

**A randomised control trial on the effectiveness of three modalities  
of tuberculosis treatment supervision under DOTs strategy in  
Ethiopia.**

**Trial protocol**

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**Definition of terms:****District tuberculosis coordinator:**

A health worker (nurse) trained in tuberculosis control responsible to organize, supervise and give technical and logistic support to health institutions in a district. He/She is a member of a district health management office responsible to oversee the aspects of TB control programme.

**Health institution-focal person:**

A health worker trained in tuberculosis management responsible for the management of patients including direct observation of treatment and tracing defaulters. He runs TB-outpatient clinics in a health facility. He is also responsible for the documentation of treatment outcome and for reporting treatment outcome to the district TB-coordinator.

**Community Health Workers (CHWs):**

These are volunteers who serve their respective communities in health related activities without salary or compensation. They are trained for 30-45 days in health related topics mainly in health promotion and serve as a link between public health facilities and the local communities. There are two categories of CHW. These are Community Health Agents (mainly involved in environmental health activities, epidemic notification, child immunization services and treatment of malaria) and Trained Traditional Birth Attendants (mainly provide antenatal care, referral of high risk pregnancy, delivery and family planning services).

**District diagnostic centres:**

These are district hospitals and health centres where the diagnosis of suspected cases of tuberculosis is made. Health centres are equipped with microscope and perform sputum smear test for Acid fast Bacillus while hospitals also carry out x-ray examinations. Suspected patients with a smear negative result in health centres are referred to district hospital for diagnosis. Both provide follow up sputum smear examination at 2<sup>nd</sup>, 5<sup>th</sup> and 7<sup>th</sup> months.

**Health worker-Tuberculosis care (HW-TC):**

This is the standard TB care adopted by the National Tuberculosis Control Programme (NTC). Pulmonary tuberculosis patients get their treatment from nearby health institutions by a trained health worker (TB focal person). Treatment includes counselling, teaching patients about TB and its treatment, management of illness during treatment and direct observation of treatment during the initial 2 months of treatment followed by a monthly follow up visit during the subsequent 6 months.

**Community health worker-Tuberculosis care (CHW-TC):**

This is an alternative option of TB care for PTB patients. Pulmonary tuberculosis patients get their treatment from convenient CHWs trained on TB care management. Patients will be observed taking their daily treatment in their village by CHWs on daily basis during the second month of treatment followed by a fortnightly visit to the CHWs' home during the subsequent 6 months. Treatment includes giving advice about side effects of treatment, positive encouragement and referral to the nearby TB focal person when patients are severely ill and defaulter tracing if patients are lost from treatment for one week. CHWs collect drugs from nearby health facilities fortnightly during which he/she should also report about the progress of her/his patients.

**Self-administered treatment (SA-T):**

It is an alternative option of the Health Worker-tuberculosis care for PTB patients with reduced daily visits for Direct Observation of Treatment (DOT) from a TB focal person. Patients with pulmonary tuberculosis diagnosis get their initial first month treatment from the nearby health institutions by a TB focal person. Treatment includes counselling, teaching patients about TB and its treatment, management of illness during treatment and direct observation of treatment during the initial month of treatment (28 days). Patients will be allowed to take their daily treatment unobserved at home from the second month till end of treatment (7 months). Patients will visit the nearby health institution every month to collect their drugs and for medical check up.

## 1. Background

Tuberculosis is a serious health concern in sub-Saharan countries which are severely hit by the HIV epidemic. The death toll of TB and HIV co-infection is still increasing with deleterious economic and social consequences. The World Health Organization (WHO) recommended DOTS (Directly Observed Therapy Short-course Strategy) <sup>1</sup> for TB control has been introduced in most countries. The strategy comprises five key components:

- a) Government commitment,
- b) Case detection through passive case finding (sputum smear microscopy for pulmonary TB suspects),
- c) Short-course chemotherapy for all smear-positive pulmonary TB cases (under direct observation for at least the initial phase of treatment),
- d) Regular, uninterrupted supply of anti-TB drugs and,
- e) Monitoring system for programme supervision and evaluation <sup>2</sup>.

The programme objectives are to identify 70% of sputum-smear positive cases and to cure 85% of them. Tuberculosis treatment comprises an initial intensive phase and a continuation phase. The initial intensive phase lasts 2-3 months of daily treatment under the observation of a health worker in most countries, while the continuation phase involves 4-6 months of daily or intermittent self-administered treatment <sup>2</sup>. Directly observed treatment consists of an observer watching the patient taking her/his medication. This method is expected to improve patients' adherence to treatment and prevent drug resistance. The WHO DOTS guideline outlines that the person observing treatment could be a health worker, trained community member or volunteer. Following the implementation of the strategy by many African countries, improvements in terms of reviving strong national tuberculosis control programmes and better access to TB treatment have been achieved <sup>3</sup>. Nonetheless, global treatment outcome targets are still not achieved by most African countries. <sup>3</sup> Patients' non-adherence to tuberculosis (TB) treatment is a major problem. Many studies conducted since the implementation of the

DOTS strategy have reported several factors as competing causes of patient's non-adherence to TB treatment in Africa or elsewhere in the developing world (Box1).

Patient-related factors including socio-demographic factors, knowledge, beliefs and attitude about TB and its treatment have been associated with poor treatment adherence. African studies reported that male patients were more likely to default than female patients<sup>4, 5</sup>. Poor adherence to TB treatment was more common among older than younger patients<sup>6, 7</sup>. Poor economic status was also associated with poor adherence to treatment in sub-Saharan Africa<sup>4</sup> and elsewhere<sup>8, 9</sup>. Patients' life style such as alcoholism and substance abuse were shown to be risk factors elsewhere<sup>10, 11</sup>. However, little is known about their effect on TB treatment adherence in Africa. Risk factors related to patient characteristics might be helpful to improve targeting among those who are at a higher risk of defaulting from TB treatment. Knowledge of these factors has little relevance for TB control programmes since they cannot explain why patients default. Most economic issues are unalterable under programme conditions.

**Box 1. Factors that affect adherence to TB treatment**

**I. Patient factors**

**Socio-demographic:**

Sex –male<sup>4, 5</sup>

Age-older age<sup>6, 7</sup>

Economic position<sup>4, 8, 9</sup>

**Life style:**

Alcoholism<sup>10</sup>

Substance abuse<sup>11</sup>

**Co-morbidity:**

HIV infection<sup>5, 12-18</sup>

**Knowledge, attitude and practice of TB:**

Knowledge of tuberculosis and its treatment<sup>6, 11, 15, 19</sup>

**II. Health care system factors**

Quality of health information and communication<sup>4, 21-24</sup>

Management of TB programme<sup>25</sup>

Access and Convenience to TB care<sup>7, 26-34</sup>



Human immunodeficiency virus (HIV) is the most important risk factor for poor tuberculosis treatment outcome in sub-Saharan Africa. The HIV epidemic has a multifaceted negative impact in the control of tuberculosis<sup>12</sup>. Both poor TB treatment adherence and high mortality during treatment among HIV positive patients have been shown to be higher than in HIV negative patients in sub-Saharan Africa<sup>5, 13-16</sup>. Because of the increased stigma<sup>17</sup> attached to both diseases patients usually delay seeking TB treatment and most tend to interrupt any such treatment. The disease also limits the earning capacity of patients<sup>18</sup> to complete their eight months of treatment. The impact of low income could be a significant problem for rural patients and among TB patients with HIV co-infection who mostly require admission to a tertiary care facility. In sub-Saharan Africa most TB patients are also HIV positive and prolonged hospital admission depletes the limited available health resource, which can potentially lead to poor quality of health services in general and TB care in particular.

The risk of defaulting has been reported to be high among patients with inadequate knowledge of tuberculosis and tuberculosis treatment in Africa<sup>6, 19</sup> or in other developing countries<sup>11, 15</sup>. Poor awareness about tuberculosis and its treatment is a major problem in sub-Saharan Africa where most people are illiterates from rural areas<sup>20</sup>. Under the DOTS strategy patients should be treated by a trained health staff or an observer. Ineffective communication between health provider and patients was a risk factor for poor treatment adherence<sup>4, 21</sup>. Good communication between patients and health providers has also been shown to improve adherence<sup>22, 23</sup>. Patients were more likely to complete treatment when they had treatment follow up from one health provider<sup>4</sup>. Health information consistent with local beliefs and an effective communication that is based on mutual respect between health providers and patients could be essential components of TB care for improving treatment adherence. Nevertheless, there are not many studies of the quality of TB health information given to patients and health providers' skills of communication. These factors had a significant effect on treatment adherence elsewhere<sup>24</sup> and they might be more relevant in sub-Saharan Africa where people have established beliefs and traditional care.

The availability of an effective management of TB control programme at all levels is critical to achieve the intended goals of the programme. Continuous supply of anti-TB drugs, training and supervision of health providers and monitoring and evaluation of TB treatment outcomes are the primary tasks of TB control staff assigned at district, regional and NTB offices. The relative importance of these managerial inputs on TB treatment adherence has never been well investigated in Africa. These inputs were assumed in the strategy without clear elucidation of indicators for their assessment. One study carried out elsewhere showed that intensive supervision of health providers by TB control staff has improved treatment completion when compared with those who received the usual supervision under programme conditions <sup>25</sup>.

Poor access to health care is a stark reality in sub-Saharan Africa. Non-adherence to TB treatment therefore could partly be ascribed to the low level of access to health care in general and TB care in particular. Patients were more likely to default when TB treatment was given from distantly located health facilities <sup>7</sup>. In many countries, the TB programme is not still fully integrated into the lower primary health care facilities, which are more accessible to the majority of the rural population <sup>26</sup>. The World Health Organization has been advocating decentralization of TB treatment from tertiary level to lower health facilities and community level in order to improve patient convenience to TB treatment and to reduce costs to patients and the health sector. Earlier observational studies showed increments in treatment outcome with decentralization of TB treatment from hospitals to lower peripheral health facilities in Africa (Table 1) <sup>27-34</sup>. Further decentralization of 'the DOT' part of the strategy using several alternative options including volunteers have been shown to achieve similar treatment outcomes with less cost <sup>35-38</sup> than the health facility-based DOT in sub-Saharan countries. These studies have clearly shown the high cost-effectiveness and affordability of a decentralized TB treatment and community resources that could be harnessed for TB control. Nevertheless, except for a few <sup>27, 32</sup> most studies failed to achieve the optimum of 85% treatment success rate among patients with smear-positive pulmonary tuberculosis. High mortality during treatment was shown in most of these studies. HIV contributes to poor treatment outcomes, but cannot be the only factor responsible for two reasons.

Firstly, the relative contributions of the interventions integrated into the pilots cannot be determined from observational studies. Secondly, there is no strong evidence from well controlled studies that account HIV, delays to TB treatment and the quality of control programme implementation. As well as HIV related mortalities, other factors<sup>39</sup> such as poor quality of care in the existing health facility-based DOTS programme, ineffective programme management of TB programme at different levels of the health system and poor adoption of the components of strategy including its 'DOT' component may be responsible for their sub-optimal TB treatment outcome.

There is ample evidence that the strategy as a package including its DOT component achieved high success rates both in observational<sup>40, 41</sup> and in well controlled studies<sup>42</sup>. Even though more emphasis was placed on the 'DOT' part of the strategy, there is no strong evidence that patients default during the first 2 months of treatment<sup>5, 7</sup> or that this arrangement improves treatment adherence in Africa<sup>3, 43</sup> or elsewhere<sup>44</sup>. What is apparent is that most patients default during the continuation phase<sup>6, 7</sup>. Non-adherence therefore appears to be more related to the poor quality of care given during the intensive and continuation phases of therapy.

| Year          | Country      | Setting         | Number patients | Type of study                       | TB supervisor   | Treatment outcome   | Intervention Effect   |
|---------------|--------------|-----------------|-----------------|-------------------------------------|---|---|---|
| 1992-1995[27] | South Africa | Rural           | 928             | Prospective                         | Various community volunteers  | 85% treatment completed   | 24% increase in treatment completion                                      |
| 1997[28]      | South Africa | Rural           | 535             | Prospective                         | CHWs, lay people and volunteers   | >85% treatment success among survivors  |   |
| 1999[29]      | South Africa | Urban           | 2873            | Comparative in two sites            | Clinic based DOT VS CB-CHW  | Cured-58%, 67% treatment success after intervention.  | 2% increase in treatment success  |
| 1998[30]      | Malawi       | Urban and rural | 6335            | Prospective                         | 4 option of DOT: hospital admission, out patient hospital, Health centre and guardians  | PTB+: 67% completed treatment<br>EPTB: - 56% treatment completed.<br>Guardians DOT: 61% completed treatment |   |
| 1998[31]      | Malawi       | Capital city    | 3761            | Prospective using historical cohort | 4 option of DOT: hospital admission, out patient hospital, Health centres and guardians   | PTB+: 64% cured , 4% completed treatment and treatment success 68%<br><br>PTB-: 50% completed treatment,    | 10% increase in treatment success<br>17% increase in treatment completion |
| 1998/99[32]   | Kenya        | majority rural  | 3244            | Prospective using historical cohort | 4 options of DOT supervision: hospital clinic, peripheral health units, community volunteers and hospitalization                    | PTB+: 88% treatment success rate<br>PTB-: 81.6% completed treatment   | 3% increase among PTB+<br>14% increase among PTB-                         |
| 1999[33]      | Uganda       |                 | 450             | Prospective using historical cohort | Patients choose DOT: 2 weeks hospitalization followed by volunteer supervision or 2 months of hospitalization                       | PTB+: 62% cured, 11.6% completed and 73.8% treatment success  | 17.6% increase in treatment success                                       |
| 2000[34]      | South Africa | Rural           | 1816            | Community intervention              | After admission patients chose a few days of admission: health facility, CHWs and lay persons or the above plus traditional healers | 77% completed treatment in intervention areas   | 2% increase for interventions area  |

Table 1: Observational studies on decentralized tuberculosis treatment in sub-Saharan Africa.

