RCTs Lecture 3
Clustered trial designs
Trial safety
Oversight of clinical trials

Greg Fox, McGill University
Outline

- Cluster Randomized and stepped wedged intervention trials
- Ethical standards in clinical trials
- Ensuring participant safety
- Study oversight
Cluster randomized trials
Demonstration

Research question:
What is the effectiveness of “DOCS” in the prevention of students falling asleep during this lecture?

Study design: Cluster randomized controlled trial
Demonstration

Primary outcome:
The proportion of students, in each group, who fall asleep during the first twenty minutes of this lecture.
Methods

Intervention:
DOCS (Directly Observed Chocolate, Short Course)

Control:
DOBS (Directly Observed Blueberry, Short Course)
Methods

Randomization by location in the lecture theatre
Group 1, 4, 5: Intervention (DOCS)
Group 2, 3, 6: Control (DOBS)
Verbal consent

1. Training
2. ‘Run in’ period
3. Implementation
Cluster randomized trials
Cluster randomized trials

A cluster RCT randomises social units or groups to differing study arms.

These groups (units of randomization) are often social units of variable size (e.g. households, health facilities, neighbourhoods, communities, schools).

Ayles, Zamstar study Lancet 2013
### RCTs versus cluster RCTs

<table>
<thead>
<tr>
<th></th>
<th>Standard RCTs</th>
<th>Cluster RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unit of randomization</strong></td>
<td>The individual subject</td>
<td>The cluster</td>
</tr>
<tr>
<td><strong>Unit of observation</strong></td>
<td>Each individual subject</td>
<td>Individuals selected from within each cluster</td>
</tr>
<tr>
<td><strong>Ethical issues</strong>*</td>
<td>Individual subject consent</td>
<td>Clusters, and/or individual subject consent</td>
</tr>
<tr>
<td><strong>Timing of the consent</strong></td>
<td>Before allocation to study arm</td>
<td>Before or after allocation to study arm</td>
</tr>
</tbody>
</table>

*Taljaard, Trials 2009*
Why choose a cluster RCT?

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It may be the most practical</td>
<td>• May require much larger sample sizes (less efficient design, owing to correlation of responses within clusters)</td>
</tr>
<tr>
<td>• Evaluates an intervention operating at a cluster level</td>
<td>• May be biased (may lack balance between arms)</td>
</tr>
<tr>
<td>• Evaluates an interventions involving health care providers who treat many patients</td>
<td>• More complex to design and analyse</td>
</tr>
<tr>
<td>• Accounts for possible ‘contamination’ of effect within clusters</td>
<td>• Ethical challenges relating to informed consent</td>
</tr>
<tr>
<td>• Enables the study of the intervention upon others not receiving intervention directly</td>
<td></td>
</tr>
<tr>
<td>• Data may be easier to obtain at a cluster level</td>
<td></td>
</tr>
</tbody>
</table>
Design issues for cluster RCTs

- **Clustering**: members of the same cluster are more likely to have the same outcome
  - Clustering has a greater impact on effect estimates when outcomes are affected by characteristics within a cluster (geography, health care delivery, self-selection)
  - ‘Between cluster variability’ (quantified by ‘intra-class correlation coefficient’, ICC)
  - Failure to account for clustering will increase type I error, and cause narrow confidence intervals
  - Sample size needs to be adjusted for the ICC
<table>
<thead>
<tr>
<th>Study (year published)</th>
<th>Country</th>
<th>Intervention</th>
<th>Units of randomization [observation]</th>
<th>Outcomes</th>
<th>Number of clusters</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thibela (NEJM 2014)</td>
<td>South Africa</td>
<td>Screening, LTBI treatment</td>
<td>Mines [all individuals in each mine / sample]</td>
<td>TB incidence at end; Prevalence of TB</td>
<td>15</td>
<td>78,744 miners eligible</td>
</tr>
<tr>
<td>Zamstar (Lancet 2013)</td>
<td>Zambia, South Africa</td>
<td>Community TB screening, household HIV care</td>
<td>Communities [Sample in prevalence survey, child cohort]</td>
<td>TB prevalence Latent TB incidence</td>
<td>24</td>
<td>8,809 children</td>
</tr>
<tr>
<td>DetecTB (Lancet 2010)</td>
<td>Zimbabwe</td>
<td>Community based TB screening (household or community)</td>
<td>Communities [sample of screened subjects; selected HHs]</td>
<td>Yield of TB , prevalence of TB in randomly selected HHs</td>
<td>46</td>
<td>110,432</td>
</tr>
<tr>
<td>ACT2 study (ongoing)</td>
<td>Vietnam</td>
<td>HH contact investigation</td>
<td>District clinic [recruited contacts by households]</td>
<td>Incidence of TB</td>
<td>70</td>
<td>24,578</td>
</tr>
<tr>
<td>ACT3 study (ongoing)</td>
<td>Vietnam</td>
<td>Community screening</td>
<td>Village (&gt;15y)</td>
<td>Prevalence after 4 years; LTBI inc. in children</td>
<td>120</td>
<td>≈120,000</td>
</tr>
</tbody>
</table>
Case studies of cluster RCTs
The ‘Active Case-finding in TB’ (ACT) studies

