Statistical Issues in the Design of a Cluster Randomized Tuberculosis Prevention Trial

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PHOENIx MDR TB Trial

• Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients
• Multinational cluster randomized clinical trial (cRCT)
• Being undertaken jointly by the NIH-funded AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT)

Use trial to illustrate issues more pertinent to cluster RCTs than individual RCTs
PHOENIx Trial Hypothesis

Treating child, adolescent, and adult household contacts (HHCs) of MDR-TB patients who are at high risk of developing TB with delamanid (DLM) will substantially reduce the risk of developing TB compared with treatment with isoniazid (INH) preventive therapy.

**Concept:**
Contacts likely to be latently infected.
Treatment will prevent development of active (MDR) TB.

Trial has an efficacy focus
Identify MDR TB patient

Identify “high risk” HHC of the patient

Treat (DLM or INH) for 6 months

Continue to follow through to 2 years for primary outcome of development of active TB

Large trial (n=3452) with large number of clusters (1752)
Why Do a Cluster Randomized Trial? (Or .... Why Not Randomize Individuals?)

• Could randomize individual HHCs
  – So identify a single HHC of each MDR TB patient (statistically: randomized HHCs are then “independent” of each other)

• But, in practice, approach would be to identify/treat all (high-risk) HHCs of an MDR TB patient

• And there might be “herd”-type effects from intervening within clusters
  – Reduced risk of secondary transmission?
  – Improved adherence?

• Trial quicker? (cost lower?)
PHOENIx MDR TB Trial: Households

“Household”

MDR TB Index Case

Contacts
Defining the Cluster: Who is a Household Contact?

- General definition: A person who currently lives or lived in the same dwelling unit or plot of land and shares or shared the same housekeeping arrangements as the index case and who reports exposure within 180 days prior to the index case starting MDR-TB treatment.
- Multi-national study, so site-specific definitions consistent with the general definition approved by protocol team.

Definition relevant if randomizing a single HHC per index case but likely more relevant when enrolling multiple HHCs (cluster) per case.
PHOENIx MDR TB Trial: Households

“Household”

MDR TB Index Case

“High risk” contact(s):
* HIV-infected, or
* Children <5y, or
* TST/IGRA positive

Not “high risk” contact(s)
PHOENIx MDR TB Trial: Households

Cluster in PHOENIx Trial

MDR TB Index Case

“High risk” contact(s):
* HIV-infected, or
* Children <5y, or
* TST/IGRA positive

Not “high risk” contact(s)
Eligibility / Consent Issues

• Household (and hence the cluster) is accessed by first identifying an MDR TB patient
  – Then need a mechanism for getting consent to access the household and approach HHCs
  – More complex if the patient is a child
  – May be complex if the patient is an adult but is not “head of the household”
  – Restrictions on “eligible” MDR TB patients arising from such consent issues may affect generalizability of results

• Need to decide whether or not all cluster members have to consent/participate in order for a cluster to be enrolled in trial
When to Randomize a Cluster?

• Individual randomized trial:
  – Confirm eligibility/consent of individual
  – Randomize individual, ideally as close as possible to when randomized intervention can be started
  – Intent-to-treat analysis: all randomized individuals included in analysis

• Cluster randomized trial, ideal:
  – Confirm eligibility/consent and enumerate eligible cluster members
  – Randomize the cluster, ideally as close as possible to when randomized intervention can be started by all cluster members
  – Intent-to-treat analysis: all randomized clusters including all enumerated cluster members included in analysis
When to Randomize a Cluster: Complexity in the PHOENIx Trial

• Practical issues may mean it takes time to evaluate each HHC and confirm eligibility, including ruling out active TB if HHC has symptoms
  – standard treatment for someone with active TB is multidrug; monotherapy inadequate

• But for HHCs already established as eligible (including no active TB), delaying study drug is potentially suboptimal
  – risk of active TB may be highest closer to exposure

• So problematic to wait to randomize until eligibility determined for all cluster members
When to Randomize a Cluster? Complexity in the PHOENIx Trial

• Could take a pure ITT approach and include potential active TB cases as part of randomized cluster even though they won’t receive randomized drug
  – But adding 1-2% event rate in both arms when only expect 5% in control arm

• Practical solution:
  – Train sites about the issue
  – Randomize cluster when first eligible HHC ready to start treatment
  – Start treatment in other eligible HHCs in the cluster as soon as possible thereafter (limited timeframe)
  – Exclude those found to have active TB from treatment and analysis