While non-adherence to TB treatment is the result of multiple factors <sup>39</sup> most studies were targeted from the perspectives of patients and TB treatment delivery in relation to the 'DOT' component of the strategy and decentralization of TB treatment. This direction has undermined our understanding of the problems of TB control, with little contribution for holistic interventions to improve TB treatment adherence in the developing world. The need for more comprehensive studies that explain operational reasons for the failure of the strategy to achieve the intended treatment effectiveness in sub-Saharan countries should be emphasized. More evidence of effectiveness of the specific components of the health facility-based DOTS strategy and community-based TB care are awaited in sub-Saharan Africa <sup>45, 46</sup>. Based on the limited evidence available, many of the competing risk factors responsible for poor TB treatment adherence are amenable to improvement and could be linked to deficiencies in the DOTS programme implementation. These include poor quality of TB services as a result of sub-optimal implementation of components of the DOTS programme in the existing health system <sup>47</sup>, patients' poor access and inconvenience to TB services and the high level of HIV-TB mortality during treatment. Studies implementing simultaneously these three major areas of intervention from the perspective of the patient under operational conditions of TB control programme would give more reliable lessons for optimum treatment effectiveness in sub-Saharan Africa.

### **1.1 Background of Ethiopia**

Ethiopia ranks 7<sup>th</sup> among those top 22 countries contributing 80% of tuberculous disease globally <sup>3</sup>; and the burden of tuberculosis is increasing despite 95% of the population having access to effective and free treatment in public health facilities <sup>48</sup>. The treatment success rate among smear positive pulmonary (PTB+) patients remained below 75% over the years 1997 to 2005 and the case detection rate (54%) is still below its global target <sup>3</sup>. Directly Observed Treatment Short course (DOTS) strategy was started in Ethiopia in 1993 with its gradual expansion to all parts of the country. Patients have free access to diagnostic services and tuberculosis (TB) treatment in all public health

institutions. Patients with symptoms suggestive of tuberculosis must be referred from clinics/health posts to health centres and/or hospitals for diagnosis. Health centres can only diagnose smear-positive pulmonary tuberculosis by direct sputum-smear microscopy, but they must refer smear-negative pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) patients to hospitals for further investigation. Hospitals are equipped with x-ray facilities and serve as the only diagnostic units for smear-negative PTB and EPTB. Currently, patients take their first 2 months of treatment under the observation of health workers in public health facilities, and are then followed by a monthly visit for medical check up during the remaining 6 months<sup>48</sup>.

In order to address non-adherence in Ethiopia, we aimed to improve both patient convenience through decentralization of treatment supervision at community level and the quality of TB care from the perspective of patients in the existing health facility-based DOTS programme, using the existing structure of the district TB control programme. Firstly, we explored ways of improving treatment outcomes in the prevailing public health system by identifying the pitfalls of DOTS programme implementation<sup>49</sup>. All components of the DOTS programme were then adopted based on local conditions. Subsequently, alternative options of tuberculosis care strategies were identified from our baseline studies to improve both the quality and patient-convenience to TB care. This study will be carried out under operational conditions using the existing district TB control management set-up in order to gain the required organizational and managerial experiences considering the possibility of scaling up. This randomized controlled trial will be conducted in 10 pilot districts using three alternative options of treatment care selected by patients, the community and health professionals as a bench mark to introduce a system of community-based tuberculosis care within the ongoing health facility-based TB programme in Ethiopia<sup>49</sup>.

## 1.2 Background of study area

The study will be carried out in Tigray region, north Ethiopia. The region has an estimated population of 4.2 million with rural residents representing 86% of the total population. There are 36 districts each with a population range of 40,000 to 120,000. Each district has between 10 to 15 big villages called *tabias* (a *tabia* is the smallest government administrative unit for an estimated population of 5000). There are 700 *tabias* in the region, each consisting of 8 to 10 small villages called *kushets* (a *kushet* is a small village with about 200 households).

Health care is provided primarily through government health institutions. Health services access, as defined by residence within 10 kilometres of a health facility, is approximately 62%. The region is predominantly mountainous and access to transport is limited in rural areas. In the order of referral from lower to higher institutions, there are 278 health posts, 26 health centres and 12 hospitals. The region also has a well-organized structure of about 6,000 trained volunteer community health workers (CHWs) which includes community health agents (CHAs) and trained birth attendants (TBAs) widely distributed in 2715 small villages<sup>50</sup>. CHAs are involved in the treatment of malaria, epidemic reporting, environmental health activities and health education; TBAs provide delivery services and family planning counselling. Both CHAs and TBAs are involved in tracing patients defaulting from TB treatment. Volunteer CHWs provide these health services to their respective communities without any remuneration. They are accountable both to their local village administration and the nearby public health facilities. Volunteers get free medical care, refresher training, material support and technical support from the nearby public health facilities. The region is also introducing a community-based health services using trained 'health extension workers' who will be deployed in rural villages.

The DOTS programme was initiated in Tigray in 1995. Currently, about 90% of health facilities are giving directly observed short-course tuberculosis treatment by trained

health workers (TB focal persons). The programme was introduced in all hospitals, health centres and in most health posts for the past 6 years. The decentralization of TB treatment from hospitals and health centres to health posts has substantially reduced treatment default from 32% in 1996 to 15% in 2003. The DOTS programme has been integrated into the lowest level health units (health posts) primarily to improve convenient access for rural patients. Despite these measures the treatment success rate among smear-positive pulmonary tuberculosis has remained below 72% (range 68% to 73%) over the years 1997 to 2004<sup>51</sup>. Smear-positive pulmonary tuberculosis cases detected every year since 1996 represent only 20% of the total new patients (all forms). Both figures signify that the risk of tuberculosis transmission in Tigray is still high. There were no prior studies conducted to investigate the reasons for the low case detection and poor treatment outcomes.

## **2. Study rational and assumption**

Both decentralization of TB treatment using alternative options of TB care at village level and the provision of patient-centred quality care in the existing health facility-based TB care are regarded as essential measures if optimal treatment outcome is to be achieved. Three possible alternative options of TB care delivery were identified by our baseline study. These are volunteer CHW-TB care, self-administered treatment and ongoing health facility-based TB care by health workers<sup>49</sup>. The major assumption is that adherence to TB treatment exclusively depends on the patients' decision and their decision to comply with TB treatment is a function of convenience to TB care and the quality of care provided by health care provider or trained care provider. The intent is to standardize all other factors (TB diagnosis, drug regimens to be used, treatment follow up and patient-centred quality care at all levels of the health system including care given by CHWs) as per the standards of NTP and WHO<sup>2, 48</sup>, but to institute different modalities of TB care with variable levels of patient convenience (in terms of distance from residence and easy access to TB care provider) under operational conditions (see definitions for the three arms). This study will therefore measure the effectiveness of the two alternative options of TB care, taking the existing health facility-based TB care as the



gold standard by integrating measures which improve both patient convenience and quality of tuberculosis care under operational conditions of district TB control programme.

### **3. The objective of the study**

The purpose of the study is to measure the treatment effectiveness of health facility-based TB care by health workers, patient-administered treatment and community-based TB care by volunteer community health workers.

#### **The hypothesis**

It is hypothesized that no significant differences in treatment outcome among the three modalities of TB care.

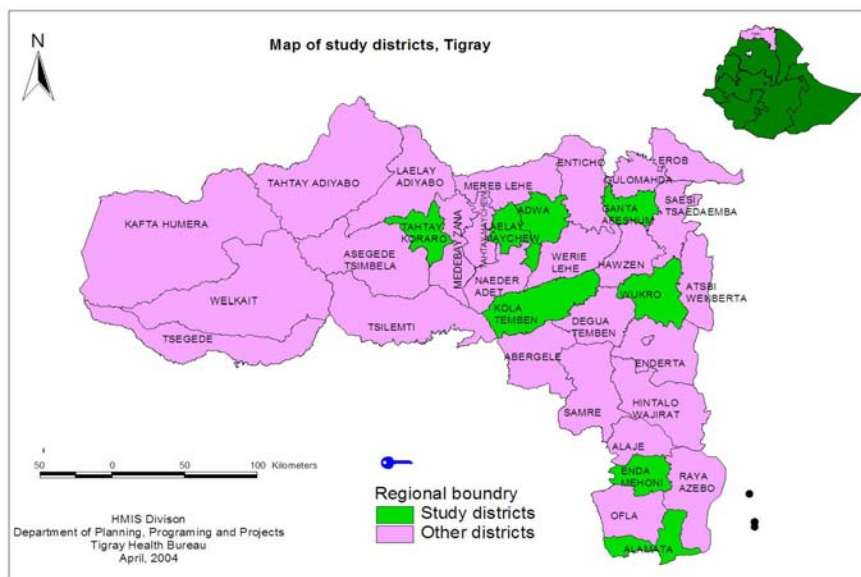
### **4. Methods**

#### **4.1 Study setting**

The study will be conducted in 10 districts which fully implemented the DOTS program in all their health facilities in order to determine whether better patient quality of care and convenience using three TB care options could improve treatment outcome (Figure 1). In the study districts there are 149 tabias and 1163 kushets with 1.2 million residents representing 30% of the total population of the region. All public health facilities (8 hospitals, 11 health centres and 48 health posts) in these districts will be included. District hospitals and health centres provide TB diagnostic services. The study districts

comprise 2316 volunteer community health workers who are functionally accountable to the public health system and an estimated population of one million.

**Figure 1: Map of Study Districts**



## 4.2 Study Design

A randomized control trial on three alternative options tuberculosis to be carried out using existing district health systems, taking into account operational conditions for the DOTS strategy

## 4.3 Study population

Patients will be recruited from the 10 study districts of all public health institutions which serve both urban and rural population. New patients diagnosed in the study districts (8 hospitals and 10 of the health centres) and those referred for treatment will be

included. Patients suspected of pulmonary tuberculosis disease will be diagnosed based on the following case definitions <sup>48</sup>:

1. A patient with at least one of the following criteria will be diagnosed as PTB+:
  - a) Two initial smear examinations positive by direct microscopy for acid-fast bacilli (AFB) or,
  - b) One initial smear examination positive by direct microscopy and culture positive, or
  - c) One initial smear examination positive by direct microscopy and x-ray abnormalities suggestive of active TB as determined by the physician.
2. A patient is diagnosed as PTB-negative when three initial smear examinations were negative by direct microscopy for AFB, and there was failure to respond to a course of broad-spectrum antibiotics, and again there were three negative smear examinations by direct microscopy and x-ray abnormalities suggestive of active TB as determined by the treating physician.

Both PTB+ and smear-negative pulmonary (PTB-) patients will be recruited to increase the generalizability of the study. The following inclusion criteria should be used to recruit patients for the study:

#### **Inclusion criteria**

- age 15 years or above,
- no previous tuberculosis treatment,
- sputum exam positive for *Mycobacterium tuberculosis*, negative sputum results with consistent clinical and chest x-ray features and,
- permanent residence in the study districts.

#### **Exclusion criteria**

- All forms PTB patients less than 15 years of age.
- PTB patients who are on treatment or those who were previously treated include defaulters, failures and transferred cases.

- Patients with known allergies to any of the anti-TB drugs in the treatment regimen.
- Patients with renal failure and previously known liver disease in whom a different short course regimen is recommended.

