therapeutic

warrant because, once drug sensitivity test results become available for the participant's baseline TB isolate, optimized background therapy is tailored for individual treatment and placebo is not expected to modify the action of optimized background therapy, nor does it substitute for a known effective intervention that is being withheld. Therapeutic procedures in the LiMiT Study that arise from the experimental procedure include the neurology examination and vision testing to screen for possible linezolid-specific adverse reactions, namely peripheral and optic neuropathy. It is likely that both of these procedures could be a part of a future standard of care should linezolid be shown to be beneficial in the treatment of multidrug- and extensively drug-resistant TB.

In contrast to therapeutic procedures, nontherapeutic procedures "are administered purely to answer the scientific question at hand."[16] Blinding is an example of a procedure that does not provide direct benefit to the study participant, but can enhance the scientific validity of clinical trials. Similarly, therapeutic procedures that are performed at a greater frequency than clinically necessary supply information that might help answer certain research questions. Their incidental benefit to the study participant is secondary to the purpose for using such procedures. Placebo is administered with both therapeutic warrant (as described above) and nontherapeutic warrant, for it would not typically be used other than to answer a scientific question.

The local standard of care calls for monthly TB sputum smears and cultures and one-time TB susceptibility testing to optimize the background regimen. Thus, biweekly TB smears, cultures, and susceptibilities are performed in the study more frequently than indicated by the local standard of care. The primary purpose for these additional procedures is to measure changes in bacterial load and characteristics at two-week intervals, not to improve management of participant care. Laboratory and imaging in the study protocol also exceed the standard of care and go beyond improving individual care. According to the local standard of care, chemistry and hematology labs should be drawn as needed per clinical suspicion of possible adverse events. To the extent that the study protocol calls for such labs to protect participants based on clinical indications, these procedures are carried out with therapeutic warrant. In the study protocol, however, these labs are scheduled at biweekly intervals during admission and monthly intervals during outpatient follow-up. Therefore, to the extent that extra procedures go beyond optimal, individual care, they are classified as nontherapeutic because they are used primarily for gains in scientific knowledge. Finally, some specimens were obtained in the LiMiT Study for purely scientific purposes, including five blood specimens obtained for future analysis of potential biomarkers for treatment response and seven blood specimens (three tablespoons total) obtained within a 24-hour period for pharmacokinetic analysis. These specimen collections for biomarker and pharmacokinetic studies are nontherapeutic procedures.

Step 2. Analyze Risk in Therapeutic Procedures. Therapeutic procedures must be consistent with competent care, and their risks must be reasonable in relation to the anticipated benefits to the participant. A reviewer should examine procedures in comparison with the local standard of care, optimal care, and the experimental intervention, as laid out in the previous section.

The risks from the experimental and control procedures themselves require further justification under the following criteria (see **Figure 1**):

• Both interventions must be consistent with competent care.

• A state of clinical equipoise must exist between the interventions—that is, there must be honest, professional disagreement or uncertainty among expert clinicians as to the preferred treatment.

• Taken together, procedures carried out with therapeutic warrant must have a favorable balance of benefits to harms.

• The comparative trial must be designed so that, if it is successfully completed, it will disturb clinical equipoise, allowing the study to answer clinical questions, shift expert opinion, and hopefully improve or expand standards of care.

Since optimized background therapy is the current standard of care for multidrug- and extensively drug-resistant TB, providing such therapy to both experimental and control arms ensures, in part, that the experimental procedure is consistent with competent care.

Clinical equipoise exists between regimens of linezolid and optimized background therapy versus optimized background therapy alone. Linezolid's in vivo and in vitro activity against tubercle bacilli suggest potential efficacy.

Furthermore, case series suggest that linezolid promotes multidrug-resistant TB culture conversion and cure or treatment completion. Linezolid also presents concerns of significant toxicity. Even so, no comparative clinical trials have been undertaken to examine the tolerability, safety, and efficacy of linezolid in combination treatment for multidrug- and extensively drug-resistant TB. Therefore, it is not known at this time whether linezolid and optimized background therapy or optimized background therapy alone is the preferred treatment for multidrug- and extensively drug-resistant TB. With limited power, the LiMiT Study is unlikely to mount substantial evidence regarding efficacy, but it could rule out linezolid from further consideration if its toxicity and safety profile prove to be unacceptable. Thus, the study might not resolve a preference for either intervention—that is, disturb clinical equipoise—but it can show whether linezolid has a provisionally acceptable safety profile and perhaps inform development of drugs in the same class. Because the trial is designed specifically to support ruling out further development of linezolid for multidrug-resistant TB, if so indicated by the data, it is consistent with the intent of the second part of Freedman's formulation of clinical equipoise.[17]

The primary benefit for the addition of linezolid is that study participants might receive more effective treatment of multidrug- and extensively drug-resistant TB, potentially prolonging and improving quality of life. The main risks of the addition of linezolid include possible adverse effects (myelosuppression, lactic acidosis, optic and peripheral neuropathies, serotonin syndrome, diarrhea, nausea/vomiting) and congenital defects (category C drug in pregnancy). (See **Table 2** .) Eligible participants begin the trial with adequate function and mobility and with acceptable levels of serum creatinine, hemoglobin, platelet count, and absolute neutrophil count; an absence of significant peripheral neuropathy; a minimum visual acuity and color vision; and no concomitant medications likely to have unacceptable drug interactions with linezolid. By limiting dosing to once daily over 16 weeks, excluding certain at-risk populations, and including regular monitoring, these risks are effectively minimized, creating a favorable benefit-harm balance. Because placebo is not substituted for a known effective treatment, its use does not introduce any risks as a therapeutic procedure.

