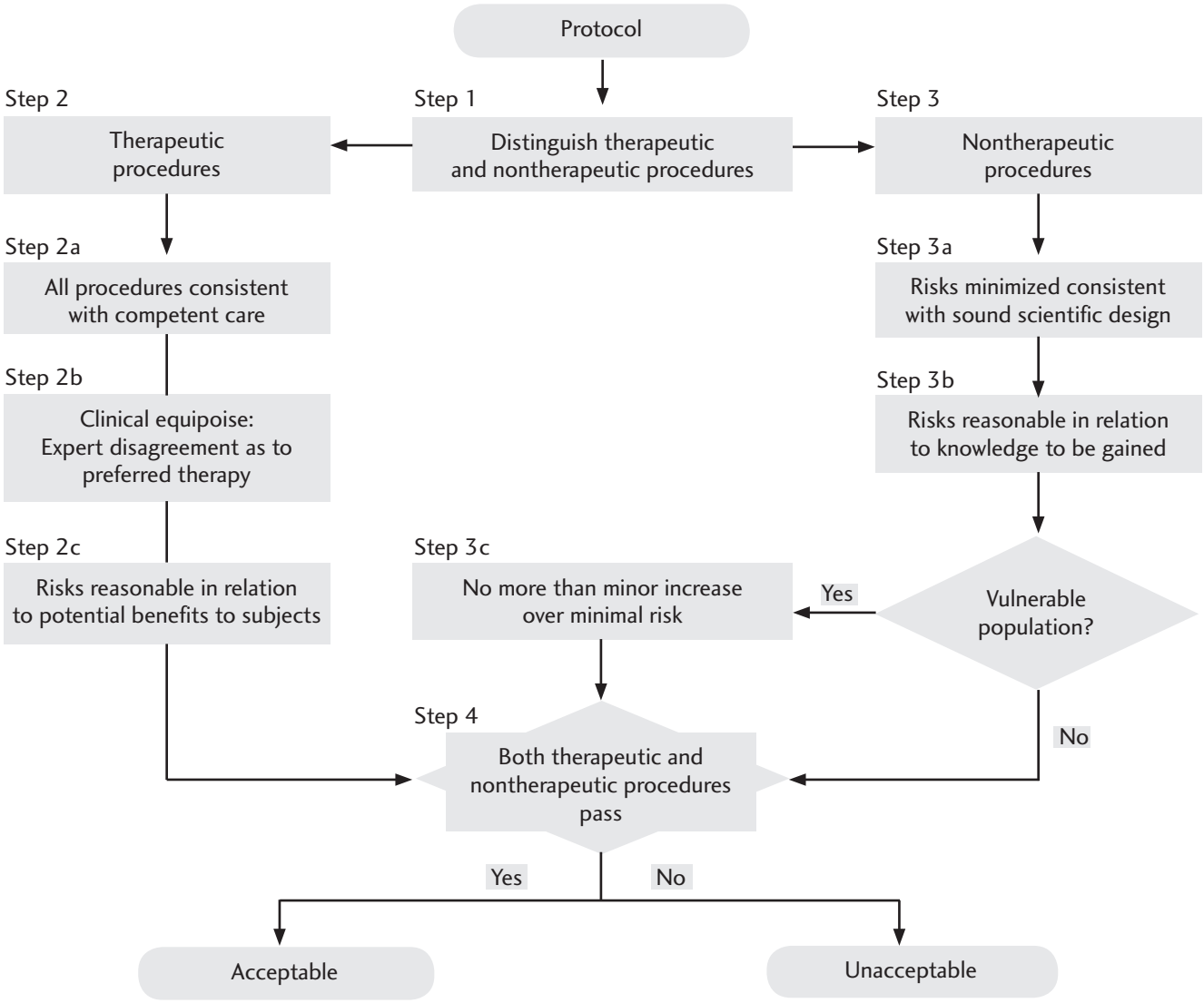
BY CHARLES M. HEILIG, DAVID CHIA, WAFAA M. EL-SADR, YAEL HIRSCH-MOVERMAN, WILLIAM R. MAC KENZIE, JUSSI SAUKKONEN, MARGARITA E. VILLARINO, AND NESRI PADAYATCHI

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

**Figure 1.**
**Flow Diagram for Applying Component Analysis to Analyze Research Risk[1]**




[1] Adapted by permission from Macmillan Publishers Ltd.: *Nature Medicine*, copyright 2004. See ref. 2, Weijer and Miller 2004.