An enrolment officer in each district will screen patients for eligibility and counsel them regarding TB treatment and the purpose of the study. Consent will be obtained from each patient. Patients will be enrolled from September 07, 2005 to September 29, 2006. The last patient completed treatment on 28/05/2007. Patients who did not satisfy the inclusion criteria will be managed as per the national standard guideline.

#### **4.4 Pre-trial measures**

##### **4.4.1 Interventions to improve the quality of TB care**

Baseline studies were conducted to determine the quality of TB diagnosis, patient care and treatment outcome and to identify alternative options TB care appropriate to local conditions. Six months prior to the trial, the limitations of the ongoing DOTS found by these studies were communicated to district health office heads, hospital directors and district TB experts in order to strengthen the quality of TB care and management of district TB programs. Specific tools that were not developed by the National Tuberculosis Program (NTP) to ensure consistent application of diagnostic criteria, patient counselling/health information, standards on supervisory support, drug supply and district evaluation were prepared in consultation with district health management experts and hospital directors. Subsequently, district TB coordinators, health institution-based TB focal persons and clinicians were trained on patient diagnosis, patient care, community-based tuberculosis care and the study protocol. Based on our baseline assessment of quality of care, the following measures which improve patient-centred care were instituted at health facility level:

1. Quality control measures to improve the quality of diagnosis.
2. Definition of what health information should be conveyed to patients,

3. Patient teaching using a one to one interactive counselling method.
4. Training of health workers in TB management (TB focal person) with particular emphasis on patient management, management of drug side effects and interpretation of treatment outcome, and reporting.
5. Treatment in patients' most convenient health facilities.
6. Provision of daily out patient TB services in health facilities.
7. Continuous support by health workers or CHWs with a workable referral system.

Tuberculosis treatment registers were translated into the local language and were modified to fit with the monitoring and interpretation of treatment outcomes at health facility level for patients in the three treatment groups. Volunteer CHWs were also trained by their nearby health institution TB focal person on patient care, drug handling, indications for referral, managing side effects, and the use of the patient adherence card. Quarterly supervisory support was given by regional experts to district health offices, while health institutions were supervised on a monthly basis by district TB coordinators. The nearby TB focal person provided technical support to volunteer CHWs during their monthly meeting in the respective health facilities. Biannual evaluation between district health staff with HQ staff and district health staff with TB focal persons was instituted. The implementation of the above measures prior to the launching of the trial created '*operational conditions*' of components of the strategy as recommended by the NTC and International Union against Tuberculosis and Lung disease (IUTL)/WHO guidelines<sup>2, 48</sup>. Strengthening the health system based on local conditions was assumed to be a basis for determining specific needs, and for creating the conditions for the development of the necessary managerial and technical skills for effective implementation of a community-based TB care.

#### **4.4.2 Selection of delivery options for TB care**

Four prominent TB care delivery options were identified from our community based survey<sup>49</sup>:

1. Volunteer CHWs TB care (CHW-TC),

2. Health worker TB care (HW-TC),
3. Self-administered treatment (SAT),
4. Family member TB care.

Further assessment regarding their reliability and implications for the DOTS strategy was made using the following selection criteria:

1. Uninterrupted supply of anti-TB drugs to patients could be ensured,
2. Quality of care comparable to the prevailing health facility based TB care could be instituted,
3. Accountability in terms of guaranteeing proper use of drugs and monthly reporting of treatment outcomes of patients to the public health system,
4. Feasibility in terms of cost when applied on a larger scale and,
5. Level of acceptance by local communities as determined from our cross-sectional study.

In addition to the prevailing health facility-based TB care, the use of volunteer CHWs and self-administered treatment are found to be appropriate options for pilot testing. Based on our criteria, care by family members had the least operational feasibility because the costs involved to families (labour cost from interruptions of daily activities and transport cost) and the health systems (health worker time and cost of training) could be high. Operational difficulties are also anticipated in setting up an appropriate system for

- a. monitoring of anti-TB drugs used,
- b. provision of health education
- c. referral
- d. monthly reporting of treatment outcome particularly among family members who could be in remote parts of the region.

The decentralization of TB care at community level using the existing volunteer CHWs program is anticipated to be a feasible option to institute most of the components of the WHO-recommended DOTS strategy. Volunteer CHWs can be trained in patient care on a continuous basis. Accountability on anti-TB drugs used and reporting on treatment

outcomes could be obtained by using the existing link between CHWs and nearby public health facilities. The services they render are appreciated by the respective communities. The self-administered treatment option is another option after critical examination of previous effectiveness studies <sup>42-44</sup>, patients' convenience to tuberculosis care and, most importantly, taking into account the views expressed by communities and patients <sup>20</sup>. Operational challenges, in which health workers could be forced to allow patients to take treatment by themselves when there are no volunteer CHWs who could offer TB care in remote areas was also considered.

#### **4.4.3 Defining intervention arms**

The final step was how optimal quality of TB care with less inconvenience could be reached among the two alternative options from patients' perspective in order to achieve treatment outcome target. These integrated interventions were therefore targeted to test treatment outcome by instituting both a comparable patient quality care and patient convenience to TB care among the three strategies. In order to do this three factors were considered.

##### *1. Epidemiological factors*

From the baseline study, most patients do not interrupt treatment during the intensive phase of treatment. But, the occurrence of death is high during the first 2 months of treatment (reference). Even though its contribution is unknown in Ethiopia, the high HIV-TB co-morbidity and mortality <sup>5, 12, 14</sup> during anti-TB therapy has been attributed in other sub-Saharan countries. Thus, proper management in health facilities during the first 28 days for patients assigned into volunteer CHW care or self-administered groups would ensure their health care needs.

##### *2. Operational factors*

The intervention was designed to be implemented under operational conditions of the district health system and the ongoing community-based volunteer CHW programme. CHWs get technical and material support from nearby health facilities.

They are required to submit their activity report at these facilities on a monthly basis<sup>49</sup>. This arrangement has been found effective in maintaining the functionality of CHWs while minimizing disruptions in their daily life. Given this operational condition, patients have to be managed in nearby health facilities for the first four weeks until proper selection and introduction with respective CHWs are made. Other operational factors in favour of this arrangement include its feasibility when scaling up the intervention, low time cost of CHWs and the health system. This operational set up was anticipated to enable TB focal persons to organize a monthly evaluation session for CHWs in their catchments.

### *3. Ethical issues*

Health interventions should be safe and minimize potential risks leading to patient morbidity and mortality. In Ethiopia a significant proportion of tuberculosis patients are also infected with HIV<sup>53, 54</sup>. The fact that assigning such patients into an intervention whose effectiveness is unknown (volunteer CHWs) or allowing them to die (self-administer group) was also regarded as unethical<sup>55</sup>.

## **4.5 Interventions**

Accordingly, all patients should receive daily TB care including observed daily doses of treatment for the first 28 days from the most convenient health facility. Patients have to be properly counselled about their illness and managed accordingly by the TB focal persons. Counselling should be conducted using a standard procedure developed from our baseline studies in order to ensure good quality of tuberculosis care. They should be taught specifically on the causes and prevention of TB, side effects of drugs, treatment adherence and the schedule for follow up examinations. During this time, the TB focal persons need to assist patients to select volunteer CHWs from their village. They should explain their role and created confidence between them. All eligible patients should be treated using anti-TB drugs recommended by the national tuberculosis control of Ethiopia<sup>48</sup>. PTB+ patients should receive weight adjusted Ethambutol (E), Rifampicin (R), Isoniazid (H) and



Pyrazinamide (Z) during the first 8 weeks of treatment followed by 6 months of EH, while PTB- should be treated with weight adjusted RHZ for two months, followed by 6 months of EH.

Patients assigned to the health worker-TB care group should be followed as per the national TB guideline <sup>48</sup>, i.e. daily observed treatment by the TB focal persons, in their respective nearby health institutions during the first 8 weeks followed by self-administered treatment for the remaining 6 months. During the continuation phase patients are expected to visit their nearby health facility every month for follow up. Supervisory support will be given to TB focal persons by the respective district TB coordinators on a monthly basis. Anti-TB drugs will be delivered to health institutions on a quarterly basis by district TB coordinators during supervision.

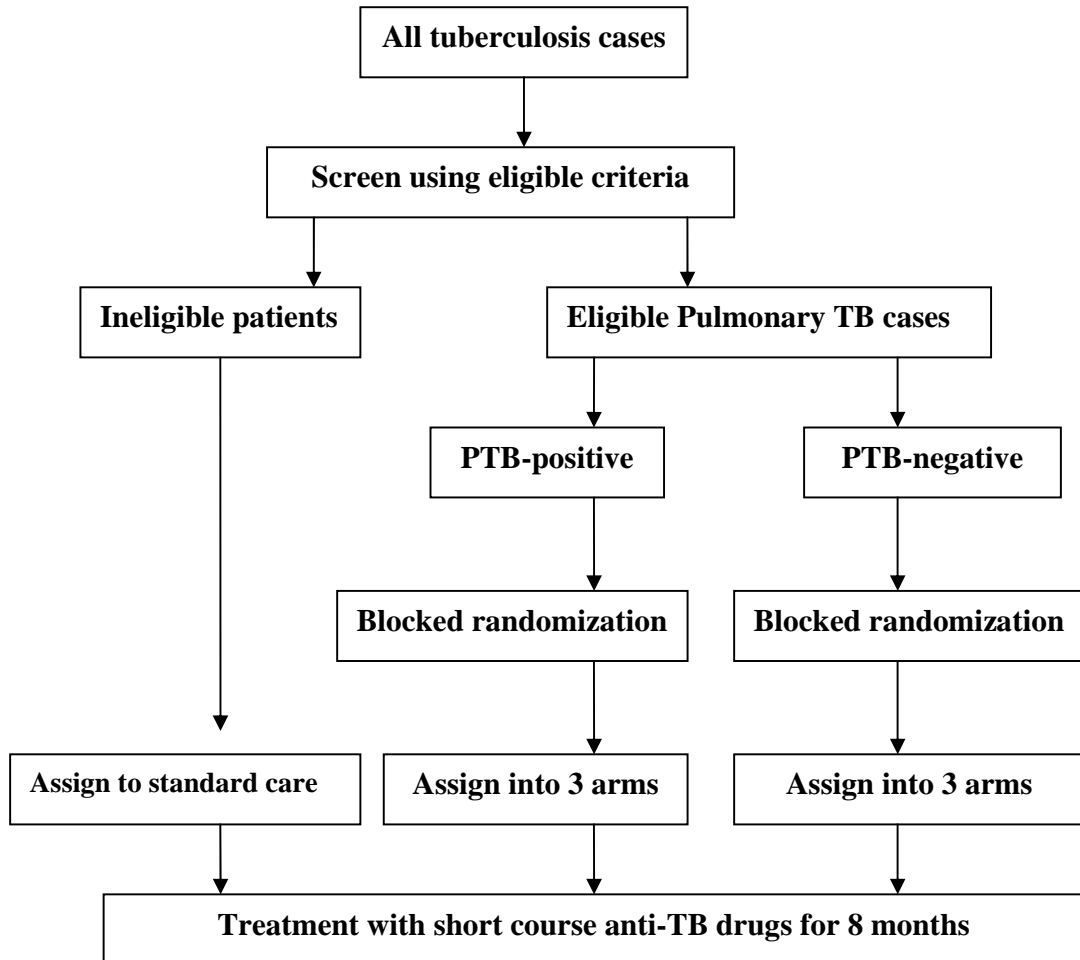
Patients assigned to the volunteer CHW-TB care group should have daily TB care by the CHWs in their villages for the second month followed by a monthly visit to the CHWs' home for the remaining 6 months of self-administered treatment. Patients are expected to visit health facility at the end of the second months and the end of treatment for sputum examination. Technical support and anti-TB drugs should be given to CHWs by TB focal persons every fortnight.

Those assigned to the self-administered treatment group should take their medication at home for seven months. They should be taught by the TB focal person to collect their anti-TB drugs fortnightly and report missed daily doses. Follow up assessment and continued support should be made by TB focal persons on a monthly basis in their nearby health facility. Patients should also be told to report when they encountered severe side effects.

