Principles and Structure of a Research Protocol

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MEDECINS SANS FRONTIERES

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)

<u>Between 1987 to 1999:</u>

- **% 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

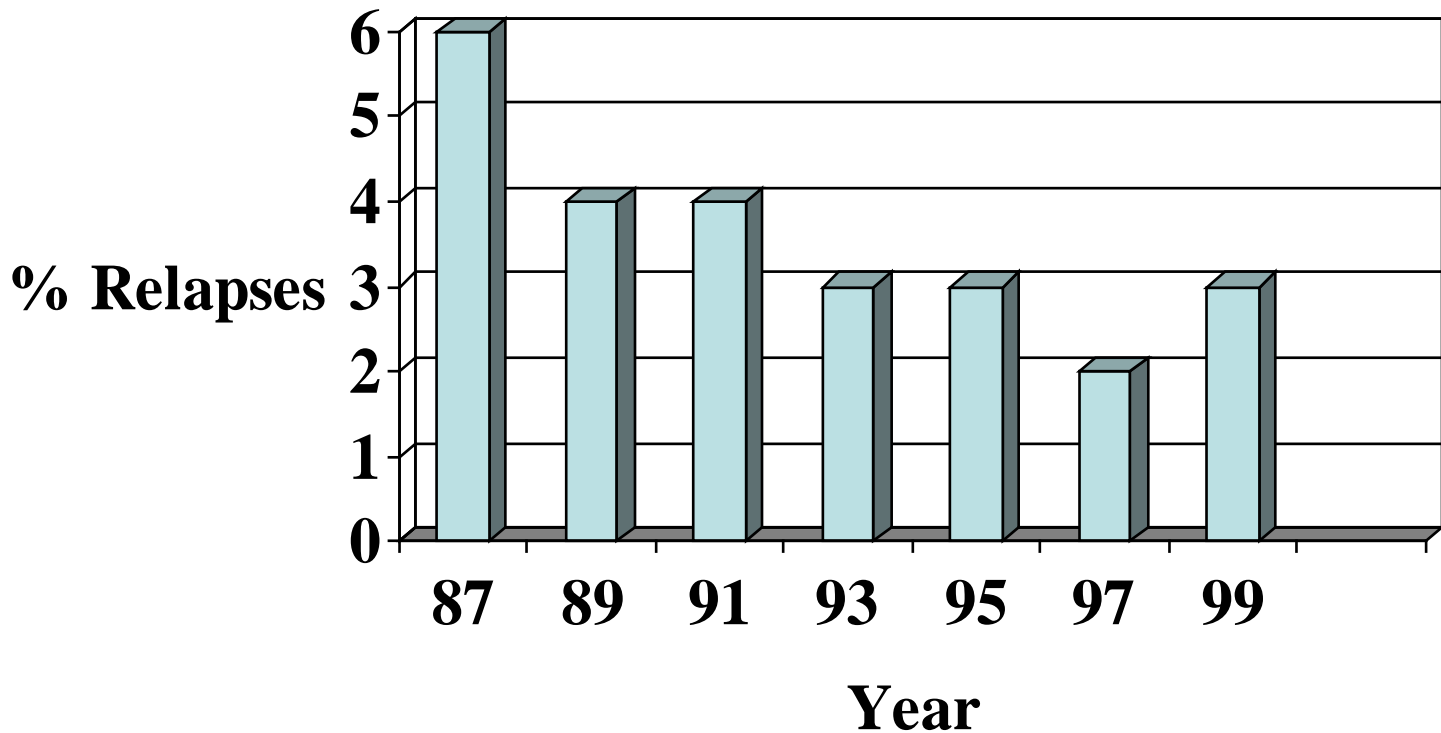|	HIV+ve	HIV-ve	
Zaire	18%	6%	(Perriens et al 1991)
Kenya	17%	0.5%	(Hawken et al 1993)
Zambia	22%	6%	(Elliott et al 1995)
S.Africa	16%	6%	(Sonnenberg et al 2001)

% Patients registered nationally with relapse smear-positive PTB in Malawi

HIV and TB in Malawi

Year	Site	No. TB	% HIV-positive
1986	Zomba	125	26
1993	Mzuzu	167	67
1994	Blantyre	665	75
1995	Zomba	793	77
2000	Malawi	512	77

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" 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

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

Setting and site visits

- <u>General:</u> 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

- <u>Site visits:</u> **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

- <u>Timing of the visits:</u> 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**

- <u>Those with previous history of TB</u> 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

- X^2 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

BUDGET

Research Activity	Costing (USD$)
Two NTP operational research officers for hotel accommodation and daily perdiems	450
Stationary	50
TOTAL	**500**

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

Results

Type of TB	Registered as "New"	Previous TB
All types	**1254**	**94 (8%)**
Sm+ve PTB	746	34 (5%)
Sm-ve PTB	282	40 (14%)
EPTB	226	20 (9%)

Only 9 out of 94 previous episodes were validated with the patient producing an Identity card

Analysis

Compared to patients with smear-positive PTB, a previous episode of TB was significantly more common in :-

- patients with smear-negative PTB
  (OR 3.5, 95% CI 2.1 - 5.7, $p < 0.001$)
- patients with EPTB
  (OR 2.0, 95% CI 1.1 - 3.7, $p < 0.05$)

Interpretation of Study

- Patients with relapse TB and recurrent TB were incorrectly registered under routine programme settings as "new patients"

- This mistake was more common in patients with smear-negative PTB and EPTB

- The reasons for these mistakes were not identified

What next?

- Results and implications of incorrect recording discussed with NTP staff at the annual NTP seminar held 3 months later

- Central Unit prepared interim guidelines about diagnosis and management of recurrent TB

- Guidelines were incorporated into revised National TB Manual about one year later

A similar study was conducted from Jan-Jun 2000

- Same aim: to determine whether patients registered with "new smear-negative PTB or new EPTB" were correctly diagnosed

- Same methodology as the study in 1999 except the focus was on smear-negative PTB and EPTB

Operational Research
Jan-Jun 2000

Type of TB	Registered "New"	Previous TB
sm-ve PTB	214	10 **(5%)**
EPTB	213	2 **(1%)**

[a big improvement on the previous year]

How did this operational research impact on the Malawi National TB Control Programme?

Malawi TB case notifications

Year	Total TB	New TB	Recurrent TB
1998	22674	22069	605 (3%)
1999	24396	23728	668 (3%)
Interventions to improve correct recording of TB cases			
2000	24846	22789	2057 (8%)
2001	27672	25217	2455 (9%)
2002	26532	23724	2808 (11%)
2003	28234	24791	3443 (12%)

Recurrent TB = relapse, failure, treatment after default, recurrent sm-ve TB