## Table 1.
## Procedures in the LiMiT Study

| *Procedure* | *Standard Care* | *LiMiT Study* | *Warrant*[1] |
|---|---|---|---|
| Admit to hospital | Initial, often for duration of treatment | Apply study procedures while in hospital | T |
| History, physical, neurology, vision | Initial | Screening | T |
| Assess concomitant medications | Each visit | Each visit | T |
| HIV testing | Initial | Screening | T |
| CD4 testing if HIV+ | Initial, 6 and 12 months | Each visit | T |
| Fasting blood sugar | Not standard | Within one month | T |
| Blood chemistry and hematology | Initial, then as needed | Each visit | T/N |
| TB sputum smear/culture | Initial, then monthly until completion | Screening, then biweekly through 16 weeks, then monthly until there are two consecutive negative monthly cultures | T/N |
| TB susceptibilities | Initial | Screening, then biweekly through 16 weeks, then monthly until completion if needed | T/N |
| Chest x-ray | Initial, then every six months or as needed | Intake, then 2, 6, 12, and 18 mos. | T/N |
| Blood specimens for future biomarker studies | NA | Five monthly visits | N |
| Catheter for intensive pharmacokinetics[2] | NA | Seven specimens over a 24-hour period | N |
| Assign OBT[3] | Initial | NA | T |
| Blinding | NA | Screening | N |
| Assign OBT + linezolid | NA | Screening | T |
| Assign OBT + placebo | NA | Screening | T/N |
| Administer regimen through directly observed therapy | Duration of treatment | Duration of treatment | T |

[1] T = therapeutic warrant, N = nontherapeutic warrant.
[2] The pharmacokinetic specimens are obtained under a separate consent process.
[3] OBT = optimized background therapy.

## Table 2.
## Benefit-Harm Analysis of Therapeutic Procedures

| *Adverse Events* | *Eligibility Criteria* | *Monitoring* |
|---|---|---|
| Myelosuppression | Hemoglobin level ≥ 9.0 g/dL<br>Platelet count of ≥ 80,000/mm$^3$ | Hematology |
| Optic neuropathy | Exclusion of subjects with poor visual acuity or color vision | Vision testing |
| Peripheral neuropathy | Exclusion of subjects with significant, preexisting peripheral neuropathy | Neurology history and physical exam |
| Serotonin syndrome | Exclusion of subjects with planned therapy using drugs with unacceptable interactions | Assessment of concomitant medications |
| Congenital defects | Women of childbearing age are not pregnant or breastfeeding and pledge to practice birth control or abstain from intercourse | No special monitoring |

## Table 3.
## Knowledge-Harm Analysis of Nontherapeutic Procedures

| *Nontherapeutic Procedure* | *Knowledge* | *Minimize Risk* |
|---|---|---|
| Neurology history and physical | Adverse event patterns | Routine examination |
| Vision testing | Adverse event patterns | Routine examination |
| Chemistry | Adverse event patterns | Add-on to therapeutic blood draws |
| Hematology | Adverse event patterns | Add-on to therapeutic blood draws |
| TB smear and culture | Efficacy information (time-to-conversion of culture) | Noninvasive specimen collection |
| TB susceptibility | Efficacy information (patterns of drug resistance) | Add-on to therapeutic TB smear/culture |
| Chest x-ray | TB progression and efficacy information | Routine examination[1] |
| Blood specimens for future biomarker studies | Biomarkers to make future studies more efficient | Add-on to therapeutic blood draws |
| Catheter for intensive pharmacokinetics | Drug activity in the body | Single stick; in-patient procedure to manage physical responses |
| CD4 cell count | HIV progression | Add-on to blood draws |
| Random assignment and blinding | Sound scientific design | No inherent nontherapeutic risk |

[1] Chest x-ray carries some risk from exposure to radiation, which is managed according to routine procedures.