## **4.5 Procedures**

A randomized controlled design is used to compare the existing HW-TC with CHW-TC and self-administered treatment (Figure 2). Eligible PTB+ and PTB- patients will be assigned using random numbers, computer generated by a statistician at regional level. To avoid disproportionate allocations among treatment groups two separate random blocks of 3 for PTB+ and PTB- are arranged. Two sets of sequentially numbered sealed envelopes for each district will be prepared. Two separate boxes containing sealed envelopes for PTB+ and PTB- will be given to the head of each district health office. The district recruiting officers should obtain the allocation arm for each patient from these district health office heads. For each district, allocation codes used should be recorded weekly by telephone. A statistician will monitor the quality of assignment by cross checking the original list in the research HQ with the sequence of patients' attendance for recruitment. Recruiting officers will be trained using a pre-tested guideline prepared to ensure that standard procedures are applied consistently in screening and informing patients. Written consent should be obtained from every patient following proper counselling, with particular emphasis on tuberculosis treatment and the alternative options of care. Patients who refused the randomly assigned method of TB care should be allowed to select either of the two remaining care options.

**Figure 2: The schema of randomization of pulmonary patients**



A request for a haemoglobin test from every eligible patient should be made by the health facility TB focal person in the diagnostic health facilities (hospitals and health centres) in order to collect serum for anonymous HIV testing before patients are sent to the district recruiting officer. Laboratory technicians should send 5 cc of serum labelled by a coding system developed by the Regional Research Laboratory (RRL) in the HQ. HIV test (Determine<sup>®</sup> HIV-1/2, Abbot Laboratories) results should be made available to the research team at the end of the trial. Baseline data should be collected from each eligible patient before he/she is referred to the most convenient health facility. Patients

are only identified by code numbers in order to maintain confidentiality about their assignment. The codes should be revealed to the study team after the preliminary data analysis and draft reporting phases are completed.

Standard treatment outcome indicators developed by the WHO and the NTP will be used to compare the effectiveness of the strategies <sup>2, 48</sup>. Treatment outcome data will be collected by a team of three tuberculosis experts who are not involved in the study. Treatment outcome of PTB+ patients will be assessed by sputum microscopy for the presence of acid fast bacilli while clinical improvements and adherence to treatment will be used to assess the outcome of PTB- patients by clinicians. Cure and treatment completion rates are used to compare treatment groups. A patient is declared cured if confirmed to be sputum smear negative at the end of treatment or one month prior to the completion of treatment and on at least one previous occasion. A patient should be recorded as "treatment completed" if smear results are not available on at least two occasions or has negative pre-treatment results and is treated for clinical reasons. A patient who had been on treatment for at least 4 weeks and whose treatment was interrupted for more than 8 consecutive weeks or for a cumulative period of more than 12 weeks should be classified as a defaulter and a patient who remains smear-positive at 5 months or later during treatment should be considered to be a failure. A patient who had started treatment for at least 4 weeks and had been transferred to another district should be recorded as transferred out.

#### **4.6 Statistical analysis**

The comparative effectiveness of health workers-TB care to that of volunteer CHW-TC and SA-TS in randomized control trials has never been reported so far. It is hypothesized that no significant difference in cure and treatment completion rate among the three treatment groups would be shown, taking the prevailing health facility-based TB care as the gold standard of care. The sample size for PTB+ (179 patients per arm) is planned to detect at least a 10% difference in treatment success rates between any of treatment groups

(assuming 85% treatment success rate in the highest arm and a baseline treatment success rate of 72%) with a power of 80% at a significant level of 5%. With the same assumption (85% treatment completion rate in the highest arm and a baseline treatment completion rate of 69%), all eligible PTB- patients (131 patients per arm) should also be included during the study period. Separate comparisons of effectiveness between the three methods of TB care will be carried out for PTB+ and PTB- patients. Comparison of effectiveness of the treatment groups will be undertaken according to the principle of intention-to-treat. The strength of association between treatment outcomes and each treatment supervision group will be determined using the chi-square test. Adjusted effects of patients' characteristics, area of residence, HIV status, time elapsed by each patient for treatment, the type of health facility and method of TB care used on treatment outcomes will be computed using logistic regression analysis.

#### **4.7 Study management**

The study will be conducted under operational conditions using the existing regional and district health structure. In addition to the PI, the study team consisted of 6 researchers from the regional HQ representing Regional Research Laboratory, Regional TB control Programme, the Health Information Unit (HIU) and Division of Epidemiology. In each district, a team consisting of 3 people (district TB coordinator, a clinician responsible for TB care in a district hospital and a district health office head) will be responsible for monitoring the overall implementation of the study. The study team at regional and district level will be involved in the implementation of both phases of the studies and training of district health staff. Experts from the WHO and NTP also contributed in the development of the interventions and the study protocol.

The research team in HQ and in each district is responsible to ensure that the study protocol and guidelines are followed at all levels of the health system. Baseline patient data has to be collected from each district health offices by two research assistants from HIU. They should checked patient records filled by district recruiting officers for their

completeness and consistency. Data will be managed by two data clerks who will be monitored by a statistician in the HQ who is also responsible for the quality of patient assignment in each district. The statistical analysis and interpretations of results by PI will be reanalyzed by a statistician from the School of Community Health Sciences, The University of Nottingham and University of Leeds and The University Leeds.

#### **4.8 Ethical consideration**

Consent should be obtained from each patient. Ethical clearance has been granted by the Regional Ethical Committee for Biomedical Research.

## **5. Detail implementation procedures**

### **5.1 Diagnosis of patients**

All patients must be diagnosed by health officers or medical doctors as per the national TB guideline <sup>48</sup>. Patients must be instructed properly how to collect and handle morning sputum specimens. Sputum microscopic results should be documented as per the national laboratory unit register. Technicians should record and submit results for each AFB slide to the TB focal person in the diagnostic health institutions (hospitals and health centres); and all slides tested have to be labelled and stored properly for quality control.

Every diagnostic measures and investigation results should be recorded for every patient. Patients should be sent to the TB focal person with all the necessary documents (patient chart, investigation results, labelled AFB slides for quality control) in order to assess the quality of diagnosis. TB focal persons must fill the TB diagnosis algorithm form (Annexes 1.1A and 1.1B) for every patient before sending the patient to the district TB coordinator.

### **5.2 Screening, counselling and assignment**

The district recruiting officer (district TB coordinator) screens all cases whether their diagnosis was as per the NTP standards. Should the district recruiting officer find any discrepancy in diagnosis from the national standard, patients have to be referred to their physician for further investigation.

The district TB coordinator will collect baseline data from all eligible patients (Annex 1.2). Patients must be counselled, based on the findings of the baseline assessment about TB and its treatment (taking drugs, side effects of drugs and the follow up protocol to be followed); and their right to change the assigned modality of TB care before signing the consent form (Annex 1.5). Detail instructions should be given on the modalities of care based on the guideline prepared for the trial (Annex 1.3) and patients' random profile codes will be collected by the district TB coordinator. The district TB coordinator should obtain signed

consent form after detailed explanation of their rights (Annex 1.5). Patients must be referred to their most convenient health institution for treatment follow up.

The district TB coordinator should register every patient into the district TB unit register. Patients will be referred to the most convenient health institution with a referral paper containing detailed instructions on the assigned arm, the regimen of drugs prescribed, and duration of treatment and the specific appointment dates of follow up smear /clinical examination in the diagnostic health institutions.

### **5.3 Interventions at supervising health institution**

Patients with a referral paper from the district TB coordinator will be registered in the health institution TB unit register by the health institution-TB focal person. Depending on the assigned arm, proper counselling on treatment and health education will be given to every patient by the respective TB focal person (Annex 1.3). Appointment dates for patient follow up visit and treatment schedule need to be properly explained to all patients.

All patients should be put on daily tuberculosis care for the first four weeks. Patients must also be observed for the first four weeks (1 week=7 days) in health facilities; and they should be counselled for drug side effects and other illnesses on a daily basis. Patients who encountered very severe illnesses must be referred to the district diagnostic health institutions (hospital or health centre). Patients should be advised on the importance of taking regularly the prescribed medications and their adherence to follow the smear test and clinical check up schedule at the diagnostic centres.

**CHW-TB care arm:** The TB focal person should make the necessary arrangements for patients assigned to CHW-TC group. These patients should be assisted to choose their convenient CHW. The TB focal person should formally introduce the patients and CHWs during this time. He should also explain their roles during treatment. The TB focal person should tell patients that CHWs (their care provider) will collect their anti-TB drugs for every fortnight from the nearby health institution for them during the remaining 7 months



of therapy. Patients assigned to CHW-TC should be told that they will receive daily care including DOT from CHWs for the second month followed by a monthly visit to CHWs' home for the remaining 6 months of self-administered treatment.

**Health worker-TB care arm:** Patients assigned to health worker-TC are expected to continue taking their drugs on a daily basis during the second month of the intensive phase followed by a monthly visit for the remaining 6 months.

**Self-administered treatment arm:** Patients assigned in the self-administered treatment group will collect their drugs from the nearest health institution for the remaining 7 months.

#### **5.4. Treatment plan**

All eligible patients should be treated using drugs recommended by the national tuberculosis and leprosy control. Eligible smear positive patients in the three arms will receive Ethambutol (E), Rifampicin (R), Isoniazid (H) and Pyrazinamide (Z) during the first 8 weeks of treatment followed by 6 'months' (1 'month' = 4 weeks) of Ethambutol and Isoniazid. Smear negative cases will be treated with RHZ for two months, followed by 6 months of EH. Pre-treatment weight must be measured in order to determine the daily doses of each drug (Table 2). These drugs are currently in use by the national tuberculosis control programme. All drugs should be taken together as a single, daily dose, preferably on an empty stomach. The drugs used are safe and effective and will be given to patients free of charge.

Table 2: Short course chemotherapy regimen for new PTB+ cases and daily dosage by pre-treatment weight.

| Duration of treatment         | Drugs            | Pre-treatment weight in kilograms |                  |          |         |
|-------------------------------|------------------|-----------------------------------|------------------|----------|---------|
|                               |                  | 20-29 kg                          | 30-37 kg         | 38-54 kg | > 55 kg |
| Intensive phase (8 weeks)     | (RHZ) 150/75/400 | 1                                 | 2                | 3        | 4       |
|                               | E 400            | 1                                 | 1 <sup>1/2</sup> | 2        | 3       |
| Continuation phase (6 months) | (EH) 400/150     | 1                                 | 1 <sup>1/2</sup> | 2        | 3       |

During the study period, patients who were previously treated for more than one month with short course, but are found to be smear positive at month five and/or month eight, re-treatment regimen (2 SE (RHZ)/1E (RHZ) / 5 E3 (RH)3) will be prescribed (Table 3).

Table 3: Re-treatment regimen by pre-treatment weight.

| Duration of treatment                    | Drugs            | Pre-treatment weight in kilograms |          |          |         |
|--|------------------|-----------------------------------|----------|----------|---------|
|  |                  | 20-29 kg                          | 30-37 kg | 38-54 kg | > 55 kg |
| Intensive phase (8 weeks)                | (RHZ) 150/75/400 | 1                                 | 2        | 3        | 4       |
|  | S                | ½ gm im                           | ¾ gm im  | ¾ gm im  | 1 gm im |
|  | E 400            | 1                                 | 1        | 2        | 3       |
| Intensive phase (third month)            | (RHZ) 150/75/400 | 1                                 | 2        | 3        | 4       |
|  | E 400            | 1                                 | 1        | 2        | 3       |
| Continuation phase (5 months, 3x weekly) | RH150/75         | 1 1/2                             | 2        | 3        | 4       |
|  | H 100            | ½                                 | 1        | 2        | 3       |
|  | E 400            | 1                                 | 1        | 2        | 3       |

Note: streptomycin should not be included in the re-treatment for pregnant women. Throughout the duration of re-treatment, including the continuation phase, the drugs must be taken under the direct observation of a health worker.

This regimen will be prescribed to smear positive treatment failures, smear positive returns after default, PTB- patients who become smear positive after 2 months of treatment, and patients who return after default from re-treatment.

### **5.5 Treatment follow up and management of PTB+**

During the entire treatment period all eligible patients will visit the diagnostic centres three times for a follow up smear. Regardless of the assigned modality of TB care, all PTB+ must have one sputum specimen examined at the end of the 2<sup>nd</sup>, 5<sup>th</sup>, and 7<sup>th</sup> month. Follow up smear results will be recorded in the laboratory unit register. The diagnosing physician will review follow up smear results and provide the specific recommended treatment regimens by NTP to the patients' local supervising health institution.

If the AFB smear is negative at the end of 8 weeks, the continuation phase can be continued. Otherwise the intensive daily treatment will be continued for another 4 weeks with E (RHZ). After an additional 4 weeks of intensive treatment, the continuation phase must be started without an additional sputum examination. If the smear result at the end of the 5<sup>th</sup> 'month' is negative, the patient will be allowed to continue the same treatment. If the smear result is positive at month 5 or more after the start of chemotherapy, smear examination will be repeated before failure can be declared. If the repeat smear examination at 5 month is positive, the patient will be declared as a failure and put on a re-treatment regimen. A patient with one prior negative smear result at the 2<sup>nd</sup> or 5<sup>th</sup> and 7<sup>th</sup> 'month' or during the last month of treatment is declared cured. If a smear is positive in either of 2 smears at 5 or 7 months of treatment, the patient is a treatment failure and must start the re-treatment regimen. When the final sputum examination cannot be done and the sputum result at 5 months was negative or not done, the patient will be declared treatment completed.