We have shown, by applying the four criteria at the beginning of this section, that the therapeutic procedures in the LiMiT Study pass the relevant requirements of component analysis.

Step 3: Analyze Risk in Nontherapeutic Procedures. Because nontherapeutic procedures are used not for the benefit of the study participants, but to generate knowledge, nontherapeutic procedures must meet a different set of criteria in order to be ethically justified:

• Risks must be minimized consistent with sound research design.

• Risks must be reasonable in relation to the knowledge that is expected to result (a favorable knowledge-harm balance).

• Vulnerable populations must be protected.

It is useful to examine the potential knowledge gained and the risk of each individual nontherapeutic procedure, then to consider them in aggregate. Focusing on individual procedures allows a systematic approach to deciding where procedures can be altered or eliminated to minimize risk and to maximize knowledge gained.

Nontherapeutic procedures should provide valid scientific information that could benefit society. In the LiMiT Study, random treatment assignment and blinding are nontherapeutic procedures that are consistent with sound scientific design, since both reduce confounding and bias that could result from selective assignment or unblinded administration and safety assessment (see **Table 3**). The overencapsulated placebo and linezolid pills have identical size, shape, and color. Because the placebo pill carries the same physical risks while swallowing as the linezolid pill, the placebo itself does not introduce any risks as a nontherapeutic procedure, and the risks due to overencapsulation may be regarded as minimal. Neurology history and physical exams, vision testing, blood chemistry, and hematology lab tests are therapeutic in nature, but might be performed at higher frequencies than is clinically necessary to document the adverse effects of each intervention. TB smears, cultures, and susceptibility tests are also therapeutic in nature but are performed at higher frequencies than is clinically necessary to provide information on efficacy of each intervention. Lastly, additional chest x-rays and CD4 cell count measurements monitor TB and HIV progression, respectively, but go beyond the local standard of care and are not strictly necessary for optimal care. These extra procedures could prove useful in adjusting for confounding or identifying risk factors for adverse events or outcomes.

Risks incurred to obtain knowledge must be reasonable, and they should be minimized by using the safest procedures available and, whenever possible, adding onto therapeutic procedures already performed. For the LiMiT Study, the risk of each nontherapeutic procedure is minimized when performed by trained personnel. Additionally, TB susceptibility testing, blood chemistry, hematology, CD4 count laboratory tests, and specimens for biomarker studies can be assessed in conjunction with specimens obtained for therapeutic purposes. Because participants are hospitalized for the duration of treatment, obtaining the seven pharmacokinetic specimens within 24 hours imposes additional risk or burden on the participants only through insertion of a catheter and the timing of the several blood draws.

The knowledge potentially gained in total from the nontherapeutic procedures of the LiMiT Study would allow investigators to answer questions regarding the toxicity, safety, and efficacy of linezolid in the treatment of multidrug- and extensively drug-resistant TB. Moreover, the risks posed by the nontherapeutic procedures can be individually and collectively minimized.

Among vulnerable populations, nontherapeutic risks are subject to an upper limit. This criterion does not apply to the LiMiT Study, which excludes children, pregnant women, and prisoners.

We have shown, by applying the three criteria at the beginning of this section, that the nontherapeutic procedures in the LiMiT Study pass the relevant requirements of component analysis.

Step 4: Combine Results of Both Analyses. The final step in component analysis is to combine the analysis of therapeutic and nontherapeutic procedures. If both sets pass their respective reviews, as we have argued for the LiMiT Study, then the risk profile of the protocol is ethically acceptable. If either or both sets failed their respective reviews, then the protocol would not be acceptable without revision to become compatible with the appropriate criteria. In some cases, fundamental design in a study will not admit any acceptable revision. For example, if placebo use is not consistent with competent care and clinical equipoise does not exist, then no amount of therapeutic risk is acceptable.

Discussion and Conclusion

We have demonstrated how to apply component analysis as a unified framework for analyzing and justifying risks in a complex clinical trial. Space limitations required that we omit details of the protocol, such as the exact dosing schedule and every planned procedure.[18] Nonetheless, each step is represented in this analysis, together with the appropriate criteria and representative decisions.

These methods apply more broadly to other kinds of research studies, including clinical observational studies and nonclinical studies. If a study does not include therapeutic procedures, as one might expect from an observational study, then the analysis would apply only to the nontherapeutic procedures, effectively focusing only on step three above. In some trials, such as behavioral interventions, it might be less straightforward to identify and analyze the therapeutic procedures. Nonetheless, the concepts of therapeutic warrant and clinical equipoise carry through: identify procedures that are carried out on the basis of evidence that they may benefit research subjects and analyze them according to the criteria for analyzing risks for therapeutic procedures (Step 2).

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