Principles and Structure of a Research Protocol

Anthony D Harries
The Union, Paris, France
MSF, Brussels, Belgium
BASIC STRUCTURE

• Background and rationale to study

• Aim and objectives (the research question)

• Methods (includes ethics submission)

• Budget and time lines

• Justification
Background and Rationale

• Country / context in which study is to be done

• The problem and what is known about it

• Are there knowledge gaps?

• Will this study fill those knowledge gaps?
Aim and Objectives

• Aim is broad

• Objectives are more specific
For example: (1)

**AIM**

To document the management and outcome of new smear-positive Pulmonary TB patients who fail first line treatment in Malawi
For example: (2)

Specific Objectives are to determine:

1. The number of new smear-positive PTB patients who failed treatment
2. The management of patients who failed
3. Their treatment outcomes on Re-Rx regimen
4. The culture and drug sensitivity results of those who failed and in relation to treatment outcomes
Methods

- **Study design** (descriptive, case-control, cohort)
- **Setting** – general and study site
- **Participants** (and study period)
- **Data variables to be collected**:  
  - exposure and outcome variables  
  - data collection instrument *(when data collected)*  
  - data validation
- **Sources of data**
- **Analysis and statistics** *(sample size, if needed)*
- **Ethics approval**
Recurrent Tuberculosis in Malawi
BACKGROUND: NTP in Malawi (1)

- Model “DOTS” Programme
- Management by District TB officers
- Excellent Monitoring and Evaluation, using Registers and quarterly cohort reporting

- 27,000 cases of TB registered per annum
- HIV-prevalence in TB patients = 70%
The problem and rationale (2)

Between 1987 to 1999:

- % Patients registered nationally with Relapse smear-positive PTB in Malawi declined from 6% to 3%
- No reported cases of recurrent smear-negative TB

BUT

- HIV-prevalence in TB patients increased from 30% to 70%
- Research literature from Africa (4 studies) showed that recurrent TB increases as HIV-prevalence increases
### Annual TB recurrence

<table>
<thead>
<tr>
<th>Country</th>
<th>HIV+ve</th>
<th>HIV-ve</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire</td>
<td>18%</td>
<td>6%</td>
<td>(Perriens et al 1991)</td>
</tr>
<tr>
<td>Kenya</td>
<td>17%</td>
<td>0.5%</td>
<td>(Hawken et al 1993)</td>
</tr>
<tr>
<td>Zambia</td>
<td>22%</td>
<td>6%</td>
<td>(Elliott et al 1995)</td>
</tr>
<tr>
<td>S.Africa</td>
<td>16%</td>
<td>6%</td>
<td>(Sonnenberg et al 2001)</td>
</tr>
</tbody>
</table>
% Patients registered nationally with relapse smear-positive PTB in Malawi

% Relapses

Year

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor
<table>
<thead>
<tr>
<th>Year</th>
<th>Site</th>
<th>No. TB</th>
<th>% HIV-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Zomba</td>
<td>125</td>
<td>26</td>
</tr>
<tr>
<td>1993</td>
<td>Mzuzu</td>
<td>167</td>
<td>67</td>
</tr>
<tr>
<td>1994</td>
<td>Blantyre</td>
<td>665</td>
<td>75</td>
</tr>
<tr>
<td>1995</td>
<td>Zomba</td>
<td>793</td>
<td>77</td>
</tr>
<tr>
<td>2000</td>
<td>Malawi</td>
<td>512</td>
<td>77</td>
</tr>
</tbody>
</table>
The research question:

Is the Malawi NTP missing recurrent tuberculosis under routine programme settings?
AIM of the Study

To determine whether patients who have been registered as “New TB” have been previously diagnosed and treated as relapse smear-positive Pulmonary TB and recurrent smear-negative TB?
METHODS
Design

• This will be a cross-sectional study involving a structured interview of TB patients

[study designs include descriptive, cross-sectional, case-control, and cohort – either prospective or retrospective]
Setting and site visits

• **General:** Malawi is a small country in Africa with high HIV and TB burden. There is a country-wide DOTS Programme and all patients spend the first two months of TB treatment in hospital receiving initial phase therapy.

• **Site visits:** All hospitals in the country that register and treat patients with TB will be visited. These include 3 central hospitals, 22 district hospitals and 18 mission hospitals.

• **Timing of the visits:** These hospitals will be visited between January and June 1999 as part of the routine NTP supervision.
Participants (patients)

• **All** patients who are in hospital receiving treatment during the initial phase and who have been registered as “New TB” will be interviewed using a structured questionnaire.

• Patients will be identified by going round the TB wards (all patients are admitted to TB wards) in a set fashion and this will include all patients in their beds.

*Patients not in their beds at the time will not be interviewed: a record will be made of TB registration number, age, sex, and type of TB.*
Variables, data collection and validation

• Variables to be collected include: -TB registration no., age, sex, type of TB, previous history of TB

• Those with previous history of TB will be asked: when, what type of TB, was treatment completed

• Data to be collected into a structured questionnaire

• Validation of data on previous TB will be done using TB identity cards wherever possible
Sources of data:

- All patients in their TB beds will be interviewed

- Patients who are out of the TB ward and cannot be traced will not be included

  [however, their age, sex and type of TB will be listed and compared with those in bed to ensure the two groups are similar]
Analysis and statistics

- Data will be entered into EPI-INFO software.
- The chi-square test will be used to compare differences in proportions between groups (odds ratios with 95% confidence intervals).
- Differences at 5% level ($p < 0.05$) to be regarded as significant.
Sample size

Not calculated because this is a national study involving all patients in hospital at the time of the visit
Ethics approval

• Study to be approved by the TB programme management group

• Ethics approval to be obtained from the Malawi National Health Science Research Committee
<table>
<thead>
<tr>
<th>Research Activity</th>
<th>Costing (USD$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two NTP operational research officers for hotel accommodation and daily perdiems</td>
<td>450</td>
</tr>
<tr>
<td>Stationary</td>
<td>50</td>
</tr>
<tr>
<td>TOTAL</td>
<td>500</td>
</tr>
</tbody>
</table>

*Research piggy-backed onto routine supervision and therefore less costly*
JUSTIFICATION

If hypothesis is correct, and previously treated patients are incorrectly registered as “new patients”, then:-

- Incorrect treatment is administered
- Incorrect data are reported to WHO
- We need to find out why and educate District TB Officers about proper management