For those smear positive patients who interrupted treatment for less than 8 consecutive weeks, their management will depend on the duration of treatment before interruption and smear result at return (Table 4). The following NTP treatment protocol will be adhered for such patients:

- For a PTB+ patient who interrupted treatment for less than 15 consecutive days after taking a short course for less than 4 weeks, the same treatment will be continued without checking his/her sputum for AFB. Similarly, a patient who

had been on treatment for 27 days or less and had not taken his/her daily doses for 2-8 consecutive weeks will restart the same treatment without checking his/her sputum for AFB.

- The same treatment will be continued in a patient who had been on a short course for 4-8 weeks and had interrupted his/her treatment for 14 days or less with negative smear result after return. If the patient on the other hand had a positive smear result after return, he/she will be prescribed the re-treatment regimen. Patients who had been on short course treatment for less than 4-8 weeks but consecutively interrupted for 2-8 weeks and were found smear negative after return, they will be put on a one month extra treatment intensive phase. If patients had smear positive result for AFB after return, they will be put on a re-treatment regimen.
- For a patient who had been on short course for more than 8 weeks and had interrupted treatment consecutively for less than 8 weeks and had negative smear result after return the same treatment will be continued. However, should he/she had positive smear result after return, re-treatment regimen should be started.

Table 4: Management of PTB+ who interrupted treatment for less than 8 consecutive weeks.

| Duration of treatment before interruption | Duration of interruption | Smear result at return | Recommended Treatment   |
|---|--------------------------|------------------------|---|
| < 4 weeks                                 | < 2 consecutive weeks    | No smear is necessary  | Continue the same treatment<br>Restart the same treatment     |
|   | 2-8 consecutive weeks    | No smear is necessary  |   |
| 4- 8 weeks                                | < 2 consecutive weeks    | Negative<br>Positive   | Continue the same treatment<br>Start re-treatment regimen     |
|   | 2-8 consecutive weeks    | Negative<br>Positive   | One month extra intensive phase<br>Start re-treatment regimen |
| > 8 weeks                                 | < 8 consecutive weeks    | Negative<br>Positive   | Continue the same treatment<br>Start re-treatment regimen     |

A patient who did not collect his/her anti-TB for a period of 8 consecutive weeks or more (after attempts to trace him/her failed) will be declared as in default. Defaulters with a positive smear after return will be registered as a new cohort and be treated with the re-treatment regimen. A defaulter patient who returns with a negative AFB smear after return will be treated with a full course of the original short course regimen. If a patient misses some days of treatment during the continuation phase, the amount of days missed will be added on at the end, so that the complete course of treatment is given.

### **5.6 Treatment follow up and management of PTB-**

Pulmonary negative patients assigned to three modalities of supervision must be assessed clinically at the end of the 2<sup>nd</sup>, 5<sup>th</sup>, and 7<sup>th</sup> month by their diagnosing physician/health officer. During the entire treatment period all eligible patients will visit the diagnostic centres or nearby clinics three times and their clinical progress will be monitored.

A physician should assess a patient whose condition has not improved or gets worse by the end of the intensive phase and two sputum specimens should be examined for AFB. If one smear is positive, two other specimens are to be examined. When an additional one more smear is positive, the patient has to start the full course of the re-treatment regimen. If the condition of the patient deteriorates while the sputum remains negative, x-ray investigation should be made. If findings on x-ray are consistent with active TB, the initial anti-TB treatment regiment should be repeated.

A smear-negative PTB patient who interrupted his/her treatment for more than 8 consecutive weeks (defaulter) must be assessed by a health officer or a physician before continuation of treatment is started and two specimens must be examined for AFB. If one of these one is positive, the patient must start the full course of the re-treatment regimen. If the smear remains negative, the patient should be treated with the original regimen. At the end 7<sup>th</sup> month a chest x-ray should be taken to compare whether the patient has shown any clinical improvement.

### **5.7 Treatment follow-up of patients changing their assigned care groups**

A patient not willing to accept the assigned arm at the time of entry into the study will be counselled to choose between the remaining 2 modalities. This patient will be followed as per the study protocol applicable to those randomly allocated. He/she will be evaluated based on the specific follow up procedures outlined for the randomly selected arm.

A patient who changed his/her arm later in the course of treatment should be counselled about his/her reasons for changing. If a patient assigned to CHWs changes to the health workers TC arm or the self-administered treatment arm, the community health worker will refer him/her to the TB focal person. The TB focal person will assign the patient based on his/her choice. The patient should be then followed as per the protocol specified for the selected arm till the end of treatment.

### **5.8 Treatment follow-up of ineligible patients**

All tuberculosis patients who do not satisfy the inclusion criteria will be managed as per the national standard guideline. Patients will be referred to the most convenient health institution. All patients will be given two months daily TB care including DOT followed by a monthly visit to the health institutions for the remaining 6 months of self-administered treatment. All patient management procedures will be applied as per the protocol for eligible patient.

## **6. Quality assurance**

The quality of the study will be ensured by minimizing error in systematic measurement (bias) and confounders. The following are potential sources of biases and confounders that should be taken care of at design stage, during implementation and analysis of the study.

## **6.1 Minimizing bias**

### **Selection bias**

This problem can occur when allocation is unconcealed or carried out using a pseudo-random method. In this study, randomly permuted blocks for each district will be developed in order to minimize disproportionate allocation of cases per intervention arm and create groups which are comparable in important prognostic and demographic factors affecting treatment outcome. The use of a sequential set of sealed envelopes will ensure concealment of patient allocation. A district health officer who is not directly involved in the study will keep the sequentially numbered envelopes in a locked box. The recruiting officer has to get the assignment from the district health officer for each patient. The quality of random allocation will be monitored by the HQ statistician on a monthly basis using the main list and other indicators. Patients not eligible for the study will be followed similarly using the standard treatment protocol.

### **Ascertainment bias**

Ascertainment bias occurs when the results or conclusion of the trial are systematically distorted by the knowledge of which intervention each participant is receiving. The persons administering the interventions (health staffs supervising patients), patients participating in the trial and the investigator assessing the outcome, could potentially introduce ascertainment bias. Blinding the assigned arms from the TB focal persons and patients cannot be achieved because of the open nature of the study design. The effect of bias introduced by care givers will be minimized by concealment to end treatment outcome. Laboratory technicians doing diagnostic and follow up AFB-sputum will be blinded to each patient's assigned intervention arm. Sputum smear slides will be numbered and kept with the TB focal person for verification by senior laboratory technician from HQ. A team of experts who are not involved in the study will assess patients' treatment outcome using the internationally recommended indicators (Annex 1.6). The codes of the three arms would not be broken until data analysis and draft reporting phases are completed.

**Information biases**

Bias arising from misclassification or error in measuring outcomes or confounding variables is a remote possibility since the study relies on WHO indicators for diagnosis and treatment outcome indicators. The quality of diagnosis will be monitored through the institution of quality control standards in all diagnostic centres, review of patient diagnostic work up and adherence to inclusion criteria during selection.

Health institution workers in charge will only know patients' assigned intervention after randomization is carried out. Adherence to treatment will be assessed using the WHO standards in order to minimize error in measurement. The assignment of a trained health institution-TB focal person is anticipated to optimize similar patient care among patients assigned to HW-TC and self-administered treatment arms. Community health workers will be trained on patient care. A TB focal person will train and monitor CHWs on a monthly basis. A monthly meeting with each CHW is anticipated to reduce variations in patient care among patients assigned to CHW-TC group.

**Preference bias**

Preference to health worker-TC group might be stronger compared to CHW-TC among patients living in urban towns. Patients refusing randomized assignment will be assigned to one of their preferred arms of TB care. Patients changing assigned intervention arms will be followed with as per the standard protocol. Bias will be minimized by 'intention-to-treat' analysis, and means that all the study participants are included in the analysis as part of the groups to which they were randomized regardless of whether they changed the arm or not.

**6.2 Confounders and prognostic factors**

The high prevalence of HIV among TB patients is expected to affect treatment outcome. The prevalence of TB-HIV co-infection is estimated 30-50% in the study districts. Because of random assignment, the proportion of HIV co-infected cases among different



intervention arms is assumed to be similar. However, there is a risk of losing patients as a result of death from AIDS that might reduce the power of the study. Anonymous HIV testing will be done in order to control confounding effects of HIV on TB treatment outcome among the intervention arms. Because of the randomization the effect of other confounders is assumed to be similar among the arms.

### **6.3 Contamination between arms**

Assignment of different methods of TB care among patients living in the same or/and different villages might remotely affect treatment outcome. This might not be a big problem in the rural parts of the region where villages are widely dispersed and the expected number of patients per village ranges from 0 to 2. It is possible that patients assigned to different arms might discuss their treatment. However, since public institutions are exclusive providers of TB treatment in the study area, this problem will not be important.

Ineligible patients will be allowed to select their most convenient health institution where they will get daily TB care during the first 2 months followed by a monthly visit for unsupervised treatment. Throughout the trial patients in the non-random arm will be followed as per the national tuberculosis control guideline.

### **6.4 Training and orientation:**

Training will be given to district health staff (health officer, TB coordinator and communicable diseases control head) and hospital medical directors. Emphasis will be given on high quality clinical care, patient management, counselling, community based care and the trial protocol. This will help to standardize service delivery and the monitoring of the progress of the study.

Health institution TB focal persons and community health workers will be trained on the management of tuberculosis, the study protocol and counselling techniques. Laboratory technicians will be trained on methods of improving the quality of AFB-sputum smear

examination. The role of the health staff and CHW will be explained during the training.

### **6.5 Institution of laboratory quality control:**

Sputum smear slides used for diagnostic and treatment follow up will be sent to the Regional Research Laboratories (RRL) at HQ for validation. Based on the findings of the reference laboratory, actions to improve the quality of diagnosis in the peripheral laboratories will be taken. Sera collected for HIV should be sent to the RRL by peripheral laboratories.

### **6.6 Supervision and evaluation:**

This study is a multi-centre trial involving 10 districts with 9 hospitals, 11 health centres and 48 clinics. The study will rely completely on the existing health structures and methods used by the TB control programme. A district TB coordinator will supervise health institutions in each district on a monthly basis using a standard checklist. Each health institution TB focal person will monitor community health workers on a monthly basis. The TB focal person will collect progress reports on every CHW involved in treatment supervision. The regional TB coordinator will supervise each district health office every month using the national supervisory checklist. Every quarter the district research team (district health officer, TB coordinator and communicable diseases control head) and the regional coordinator will assess the progress of the trial in relation to the study protocol. Supervisory visit findings should be reported at each level for active management of the TB programme. Evaluation of supervisory reports should be made before the preceding supervisory visit at each level.

Evaluation comprising TB focal persons, hospital directors, heads of health centres and district health office heads and district TB coordinators will be conducted in each district every quarter as per the NTP guidelines. Biannual evaluation will be made at regional level with regional TB experts, district TB coordinators, district health office heads, RRL head and hospital directors.

## **7. Responsibilities of investigators and institutions**

### **7.1 Responsibilities of investigators:**

The principal investigator (Dr. Mengiste Mesfin) is responsible for overall management of the trial. The principal investigator will address problems as they are experienced but those requiring major decisions will be communicated to the research manager (Professor Madeley J Richard) and other co-investigators.

### **7.2 Responsible institutions:**

The University of Leeds, Nuffield Centre for Health and International Development is responsible for the trial.

### **7.3 Collaborating institutions:**

The University of Nottingham, Division for Epidemiology and Public Health sciences, Regional Health Bureau of Tigray, Department for Diseases prevention and control and The Ethiopian National Tuberculosis and Leprosy Control Programme will provide technical, financial and material assistance.

### **7.4 Responsibilities of regional department for diseases prevention and control:**

The regional head for TB and leprosy control and the TB expert will be responsible for the management of the study. These include training, logistic supply, monitoring (diagnosis, treatment protocol and follow up) and conducting quarterly evaluations with the district health office team.