**ACT2 study**: A cluster randomized trial of household contact investigation in Vietnam

**ACT3 study**: A cluster randomized trial of community screening using Xpert in Vietnam
Hypothesis:

A program of targeted active case finding among household contacts of TB patients will significantly increase the detection of active TB, compared to usual passive case-finding.
ACT2: A cluster RCT of household contact investigation

3,500 smear positive TB patients
10,000 contacts

3,500 smear positive TB patients
10,000 contacts

Screening for TB at 0, 6, 12 and 24 months

Usual follow-up Review at 24 months
<table>
<thead>
<tr>
<th>Inclusion criteria for index patients</th>
<th>Inclusion criteria for household contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged 15 years or older</td>
<td>• Any age</td>
</tr>
<tr>
<td>• Acid-fast bacilli positive</td>
<td>• Living in the same household, within the past 3 months</td>
</tr>
<tr>
<td>pulmonary TB - either:</td>
<td></td>
</tr>
<tr>
<td>• 1 positive sputum smear with</td>
<td>• Not currently taking anti-TB treatment</td>
</tr>
<tr>
<td>chest Xray changes;</td>
<td></td>
</tr>
<tr>
<td>• 1 positive sputum smear and a</td>
<td></td>
</tr>
<tr>
<td>positive culture, or</td>
<td></td>
</tr>
<tr>
<td>• 2 positive sputum smears.</td>
<td></td>
</tr>
</tbody>
</table>
Intervention at pilot sites and screening districts

Baseline

6 months

12 months

24 months

Interview, CXR

Sputum culture if suspicion of TB

Interview, CXR

Sputum culture if suspicion of TB

Interview, CXR

Sputum culture if suspicion of TB

Interview, CXR
### Number of clusters by region and setting

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total clusters</strong></td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td><strong>By region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Centre</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>South</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td><strong>By setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rural</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Urban</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>
## Baseline characteristics of contacts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>%</td>
</tr>
<tr>
<td>Total contacts</td>
<td>14,332</td>
<td></td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>2594</td>
<td>(18.4%)</td>
</tr>
<tr>
<td>15 – 24 years</td>
<td>2628</td>
<td>(18.7%)</td>
</tr>
<tr>
<td>25 - 39 years</td>
<td>3540</td>
<td>(25.1%)</td>
</tr>
<tr>
<td>40 - 59 years</td>
<td>4047</td>
<td>(28.7%)</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>1279</td>
<td>(9.1%)</td>
</tr>
<tr>
<td>Median age, years (IQR)</td>
<td>31.9</td>
<td>(19 - 48)</td>
</tr>
<tr>
<td>Male gender</td>
<td>6009</td>
<td>(42%)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>382</td>
<td>(2.7%)</td>
</tr>
<tr>
<td>Centre</td>
<td>2,049</td>
<td>(14.3%)</td>
</tr>
<tr>
<td>South</td>
<td>11,901</td>
<td>(83%)</td>
</tr>
<tr>
<td>Past history of TB</td>
<td>286</td>
<td>(2.0%)</td>
</tr>
<tr>
<td>Previously diagnosed HIV</td>
<td>25</td>
<td>(0.2%)</td>
</tr>
</tbody>
</table>
Data management