• Risk if trial is open-label is that an eligible HHC might decide not to participate based on knowledge of randomized assignment so contaminating ITT analysis
  – [But such knowledge might affect retention anyway]

• Blinding (and modified ITT approach) might mitigate this problem
Stratified Randomization

- Randomizing clusters makes it more complex to account for individual level risk factors through stratification
- PHOENIx: Particular interest in the smaller “high risk” groups, eg HIV-infected individuals
- Could stratify by whether or not cluster includes an HIV-infected contact
  - Not straightforward if haven’t evaluated all eligible contacts when randomization occurs
- Stratifying by geographical site likely to help as considerable heterogeneity among sites in many factors (eg HIV prevalence low at some sites, high at others)
Cluster RCTs: Correlated Outcomes

• Basic issue in cluster RCTs: outcomes are likely to be more similar among members of the same cluster than among members of different clusters
  – Intra-cluster correlation

• PHOENIx trial:
  – Contacts in same HH likely to be infected by same MDR TB patient
  – Live in same environment
  – May have genetic factors that affect risk of active TB

• Trial design and analysis needs to take account of this correlation
Correlated Binary Outcomes: Example of What Might be Observed at Household-Level with Overall 4% of HHCs Having Active TB

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Number of active TB cases observed in household</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>“Independent” outcomes</td>
<td>88.47%</td>
</tr>
<tr>
<td>Correlated outcomes</td>
<td>91.66%</td>
</tr>
</tbody>
</table>

Possible method of analysis for cluster RCTs: Summary statistic method
Statistical Analysis of Cluster RCTs

• Model for household contact-level outcome:
  – eg, logistic regression model that describes marginal log odds ratio of having active TB by 2 years to compare randomized treatments
  – generalized estimating equation (GEE) approach for fitting marginal model takes account of correlated outcomes
  – Provides standard framework for adjusted analyses and subgroup analyses etc.

• Handling losses to follow-up adds complexity
  – To compare treatments, could use Kaplan-Meier estimates at 2y with SE obtained taking account of correlation
  – Assumptions for model-based (time-to-event) analysis may be difficult to justify in PHOENIx
PHOENIx: Stratified Analysis

- Considerable interest in evaluating differences between randomized drugs in each of the three high risk group (children <5y; HIV-infected; TST/IGRA+)
- Could use Kaplan-Meier estimates at 2y for each randomized drug in each risk group separately (with SEs in each risk group obtained taking account of correlation)
- Then weighted average of the three estimated differences to provide an overall estimate of treatment difference (stratified analysis)
  - SE for weighted average more complex as same HH could contribute to two or three risk group strata, so the three estimates are correlated
Sample Size for Cluster RCTs

• Correlated outcomes means less information per HHC in a cluster RCT compared with an individual RCT
• So need more HHCs in a cluster RCT than individual RCT to achieve same power
• “Design factor” (or “inflation factor”) measures the relative increase for cRCT versus iRCT
• Widely used approximation for the design factor is:
  – $\{1+ [m-1] \rho\}$, where $m$ is the mean cluster size (mean number of high risk contacts per HH) and $\rho$ is the intra-cluster correlation.
  – In practice, $\rho$ often (very) small but impact on sample size can still be large as being multiplied by $(m – 1)$
Sample Size for Cluster RCTs

• PHOENIx trial: currently assuming $m=2$ and $\rho=0.15$, giving design factor of 1.15
  – so need 15% increase in number of HHCs compared to design where randomizing “independent” HHCs

• Better approximation for design factor is:
  – $\{1+ [m \ (1+CV^2)-1] \ \rho\}$ where CV is the coefficient of variation for the number of high risk contacts per HH
  – PHOENIx trial currently assuming $CV^2 = 0.6667$, giving design factor of 1.2

• PHOENIx Feasibility Study will help refine estimates of $m$, $\rho$ and $CV$
  – potentially can then estimate design factor directly by comparing variance of incidence estimator taking account of correlation with estimator that (incorrectly) ignores the correlation
Data Sharing

• Big push by many organizations (EMA, NIH, journals, etc) for clinical trial data to be made available
• Data sharing under a Data Usage Agreement may not raise particularly different issues for a cluster versus individual RCT
• Public access data sharing more complex for a cluster RCT
  – eg releasing age/sex/race/ethnicity of a group of individuals in the same HH probably does make it easier to identify that HH
Conclusion

• At one level just doing a trial in which clusters rather than individuals are randomized

• The devil is, however, in the details ...... significant practical and ethical details