### **7.5 Responsibilities of the regional research laboratory:**

The poor quality of pulmonary tuberculosis diagnosis is a major problem in the study districts. The institution of quality control in all peripheral laboratories is important. The quality checks on sputum smears in particular will ensure correct classification of pulmonary negative cases whose smear results were found to be negative. The results of

quality control sputum smears should also be analyzed. To keep the results of HIV test confidential, blood serum collected from each eligible patient should be sent to the RRL for analysis. To strengthen diagnostic services, the RRL will be responsible and must:

- Assign one coordinator responsible for quality control (QC).
- Provide results of QC to the regional TB control division in no later than one week.
- Identify quality problems and take measures to improve the problems on a continuous basis.
- Document progress regarding quality of AFB for each diagnostic centre.
- Conduct regular onsite supervision with the TB control division.

#### **7.6 Responsibilities of the regional health information unit.**

The regional health information management unit will be responsible to monitor the quality of randomisation, data processing (keeping records, collection, and quality control).

#### **7.7 Responsibilities of the district health office team:**

The head of a district health office is responsible for the overall management of TB control programme. He will monitor progress and take necessary actions regarding logistic supply, training, supervising and reporting to the regional HQ.

The district TB coordinator is responsible in executing the following tasks, and therefore will:

- Decide whether a patient is correctly diagnosed as per the national standard. If there is discordance between the diagnostic standard, consultation with the responsible health staff will be made for further diagnostic and therapeutic interventions.
- Interview patients about baseline characteristics and assess their eligibility for the trial.
- Determine the most appropriate supervising health institution with the patient.
- Counsel on the modalities of TB care available to the patient.

- Obtain randomly assigned arm for each patient from a district health officer where the sealed envelope will be kept.
- Obtain consent from patients randomized.
- Provide detailed counselling about the treatment follow up schedule to which the patient should adhere and the role of the assigned care provider.
- Document a written consent from each patient.
- Register each patient in the district unit treatment register.
- Ensure all AFB-slides and serum for HIV are taken and kept properly for quality control.
- Write detailed instructions to the selected supervising health institution TB focal person on treatment follow up schedule and about modality of TB care group.
- Conduct monthly supervision of the lower health institutions using the standard checklist in order to monitor overall TB programme.
- Provide technical and logistic support to TB focal person in lower health institutions.
- Send quality control slides and sera for HIV to the regional research laboratory on a monthly basis.

## **7.8. Responsibilities of health institutions:**

### **District hospitals:**

Hospitals are responsible for the diagnosis of PTB- and EPTB. This is because of the availability of better diagnostic facilities, qualified physicians and senior laboratory technicians. The institution of better organization and management of TB services in hospitals is therefore critical in order to improve the quality of diagnosis of patients in the study districts. The ingredients of better organization of TB services in hospitals include: the availability of a responsible physician for TB, a senior laboratory technician trained in TB and a nurse responsible to run a TB clinical sessions in outpatient and inpatient wards. Hospital directors are responsible for the organization

and management of efficient TB services. The following tasks will be required in order to ensure better quality care for all forms of TB patients:

- Assign a permanent physician or health officer responsible for reviewing diagnostic standards and putting patients with the appropriate treatment regimen.
- Assign a permanent TB focal person (a nurse) who is also responsible for the routine TB treatment in outpatient clinics, the documentation of treatment outcome and the monitoring of drug supplies. The TB focal person will be responsible for contacting the district TB coordinator whenever a TB patient is admitted to hospital. Discharged patients and patients referred from other districts will be referred to the district TB coordinator by the focal person. He/she is also responsible for keeping all the necessary patient documents (patient card, laboratory results and prior treatments given) for review by the district TB coordinator and for running the TB ward in hospitals. The pharmacist should get the approval of the TB focal person in order to distribute anti-TB drugs to patients admitted in other wards for severe TB or/and other illnesses.
- Ensure the criteria for patient admission to the TB ward are adhered in order to maximize appropriate use of hospital resources.
- Develop capacity to improve the quality of diagnosis based on the results of quality control from the regional research laboratory and the district health office on a continuous basis.

**Health centres:**

The district health centres will be responsible for treatment follow-up of all pulmonary patients diagnosed in a health centre or elsewhere (in the same district hospital or other district units). Pulmonary positive patients getting their treatment from clinics are referred for follow up AFB-sputum exam to health centres. Good organization of the TB control programme is of paramount at health centres in order to ensure patient adherence to treatment. The presence of a trained TB focal person is crucial. Health centre heads are expected to assign a full time nurse responsible for the management of patients with all categories of tuberculosis diagnosis. Health centre heads have to monitor the overall

management of TB control in general and the tasks of the TB focal person in particular.

The health centre TB focal person is required to:

- Provide daily TB care in the outpatient clinic,
- Document treatment outcome and monitor drug supply,
- Contact the district TB coordinator whenever a new TB patient is diagnosed in the health centre.
- Keep all the necessary patient documents (patient card, laboratory results) for review by the district TB coordinator.
- Collect labelled AFB-slides and serum for HIV from each patient.
- Review how patients were diagnosed based on the national diagnostic standard before starting treatment.
- Provide technical and material support to community health workers in her/his catchments areas.
- Monitor drug supply of anti-TB drugs and document treatment outcome of patients in the CHW-TC group.

**Health post-TB focal person:**

A health post-TB focal person must:

- Carry out daily TB care including DOT of all patient during the first month irrespective of their assigned arm of supervision.
- Arrange a meeting between CHWs (care providers) and patients during the first 4 weeks of treatment period.
- Give instructions to patients and CHWs about treatment and follow up visits.
- Instruct CHWs how to report treatment adherence of patients during a monthly meeting.
- Document the treatment progress of all patients.
- Institute defaulter-tracing mechanisms with the local community and CHWs.
- Monitor anti-TB drug supply and other necessary materials.
- Keep all the necessary patient documents (unit treatment register and adherence card for community health workers and anti-TB drugs distribution record) for review by the district TB coordinator.

- Provide technical support and anti-TB drugs to CHWs on a monthly basis.
- Notify a district TB coordinator when a patient changes his original assigned method of TB care group, is lost to follow up or dies during treatment.

**Volunteer Community Health Workers:**

- Provide care including Observation of treatment of patients assigned on a daily basis during the second month of the intensive phase.
- Give anti-TB drugs and advise the patient on a monthly basis till the end of the continuation phase.
- Document any daily treatment missed by the patient during the second month of intensive phase.
- Document the number of daily doses remaining with the patient at the end of every month and missed appointment days.
- Notify and encourage the patient to go for follow up visits to the respective health institution.
- Refer patients to respective health facility whose illness is worsening or who are suffering from side effects.
- Refer patients when they request to consult a health worker during the course of treatment.
- Refer patients to the supervising health institution when they request to change the CHW-TC arm and place of residence.
- Contact patients when they missed their daily doses during the second month of intensive phase, and when they do not collect their monthly drugs during the 6 months continuation phase.
- Document those patients lost for follow up, who die during treatment or refuse to take drugs.
- Report to the respective health institution on a monthly basis.
- Collect anti-TB drugs from the respective health institution monthly.
- Trace defaulters and refer them to the health institution-TB focal person.



- Keep all the necessary patient documents (adherence card, anti-TB drugs distribution record) for review by the TB focal person on a monthly basis.
- Consult the respective TB focal person if he/she decides to leave the area.

## **8. Data processing and analysis**

### **Records**

Patient charts will be kept with the institutional TB focal person. Baseline information collected from patients will be sent to HQ. HIV test results of individual patients will be kept confidentially at RRL till the end of the trial. The national tuberculosis control records (unit treatment registers) will be used to assess treatment outcome.

### **Data entry**

Baseline interview records with coded intervention arms will be collected from districts every month. A distinct code number will be assigned to every patient. Data will be entered in SPSS and EPI programmes in order to check for any inconsistency. Two data technicians will enter and clean the data. The health management and information unit will monitor data processing.

### **Data analysis**

Treatment outcome indicators will be used to compare effectiveness of the arms based on the principles of 'intention to treat basis'. Chi-square and confidence intervals will be calculated for each intervention effect. The effect of potential confounders on treatment outcome will be controlled using logistic regression analysis. A separate analysis will be made for smear negative pulmonary TB patients assigned into the three arms.

### **Writing and reporting**

The primary investigator will be responsible for analysing, writing and reporting the study results to the relevant bodies including publication in medical journals 12 months after the commencement of the study.

### **Duration of the study**

Patient recruitment will take 12 months to secure the required sample size. Follow up of the last recruited patients will require another eight months. The total duration of the study will be 24 months. The final analysis and writing up of reports will take 8 months.

## **9. Ethical consideration**

The fundamental ethical principles will be applied as described in the ‘Declaration of Helsinki, 1975’ which was developed with special reference to developing countries in the ‘Proposed International Guidelines for Biomedical Research Involving Human Subjects’<sup>55</sup>. The main principles as applied to this study include the following:

### **Scientific merit**

To be ethical, the research must have scientific merit. Tuberculosis is a major burden in the developing countries, particularly in sub-Saharan Africa. Poor access to TB care, low adherence to treatment and high HIV transmission are aggravating the transmission of tuberculosis and the emergence of anti-TB drug resistance. Prolonged admission to hospital for direct observation of tuberculosis treatment overburdens health staff, scarce resources and patients. Decentralization of TB care to a lower level of health institution, more accessible to patient residence, has been shown to improve adherence to treatment in Tigray. The institution of a patient-centred TB care in the ongoing facility-based DOTS program and further decentralization of TB care using volunteer community health workers might improve patient adherence to treatment by minimizing interruption in their daily life. The burden on health services would also be reduced both in terms of staff time and resources at all levels.

Nevertheless, the relative effectiveness of such initiatives needs to be assessed before their wider scale use in Ethiopia. Several observational studies have documented

improvement in adherence to treatment by using CHW or volunteer supervisors. There is no conclusive evidence on the relative effectiveness of 'direct observation of patients taking treatment' in improving treatment outcome. The success of DOTS strategy has been attributed to the strengthening of the health system by instituting the other components of DOTS strategy. In addition to strengthening the ongoing health institution based TB care, the relative effectiveness of the two additional modalities of care (patient-administered treatment and care by CHWs) need to be established by well controlled studies before scale up. The results from the study are likely to provide additional answers to the research questions being raised. The findings of the research could be applicable in Tigray where community participation is widely practiced as part and parcel of local development.

#### **Equitable selection of subjects**

The potential benefits of the research are paramount both to patients and communities. It is an accepted practice in Ethiopia that all TB cases get anti-TB treatment at no cost to the public health sector. All pulmonary TB patients fulfilling the inclusion criteria will be included irrespective of their social and economic background. The inclusion of PTB- cases, which currently represent 45% of all TB cases, is expected to improve generalizability of the study. Extra-pulmonary patients and pulmonary patients not fulfilling the inclusion criteria will be provided with similar treatment and follow up care as per the national standard.

#### **Informed consent**

Informed consent to the assigned modality of TB care by random allocation will be obtained for all eligible patients. Patients will be informed about the purpose of the study and the alternative modalities of TB care. Description of benefits of each modality of TB care will be given in order to guarantee informed consent. Patients will be informed about their right to decline the randomly assigned arm. Explanation about the remaining alternatives will be given. Patients will also be informed about their right to change the methods of care at any time. Signed consent forms will be obtained from

each patient participating in the study. Serum for anonymous HIV testing will be collected from each patient. HIV test results will only be used as a prognostic factor for the effectiveness of treatment and in order to determine the proportion of HIV positive patients.

### **Confidentiality**

Information collected will be confidentially maintained and reports will only be released to others after the investigators have carried out analysis. To maintain confidentiality and blind the investigators, patients participating in the study will be identified by specific code numbers developed by a statistician in HQ. The regional research laboratory will identify patients' sera for HIV by specific code numbers assigned to a patient. Anonymous HIV test results will only be given to investigators after the effectiveness of the study is reported. Any data collected regarding a patient will be confidential.

### **Coercion**

Patient coercion and deception to accept assigned arm will not be practiced. All patients (both eligible and ineligible) will be required to sign an agreement paper to complete the prescribed treatment in the presence of a witness. This is a national TB control standard procedure that is being practised elsewhere in the country.

### **Stopping rule and changing the design**

Monitoring of the enrolment rate and that of patients changing their assigned intervention arms will both be done on a monthly basis. Though least likely to happen, changing the study design will only be considered when one of the following conditions is being met. The first criteria will be when the number of patients not consenting exceeds those willing to participate two months after the onset of the study. The second criteria will be when the proportion of randomized patients changing arms exceeds by 30% or more the proportion of patients joining the study. If either of these two problems

happens, it could lead to loss of study power because of small number of patients per intervention arm and hence the prolongation of the study.