3G network

3G network
ACT2 cluster RCT: key lessons

• DESIGN:
  – Clustering accounted for health system structure
  – Sample size calculations: large number of clusters
  – Intervention: Relatively simple, scalable
  – Balanced randomization strategy

• IMPLEMENTATION
  – Challenges standardizing the intervention
  – Run-in period to assess suitability (pre-randomization)
  – Collaboration between Vietnamese and Australian teams
  – Implemented multiple ‘add on’ studies (costings, barriers to care, MDR contacts)
  – Monitoring and evaluation critical
# Stepped wedge vs cluster RCT

## Cluster RCT

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Time 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

## Cross-over study

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Time 1</th>
<th>Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

## Stepped-wedge study

(cross over in one direction)

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Each cell represents a data collection point.
Features of stepped wedge studies

- Stepped wedge studies is a semi-randomized study design
- Stagger an intervention by clusters over time
- Every site receives the intervention
- Data collected at each step, as new participants start
- Can randomize which sites start (or match/stratify)
- Power improves with increasing number of steps
### Why choose a stepped wedge design?

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>It may be the most practical</strong></td>
<td>• Same disadvantages as cluster RCTs</td>
</tr>
<tr>
<td>• All individuals receive intervention (when thought to be beneficial)</td>
<td>• Usually more efficient than parallel cluster RCTs (smaller design effect for fixed clusters)</td>
</tr>
<tr>
<td>• Clusters act as their own controls</td>
<td>• Bias may arise from changing characteristics of clusters over time</td>
</tr>
<tr>
<td>• Require smaller sample sizes than parallel group designs</td>
<td>• Complex sample size calc. and analyses (account for design in analyses)</td>
</tr>
<tr>
<td>• Possible to analyse effect of time on outcomes</td>
<td></td>
</tr>
<tr>
<td>• Recruitment may be easier (people know they will receive intervention)</td>
<td></td>
</tr>
<tr>
<td>• May be more efficient, if less clusters are available</td>
<td></td>
</tr>
</tbody>
</table>

Woertman, J Clin Epidemol 2013
Example: ThRIO study

Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial

Betina Durovni, Valeria Saraceni, Lawrence H Moulton, Antonio G Pacheco, Solange C Cavalcante, Bonnie S King, Silvia Cohn, Anne Efron, Richard E Chaisson, Jonathan E Golub

Summary

Background Preventive therapy for tuberculosis in patients with HIV is effective, but it has not been widely implemented in moderate or high-burden settings. We assessed the effect of widespread use of isoniazid preventive therapy on rates of tuberculosis and death in people with HIV in Brazil.

Methods We did a stepped wedge, cluster-randomised trial with patients actively enrolled in 29 HIV clinics in Rio de Janeiro. Clinic staff were trained in tuberculosis screening, use of tuberculin skin tests, and use of isoniazid preventive therapy. Clinics were randomly allocated a date to begin the intervention period, with two clinics beginning the intervention every 2 months starting from Sept 1, 2005. The primary outcome was tuberculosis incidence alone or combined with death in the control versus intervention periods until Aug 31, 2009. This trial is registered at ClinicalTrials.gov, number NCT00107887.

Results Of 17,413 patients in the cohort, 12,816 were eligible for the intervention. Overall, there were 475 tuberculosis cases and 838 deaths. The intervention increased the rate of patients receiving skin tests from 19 per 100 person-years to 59 per 100 person-years, and from 36 per 100 person-years to 144 per 100 person-years for those eligible for isoniazid

Why not do a conventional RCT?
**Example: ThRIO study**

<table>
<thead>
<tr>
<th>Study (year published)</th>
<th>Country</th>
<th>Intervention</th>
<th>Units of randomization [observation]</th>
<th>Outcomes</th>
<th>Number of clusters</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durovni (2013)</td>
<td>Brasil</td>
<td>TST and INH for HIV patients</td>
<td>HIV clinics</td>
<td>Incidence of TB disease</td>
<td>29</td>
<td>17,413</td>
</tr>
</tbody>
</table>