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**Annexes:**

**Annex 1.1A: Diagnostic work up assessment of a new smear positive pulmonary tuberculosis patient.**

**A. Diagnosis assessment based on the national algorithm:**

1. Does the patient have additional signs of other organ involvement? 1. Yes 2.

No....\_\_\_\_\_

2. If any other organs are affected besides the lung, select suspected diagnosis?

1. Tuberculous lymphadenitis

2. Tuberculous pleurisy

3. TB of bones and/or joints

4. Intestinal TB

5. TB meningitis

6. Others

specify\_\_\_\_\_.....\_\_\_\_\_

3. The diagnosis was made by:

1. A medical doctor (specify name)\_\_\_\_\_

2. A health officer (Specify name)\_\_\_\_\_

3. A nurse (specify name)\_\_\_\_\_

4. If the diagnosis is smear positive pulmonary tuberculosis (PTB+), please answer the questions in table 1 below based on supportive evidences. Supportive documents must be reviewed in order to ascertain the diagnosis as per the national diagnostic algorithm.

**Table 1: Diagnostic criteria for pulmonary positive cases.**

|   | <b>Investigations and supportive evidences of TB diagnosis</b>   | <b>1. Yes</b> | <b>2. No</b> |
|---|--|---------------|--------------|
| 1 | Of the 3 smear slides done for the first time, 2 slides were positive.   |               |              |
| 2 | Of the 3 or 2 slides done for the second time, 2 slides were positive.   |               |              |
| 3 | The patient has been treated with broad-spectrum antibiotics after negative AFB-smear result.                                |               |              |
| 4 | No improvement in clinical condition after treatment with antibiotics.   |               |              |
| 5 | Of 2 or 3 smear slides done for the third time after the patient was treated with antibiotics, 1 slide was positive for AFB. |               |              |
| 6 | Sputum culture was positive for AFB  |               |              |

4. The diagnosis of smear positive pulmonary tuberculosis is correct when the response to question numbers either 1 or 2 and 3 to 6 in combination in table 1 is 'yes'. Based on the responses to question numbers 1 to 6, is the diagnosis of the patient as smear positive pulmonary tuberculosis correct?

1. Yes (**proceed to part B and assess eligibility**)
2. No (**the patient should not be registered for treatment and should be re-evaluated**)\_\_\_\_\_

## B. Assessment of eligibility of a smear positive pulmonary tuberculosis patient

### Instructions:

- Please critically examine before eligibility assessment that the patient was correctly diagnosed as per the national guideline.
- Information on the diagnosis of a patient with transfer paper who was on short course regimen for other district unit should be known before his entry as eligible case.
- Please critically review documents whether the patient had been on treatment previously in the same.
- Please fill table 2 for a smear positive pulmonary tuberculosis patient.

**Table 2: Assessment of eligibility criteria for a smear positive pulmonary tuberculosis patient.**

|          | <b>Inclusion criteria</b>   | <b>1. Yes</b> | <b>2. No</b> |
|----------|---|---------------|--------------|
| <b>1</b> | Is the patient's age 15 year or older (nearest year)?   |               |              |
| <b>2</b> | Is the patient permanent resident in the district?  |               |              |
| <b>3</b> | The patient has no history of allergy to any of the anti-TB drugs   |               |              |
| <b>4</b> | The patient has no history of allergy or chronic disease in which a different short course regimen is recommended for TB treatment. |               |              |
| <b>5</b> | Is the patient a new smear positive pulmonary tuberculosis case?  |               |              |

5. An eligible patient should satisfy inclusion criteria 1 to 4 ('yes' response) outlined in table 2. Based on your assessment, is the patient eligible for the study as smear positive pulmonary tuberculosis case?

1. Yes, the patient is eligible for entry (**Proceed to annex II**)
2. No, the patient is not eligible for entry (**manage the patient as per the standard treatment protocol**)

**Annex 1.1B: Diagnostic work up assessment of a new smear negative pulmonary tuberculosis patient.**

**A. Diagnosis assessment based on the national algorithm:**

1. Does the patient have additional signs of other organ involvement?  
1. Yes 2. No.....
2. If any other organs are affected besides the lung, select suspected diagnosis?
  1. Tuberculous lymphadenitis
  2. Tuberculous pleurisy
  3. TB of bones and/or joints
  4. Intestinal TB
  5. TB meningitis
  6. Others specify.....
3. The diagnosis was made by:
  1. A medical doctor (specify name).....
  2. A health officer (Specify name).....
  3. A nurse (specify name).....

**If the diagnosis is smear negative pulmonary tuberculosis (PTB-), please answer the questions in table 1 below based on supportive evidences. Supportive documents must be reviewed in order to ascertain the diagnosis as per the national diagnostic algorithm.**

**Table 1: Diagnostic criteria for smear negative pulmonary cases.**

|   | <b>Investigations and supportive evidences</b>   | <b>1. Yes</b> | <b>2. No</b> |
|---|--|---------------|--------------|
| 1 | None or 1 out of 3 smear slides done for the first time were positive.   |               |              |
| 2 | None out of 2 smear slides done for the second time were positive.   |               |              |
| 3 | The patient has been treated with broad-spectrum antibiotics after negative AFB-smear results.                   |               |              |
| 4 | No improvement in clinical condition after treatment with antibiotics.   |               |              |
| 5 | None out of 3 smear slides done for the third time after the patient was treated with antibiotics were positive. |               |              |
| 6 | Chest x-ray taken BEFOR the patient was treated with antibiotics is suggestive of pulmonary tuberculosis.        |               |              |
| 7 | Chest x-ray taken AFTER the patient was treated with antibiotics is suggestive of pulmonary tuberculosis.        |               |              |

4. The diagnosis of smear negative pulmonary tuberculosis is correct when the response to question numbers 1 to 5 is 'yes' and the response to question 6 or 7 is 'yes' in Table 1. Based on the responses to question numbers 1 to 7, is the diagnosis of the patient as smear negative pulmonary tuberculosis correct?

1. Yes (**proceed to eligibility assessment part B**)
2. No (**the patient should not be registered for treatment and should be re-evaluated**).\_\_\_\_\_



## B. Assessment of eligibility of a smear negative pulmonary tuberculosis patient

### Instructions:

- Please critically examine before eligibility assessment that the patient was correctly diagnosed as per the national guideline.
- Information on the diagnosis of a patient with transfer paper who was on short course regimen for other district unit should be known before his entry as eligible case.
- Please critically review documents whether the patient had been on treatment previously in the same.
- Please fill table 2 for a smear negative pulmonary tuberculosis patient.

**Table 2: Assessment of eligibility criteria for a smear negative pulmonary tuberculosis patient.**

|          | <b>Inclusion criteria</b>  | <b>1. Yes</b> | <b>2. No</b> |
|----------|--|---------------|--------------|
| <b>1</b> | Is the patient's age 15 year or older (nearest year)?  |               |              |
| <b>2</b> | Is the patient permanent resident in the district?   |               |              |
| <b>3</b> | The patient has no history of allergy to any of the anti-TB drugs  |               |              |
| <b>4</b> | The patient has no history of chronic disease in which a different short course regimen is recommended for TB treatment. |               |              |
| <b>5</b> | Is the patient a new smear negative pulmonary tuberculosis case?   |               |              |

5. An eligible patient should satisfy inclusion criteria 1 to 4 (yes response) outlined in table 2. Based on your assessment, is the patient eligible for the study as smear negative pulmonary tuberculosis diagnosis?

1. Yes, the patient is eligible for entry (**proceed to annex 2.2**)
2. The patient is not eligible for entry (**manage the patient as per the standard treatment protocol**)

**Annex 1.2 Baseline data on eligible pulmonary tuberculosis patient.**

**A. General background information**

1. Patient code number.....\_\_\_\_\_
2. Name of woreda.....\_\_\_\_\_
3. Name of residence tabia.....\_\_\_\_\_
4. Name of residence Kushet.....\_\_\_\_\_
5. Name of residence Gott.....\_\_\_\_\_

**B. Socio-demographic characteristics of the patient**

6. Age in years.....\_\_\_\_\_
7. Sex: 1.Male      2. Female.....\_\_\_\_\_
8. Marital status:  
1.Married 2.Single 3.Divorced 4. Widowed 5.Separated.....\_\_\_\_\_
9. Place of residence:  
1.Urban 2.Rural.....\_\_\_\_\_
10. Occupation:  
1.Farming      2.Government employee      3.Trader 4.Self-employed  
5.Commercial sex worker 6.Dependent on family  
7.Housewife      8.Others specify.....\_\_\_\_\_
11. Educational status:  
1.Illiterate      2. Read/write  
3.Primary schooling 4. Secondary or above.....\_\_\_\_\_
12. The number of people living with the patient.....\_\_\_\_\_
13. Duration of living in current community in years.....\_\_\_\_\_
14. The number rooms used by people.....\_\_\_\_\_
15. Do you currently receive food assistance from the government?  
1.Yes      2.no.....\_\_\_\_\_

### C. Assessment of health seeking behaviour

16. How many days were you sick before you made the first consultation to a government health institution?.....\_\_\_\_\_

17. What actions did you take before the first visit to government health institution?

|      | Actions taken                    | The number of days spent |
|------|----------------------------------|--------------------------|
| 18.1 | Did nothing                      |                          |
| 18.2 | Took herbal medicine             |                          |
| 18.3 | Consulted private practitioner   |                          |
| 18.4 | Consulted private pharmacist     |                          |
| 18.5 | Treated with holy water          |                          |
| 18.6 | Consulted community health agent |                          |
| 18.7 | Others specify                   |                          |

19. Assess referral and admissions in government health institution. List the name of health institutions consulted by the patient from the first to the last. Fill the appropriate responses for each health institution.

|      | Order of consultation | Name and type of health institution consulted | How was consultation made: 1. Referred<br>2. Self-referred | The number of days of admission |
|------|-----------------------|---|--|---------------------------------|
| 19.1 | First consultation    |   |  |                                 |
| 19.2 | Second consultation   |   |  |                                 |
| 19.3 | Third consultation    |   |  |                                 |
| 19.4 | Fourth consultation   |   |  |                                 |
| 19.5 | Fifth consultation    |   |  |                                 |

**D. Assessment of patient's knowledge, attitudes and practices regarding TB**

**Instruction: Questions 20 to 28 should not be probed.**

20. Have ever heard about pulmonary tuberculosis?

1. Yes                      2. No (skip to 27).....\_\_\_\_\_

21. What do you think is the main cause of pulmonary tuberculosis?

1. Bacteria                      2. Evil spirit    3. Gods will  
4. Exposure to cold            5. I don't know            6. Others specify....\_\_\_\_\_

22. What do you think about the main reason you get tuberculosis disease?

1. I had contact with a person with TB  
2. I got it from evil spirit  
3. I got it as a result of exposure to cold  
4. I have inherited from family  
5. Poor nutrition  
6. Gods will/chance  
7. I don't know  
8. Others specify.....\_\_\_\_\_

23. Do you believe some one in your family could be diseased from you?

1. Yes                      2.No                      3. I don't know (skip to 25)....\_\_\_\_\_

24. If no, what is the main reason you think so?

1. It is gods will to be diseased  
2. Family takes the necessary care  
3. It is not transmitted from one to another  
4. Other specify.....\_\_\_\_\_

25. Are you worried if someone knows about your disease?

1. Yes                      2. No (skip to 27).....\_\_\_\_\_

26. If yes, what is your main reason for this?
1. I might be isolated
  2. People relate it with HIV infection
  3. Not to bother my family about the disease
  4. Lost hope to be cured
  5. Others specify.....\_\_\_\_\_

**E. Assessment of Patient's preference supervising health institution**

27. Name of health institution you would prefer to be followed for treatment?

1. A health centre, specify name\_\_\_\_\_
2. A hospital, specify the name\_\_\_\_\_
3. A health station, Specify name\_\_\_\_\_
4. A health post, specify the name\_\_\_\_\_

28. The main reason for choosing the above institution:

1. Near to residence
2. To get better-qualified health worker
3. Better diagnostic facility
4. Good reception by the staff
5. Better drug supply
6. Other specify.....\_\_\_\_\_

### **Annex 1.3: Procedures for counselling and assignment of eligible pulmonary tuberculosis patient.**

The following procedures should be strictly followed in order to ensure that a patient is well informed about his illness, the drugs and modalities of treatment supervision that will be provided.