*Figure 1* Clinics 1 and 2 entered the intervention period in first month of the trial (September 2007) and the intervention period in month 3. Two clinics will continue to be phased-in to the intervention period through January 2008. Prior to starting the intervention, all events and person time accumulating within a clinic will be attributed to the control arm of the study ( []). Once a clinic begins the intervention, all events and person time will be attributed to the intervention arm of the study ( []). After 38 months (January 2008), all clinics will have begun the intervention.
<table>
<thead>
<tr>
<th>Study (year published)</th>
<th>Country</th>
<th>Intervention</th>
<th>Units of randomization [observation]</th>
<th>Outcomes</th>
<th>Number of clusters</th>
<th>Number of individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durovni (2013)</td>
<td>Brasil</td>
<td>TST and INH for HIV patients</td>
<td>HIV clinics</td>
<td>Incidence of TB disease</td>
<td>29</td>
<td>17,413</td>
</tr>
</tbody>
</table>
Example: THRio study

• Intervention:
  – Training clinics to implement TB screening
  – TST to be performed
  – IPT given for all TST+ and all contacts

• Randomization using restricted design (incorporating clinic characteristics – HIV, education, mean CD4+, geography)

• Intervention achieved 13% reduction in TB, 28% reduction in TB and death (adjusted Cox proportional hazards)
Part II

Participant safety in clinical trials
Ethical conduct of clinical trials

• Protecting the rights, safety and well-being of trial subjects is a key responsibility of study investigators

• The principles for conducting clinical trials have been enshrined in key international standards:
  – Nuremburg Code (1947)
  – Declaration of Helsinki (1964)
  – ICH Guidelines for Good Clinical Practice for studies of pharmaceutical products (1996)
Informed consent

- Informed consent ensures a participant fully understands the risks and benefits of participating, and that it is their decision to participate or not.
- Written informed consent is most common in clinical studies, although sometimes verbal consent is sufficient (e.g. ACT3 study).
- Participation must not be coerced and potential participants must have negative consequences for declining to participate.
Ensuring safety in clinical trials

- Safety is central to clinical trial integrity
- Safety of study participants needs to be addressed at each stage of planning and implementation of the trial
- The way in which safety is addressed will depend upon the nature of the intervention
Ensuring safety in clinical trials

- Design of trial
- Developing procedures
- Training and launch
- Recruitment and intervention
  - Managing adverse events
- Trial reporting
Safety in clinical trials

At the design stage of trial

- Ensure the study will address an important question
- Establish that intervention and control are likely to be safe
- Establish whether safety can be monitored adequately with available resources.
- Designate stopping points to evaluate safety (if applicable)
- Obtain appropriate IRB oversight
Safety in clinical trials

Developing study procedures
- Establish detailed procedures to identify, manage and report adverse events
- Develop forms and processes for adverse event reporting
- Ensure protocols address foreseeable safety concerns
- Establish a Data Safety Monitoring Board (DSMB), if appropriate
Safety in clinical trials

Training and study launch
- Train research staff about how to report adverse events
- Verify that clinical oversight is appropriate at each site
- Explain scheduled study oversight and safety review processes
Safety in clinical trials

Design of trial

Developing procedures

Training and launch

Recruitment and intervention

Managing adverse events

Trial reporting

Recruitment and intervention

- Maintain close communication between investigators and researchers
- Ensure safety data is included in scheduled reporting
- Ensure DSMB receives reports
- Perform regular, scheduled supervisory visits (depending on scale of study)
- Apply pre-designated safety review (if applicable)
Safety in clinical trials

Managing adverse events

- Identify separate criteria for severe / life threatening Aes
- Manage urgent clinical events safely and appropriately
- Ensure appropriate authority is notified promptly of severe events
- Inform sponsor / IRB of severe adverse events
Adverse events

- **Adverse events** are any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment
  - Includes unfavourable clinical signs or test results

- **A serious adverse event** is any untoward medical occurrence occurring during an intervention that results in death, is life-threatening or requires hospitalisation or causes persistent disability

ICH Guidelines, 1996
Adverse event reporting

- Study protocols should specify the processes that will be followed in the event of adverse events.
- All **serious adverse events** should be reported immediately to the sponsor (in study protocol).
  - Immediate reports must be followed by detailed written reports (which should be de-identified) to the study sponsor and IRB / IEC.
- Adequate medical care must be provided to a subject for any adverse events, including clinically significant laboratory abnormalities, related to the trial.
- The form of adverse event reporting will depend upon the intervention.

ICH Guidelines, 1996
Adverse event reporting

Adverse events should be clearly documented:

• Describe clinical assessment and relevant tests
• Define management plan, including follow-up
• Report outcome of management
Adverse event reporting

- A study binder can be a useful way of collating safety information:
  - Reporting of adverse events, including resolution
  - Monitoring log
  - Monitoring visit reports
  - Correspondence regarding patient care
Safety in clinical trials

**Design of trial**

**Developing procedures**

**Training and launch**

**Recruitment and intervention**

**Managing adverse events**

**Trial reporting**

- Report the incidence of adverse events (drug trials)
- Report the safety processes in place for participants
- All important harms in both groups should be reported (CONSORT reporting guidelines for RCTs / Cluster RCTs)
Oversight of clinical trials
Site monitoring visits

Site monitoring visits play an important role in study oversight.

The function of monitoring visits include:

- Strengthen relationships between investigators and staff
- Ensure rights and well-being of subjects
- Ensure data are accurate and verifiable source documents
- That the trial is being conducted consistently with the protocol and GCP guidelines (as appropriate)
- Review study documents, including safety reports
- Review any difficulties with recruitment

See also: Global Clinical Trials, Chin and Bairu eds, 2011 Elsevier
Oversight of clinical trials

- Investigators
  - Trial Coordinator
    - Site coordinator
      - Research staff
      - Research staff
      - Study participants

Study oversight groups:
- Data Safety Monitoring Board
- Trial Advisory Committee
- Expert Panels (Clinical, Laboratory)
- Institutional Review Board / External Ethics Committee
- Internal / external auditor
## Responsibilities in a clinical trial

### Coordinators and Research staff

<table>
<thead>
<tr>
<th>Site coordinators</th>
<th>Local research staff</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Implement the research protocol as written</td>
<td>• Ensure subject safety</td>
</tr>
<tr>
<td>• Strictly adhere to inclusion and exclusion criteria</td>
<td>• Determine if immediate intervention is needed for an adverse event, and manage according to protocols</td>
</tr>
<tr>
<td>• Continued adherence to the protocol throughout the study</td>
<td>• Document AE/SAE</td>
</tr>
<tr>
<td>• Monitor subject status (e.g. subject wellbeing, toxicity, minimise risk)</td>
<td></td>
</tr>
<tr>
<td>• Monitor safety data collection</td>
<td></td>
</tr>
<tr>
<td>• Adhere to pre-defined stopping rules</td>
<td></td>
</tr>
</tbody>
</table>
### Data Safety Monitoring Board (DSMB)

<table>
<thead>
<tr>
<th>What is this?</th>
<th>In some studies, an independent data safety monitoring board may be appointed to ensure participant safety. Most studies don’t require this.</th>
</tr>
</thead>
</table>
| **Main roles**        | • Review safety data to protect study subjects from harm  
                        • Perform interim analyses to avoid prolonged exposure to an unnecessary therapy  
                        • Consider premature trial termination, if applicable |
| **Membership**        | Independent experts with relevant experience                                                      |
| **Reports to…**       | Trial advisory committee  
                        Institutional Review Board and other regulators       |
**Advisory Committee**

<table>
<thead>
<tr>
<th>What is this?</th>
<th>A panel of independent experts that may be appointed by the Investigators to provide technical advice about scientific or implementation issues</th>
</tr>
</thead>
</table>
| Main roles   | • Provide expert advice to ensure optimal scientific quality and study safety  
• Provide independent evaluation of the scientific merit of a study |
| Membership   | Clinicians, trialists, technical experts, patient representatives  
An expert clinical panel may provide specific advice relating to one area of the study (e.g laboratory) |
| Reports to... | Study Investigators  
May be independently appointed by a governing research institutions |
### IRBs / IECs

#### What is this?
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial (ICH, 1996).

#### Main roles
- Safeguard the rights, safety and well-being of all trial subjects
- Reviewing, approving and providing continuing review of trial protocol and amendments
- Reviewing and approving consent mechanism for study participants

#### Membership
- At least 5 members, including one whose primary area of interest is non-scientific
- At least 1 member who is independent of study site

#### Reports to...
Institutional authority

See ICH Guidelines for more detail.
What is this? | A study auditor may be asked by study sponsors to perform trial quality assurance
---|---
**Main roles** | • **Independently** review the study, separately from routine monitoring and quality control  
• Review of all trial related activities and documents to determine whether they comply with: (a) protocol; (b) sponsor’s requirements; (c) Good Clinical Practice; (d) Applicable regulatory requirements  
• Reviews original documents  
• Provides a report (audit trail) to the sponsor, and if requested to the regulatory authority

**Membership** | Independent experts with relevant experience  
Individuals trained to conduct audits

**Reports to…** | The study sponsor / Institution
Acknowledgements for ACT2 and ACT3 studies

National Tuberculosis Program
A/Prof Nguyen Viet Nhung
A/Prof Dinh Ngoc Sy

Pham Ngoc Thach Hospital
An Giang, Binh Dinh, Ca Mau
Can Tho, Da Nang, Ha Noi,
Tien Giang, Ho Chi Minh City,
Vinh Phuc Tuberculosis Programs

National Institutes of Hygiene and Epidemiology
Dr Nguyen Van Anh

Australian National Health and Medical Research Council (NHMRC)
Woolcock Institute of Medical Research, Sydney
Dr Carol Armour, Director and staff
Woolcock Institute of Medical Research, Vietnam
Dr Nguyen Thu Anh

And, most importantly, the people of the participating provinces
Recommended reading

- ICH harmonised tripartite guideline for Good Clinical Practice E6(R1), 1996
- International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS, Geneva 2002
Research question:

In a high burden setting for TB, what is the effect of community-wide screening for TB using the Xpert MTB/RIF platform annually for four years, compared with usual TB control practices, on the prevalence of culture-proven TB?
Overview of ACT3 study design

Ca Mau province

Intervention
60 sub-communes (clusters)

Year 1
All adults: Questionnaire + sputum (Xpert)

Year 2
All adults: Questionnaire + sputum (Xpert)

Year 3
All adults: Questionnaire + sputum (Xpert)

Year 4
All adults: Questionnaire + sputum (Xpert + smear + culture)
All school entry children (age 6): QuantiFERON

Control
60 sub-communes (clusters)

Year 4
All adults: Questionnaire + sputum (smear + culture)
All school entry children (age 6): QuantiFERON

Provincial prevalence survey
Annual screening cycle in each village

1. Planning
   - Lessons Learned
   - Logistic preparation
   - 6 weeks before screening

2. Surveying
   - Logistic preparation
   - 2 weeks before screening

3. Screening (6-8 days)
   - Logistic preparation
   - 1 week before screening

4. Post screening/Follow up
   - Follow up with culture results from Can Tho hospital
   - Follow up for TB treatment (6-9 months)
   - Report to TC

2 days after screening:
- Screening report (base on the database)
- Financial report
- Unplanned issues
- Inventory checklist
- Missing data (if need)

On the last day
Brief report about screening results to the CPC (commune people committee), health port and AP leader

Day 1: Screening venue arrangement (chairs, panels, banners)
Day 2-10: Screening
- Screening processing
- Transportation of samples to lab
- Second time of sputum collection for cases with GeneXpert (+)
- Evaluate work efficiency, participation rate and collected sputum samples
Data management

3G network

![Mobile device interface with 3G network indication]
ACT3 cluster RCT: key lessons

• DESIGN:
  – Choice of province: to minimise migration effect
  – Clusters chosen to reduce contamination
  – Screening intervention: Xpert, not Xray (context, access)
  – Duration of follow-up: 4 years

• IMPLEMENTATION
  – Participation rate: currently >90%
  – Laboratory capacity
  – Human resources a key priority
  – Reporting and data management is essential (paper based can be fine)