1. Educate the patient about his illness (the diagnosis, the cause, how it is transmitted, consequences if untreated and how to prevent the disease).
2. Educate the patient about treatment (the drugs and their doses, when to take them, the duration of treatment, the anticipated minor side effects, what actions should be taken when severe side effects are encountered and the health services will be free of charge till the patient gets cured).
3. Educate the patient about his obligations (taking drugs on daily bases as prescribed, health consequences when treatment is interrupted both to the patient, his family and the community, the difficulty of curing him if he develops resistance).
4. The patient should be informed to advise members of his family or neighbours have signs and symptoms of pulmonary TB to seek care in health institutions.
5. Determine whether patient's residence is in the catchments of the study area.
6. Select the most convenient health institution with the patient.
7. After the most convenient supervising institution is selected in consultation with the patient, the next task is to select the three modalities of supervision. In order to identify one of the arms of supervision, follow the following instructions.

#### **A. If the patient is smear positive pulmonary TB case:**

- Open opaque envelope in sequence for pulmonary positive patients,
- Identify the arm of supervision in the envelope,
- Give details about each of treatment supervision assigned to the patient:

**1. If the patient is assigned to health worker treatment supervision please provide the following information to the patient before asking consent:**

- The patient should visit the convenient health institution on daily bases during the first 8 weeks to take treatment.
- At the end of 8 weeks the patient should submit sputum for laboratory check up.
- The patient should visit the health institution on a monthly basis for 6 months during the continuation phase. Drugs that given to the patient should be taken on daily basis at home.
- At the end of 5<sup>th</sup> month of treatment the patient has to visit the district diagnostic centres for sputum check-up.
- At the end of 7<sup>th</sup> months of treatment the patient has to visit the district diagnostic centres for the final sputum check-up.
- If the patient accepted the allocated arm, singed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.
- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**2. If the patient is assigned to self-administered treatment supervision, please provide the following information before asking consent:**

- The patient should visit the health institution on daily basis for the first 4 weeks on daily basis in the selected health institution followed by a monthly visit for the remaining 7 months. Drugs should be taken on daily bases at home during the continuation phase.
- At the end of 8 weeks, the patient should visit the district diagnostic centres for sputum for check up.
- At the end of 5<sup>th</sup> month of treatment the patient has to visit the same district diagnostic centres for sputum check-up.
- At the end of 7<sup>th</sup> months of treatment the patient has to visit the same district diagnostic centres for sputum check-up.
- If the patient accepted the allocated arm, singed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.

- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**3. If the patient is assigned to community health worker treatment supervision, inform the patient the following before asking consent:**

- The patient should visit the selected health institution on daily basis only for the first 4 weeks.
- The patient will be treated on daily basis for the second 4 weeks in her/his village by selected CHW.
- He should be informed that during the remaining 6 months he/she should visit CHWs fortnightly to collect drugs and get advice. Drugs should be taken on daily bases at home during the continuation phase.
- Give reassurance about the similarity of care between CHWs and health institutions.
- Once the patient selects the convenient CHW, inform him/her when to see the nearby health institution.
- Inform the patient to visit the diagnostic centre for sputum check up at the end of the 2<sup>nd</sup>, 5<sup>th</sup> and 7<sup>th</sup> month.
- If the patient accepted the allocated arm, signed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.
- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**B. If the patient is a smear negative pulmonary TB case:**

- Open opaque envelop in sequence for pulmonary negative patients,
- Identify the arm of treatment supervision in the envelop,
- Give details of explanation about each options of treatment supervision assigned to patients.



**1. If the patient is assigned to health worker-treatment supervision, please give the following information before asking consent:**

- The patient should visit the convenient health institution selected on daily bases during the first 8 weeks for treatment.
- At the end of 8 weeks the patient should visit the diagnostic centre for medical check up.
- The patient should visit the health institution on a monthly basis for 6 months during the remaining treatment period.
- Drugs should be taken on daily basis at home.
- At the end of 5<sup>th</sup> and 7<sup>th</sup> month of treatment the patient has to visit the district diagnostic centres for medical check-up.
- If the patient accepted the assigned method, signed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.
- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**2. If the patient is assigned to self-administered treatment supervision, please explain the following information before asking consent:**

- The patient should visit the selected health institution on daily basis only for the first 4 weeks followed by a monthly visit for the remaining 7 months.
- Drugs should be taken on daily bases at home during the continuation phase.
- At the end of the first 8 weeks, the patient should visit the district diagnostic centres for clinical check up.
- At the end of 5<sup>th</sup> and 7<sup>th</sup> months of treatment the patient has to visit the same district diagnostic centres for clinical check-up.
- If the patient accepted the allocated arm, signed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.
- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**3. If the patient is assigned to community health worker treatment supervision, inform the patient the following before asking consent:**

- The patient should visit the selected health institution on daily basis only for 4 weeks.
- The patient will be treated on daily basis for the second 4 weeks in her/his village by the selected CHW.
- He should be informed that during the remaining 6 months he/she should visit CHWs fortnightly to collect drugs and get advice. Drugs should be taken on daily bases at home during the continuation phase.
- Give reassurance about the similarity of care between CHWs and health institutions.
- Once the patient selects the convenient CHW, inform him/her when to see the nearby health institution.
- Inform the patient to visit the diagnostic centre for clinical check up at the end of the 2<sup>nd</sup>, 5<sup>th</sup> and 7<sup>th</sup> month.
- If the patient accepted the allocated arm, signed consent form (annex 2.4) and patient profile forms (annex 2.5) should be filled.
- If the patient declined to accept the allocated arm, follow instructions given in annex 2.3-C.

**C: If an eligible patient refused the randomly assigned treatment supervision:**

- The district TB coordinator should collect patient's main reason for refusing the assigned modality of treatment supervision.
- Explain about the remaining two modalities of supervision so that he/she will be able to select the most convenient one.
- Once the patient selected his/her preferred modality of supervision, detailed instruction about it must be given as specified above (annex 2.3- A, B).
- Both patients' original arm of treatment supervision and the second preferred arm selected should be recorded in the patient allocation assessment profile form (annex 2.4).

**Annex 1.4: Patient allocation profile assessment form**

1. Name of diagnosing health institution \_\_\_\_\_ code \_\_\_\_\_
2. Name of patients Tabia of residence \_\_\_\_\_ code \_\_\_\_\_
3. Name of patients kushet of residence \_\_\_\_\_ code \_\_\_\_\_
4. Name of patient's got of residence \_\_\_\_\_ code \_\_\_\_\_
5. Name of supervising health institution selected \_\_\_\_\_ code \_\_\_\_\_
6. Randomly assigned intervention arm code..... \_\_\_\_\_
7. Changed alternative intervention arm code at entry..... \_\_\_\_\_
8. Area of residence: 1. Urban                      2. Rural..... \_\_\_\_\_

Instruction: Please answer the following in the appropriate section for patient's main reason for changing the randomly assigned modality of treatment supervision.

29. The main reason given by the patient for changing randomly assigned in CHW-TS:

1. I live near the supervision health institution
2. I do not trust the capacity of CHWs
3. I can manage to take care of myself
4. Others specify \_\_\_\_\_

4. The main reason given by the patient for changing randomly assigned in self-administered treatment:

1. I need a close attention by a health worker
2. It is too far to visit the supervising health institution on a monthly basis
3. I can not stay in town for different reason (economic or shelter)
4. Others, specify \_\_\_\_\_

5. The main reason given by the patient for changing the randomly assigned in health worker-TS:

1. I can not stay in town for economic or other reasons
2. It is to far to visit the supervising health institution during the first 2 months
3. It is too far to visit the supervising health institution on monthly bases during the continuation phase.
4. Others, specify \_\_\_\_\_

### **Annex 1.5: Information for eligible patients and obtaining consent.**

The investigations carried out confirmed you are suffering from pulmonary tuberculosis. Pulmonary tuberculosis is a disease caused by very small organism that can't be seen by the naked eyes. The disease is transmitted from a sick person to a healthy person by cough. The disease could be fatal and can only be cured in most cases by modern treatment. Effective cure from treatment is achieved when a patient takes the drugs every day for eight months.

Treatment of tuberculosis disease is only given in public health institutions throughout the region. The existing treatment protocol in practice is that every patient should take treatment under the observation of a health worker in a health institution for the first two months. The direct observation of treatment on daily basis during the first 2 months is intended to ensure that the diseased person does not transmit to others such as family members, neighbours and other members of community. Following the 2 months daily-observed treatment, a patient is expected to visit his/her nearby health institution to collect drugs on a monthly basis and take the prescribed medication by him/herself. Once a patient took treatment under observation for two months, he/she has no risk to transmitting the disease to others. The role of a health worker during the remaining treatment period is to encourage the patient to complete his/her treatment.

Even though the directly observed treatment by a health worker in a health institution is assumed to encourage patients to complete their treatment, it seems difficult for most patients. Sick patients irrespective of their place of residence are expected to visit a health institution every morning during the first 2 months followed by a monthly visit for the next 6 months. Such an arrangement creates problem in getting treatment to patients living far away from supervising health institutions. The existing schedule of treatment also burdens the scarce health manpower in health institutions.

To decrease inconveniences to patients in getting their treatment so that they complete the 8 months of treatment, two alternatives of treatment supervision methods have been

designed. One strategy is to give the anti-tuberculosis drugs to community health workers who will be supervising patients taking their drugs on daily bases during the second month of treatment. Patients have to visit CHWs home instead of going to health institutions once in a month to collect their drugs and get treatment advice.

The second strategy is to instruct the patients to take their medication at home without observation by health workers during the second month. Patients who will be treating themselves are expected to come to the nearby health institutions every month to collect their drugs and get health advice during the remaining 7 months. We believe these two alternative strategies could be equally effective in ensuring patients complete their treatments.

The intention of this study is to assess which of the strategies are effective so that they could be applied in a wider scale. To conduct this study you are assigned to one of the three methods of treatment supervision by chance. Whether you accept or decline the method of supervision assigned by chance, you will be treated with the same drugs and follow up examinations free of charge. If your condition does not improve after two months of treatment or more, further three months of drug treatment will be provided under the direct observation of a health worker or a CHW followed by a monthly visit for 5 months. This problem happens if you do not take drugs on daily basis as prescribed by your physician.

To ensure there is improvement with the treatment given, you are required to visit a nearby health institution with diagnostic services for clinical and sputum smear examination at the end of 2<sup>nd</sup>, 5<sup>th</sup> and 7<sup>th</sup> months of treatment. The follow up visits will ensure that you are getting the right drugs and to make sure you are cured. The three visits to diagnostic centres are a standard requirement to be complied whether you accepted or declined the assigned arm.

Taking your drugs without interruption and participating in the study will help not only you but also your family and the community at large for us to be able to institute convenient methods of treatment supervision in future.

If you wish to decline from the allocated arm, you will be allowed to select one of the remaining two methods of supervision.

Your medical records (history records and laboratory results) will be kept in safe place so that researchers would be able to review them. Your name will be kept confidential by assigning specific codes.

**Consent form:**

I.....accepted the assigned methods of treatment supervision and agree to comply with the treatment protocol. The purpose of the study, the way I am supposed to get treatment and follow up examinations; and the expected problems of each methods of treatment supervision have been explained to me. I have clearly understood about the study. Should I have any queries about the study, I am advised to ask my treatment supervisor. I clearly understand my rights to change a method of treatment supervision at any stage after notifying a health worker responsible for tuberculosis control in the nearby health institution.

Patient code:.....

Patient's address:

District code:.....

Tabia/keble code: .....

Gott/village code : .....

Patient's signature:.....

Name of consenting personnel:.....

Name of health institution:.....

Witness name:.....

Date: .....

## **Annex 1.6. Definitions of treatment outcome indicators**

The following indicators of tuberculosis treatment outcomes recommended by WHO<sup>2</sup> and the NTP<sup>48</sup> will be used to assess effectiveness of the three arms.

**Cured patient:** A patient is declared cured when his/her smear result is negative at, or one month prior to the completion of treatment and on at least one previous occasion (usually at the end of the 2<sup>nd</sup> or 5<sup>th</sup> month).

**Treatment completed:** A patient who has completed treatment but in whom smear results are not available on at least two occasions, usually at the end of the 2<sup>nd</sup>, 5<sup>th</sup> or 7<sup>th</sup> /11<sup>th</sup> months prior to the completion of treatment or if a patient had negative pre-treatment results and had been placed on treatment for clinical reasons.

**Default:** A patient who has been on treatment for at least 4 weeks and whose treatment was interrupted for more than 8 consecutive weeks or for a cumulative period of more than 12 weeks.

**Treatment failure:** A patient who remains or becomes smear-positive at 5 months or later during treatment is considered as failure.

**Died:** A patient who died from any cause during the course of treatment.

**Transferred out:** A patient transferred to another district (reporting unit) after he/she started treatment for at least 4 weeks.





**2. CHW PATIENT FOLLOW-UP UNIT REGISTRATION**

1. Name of patient under CHW-care \_\_\_\_\_
2. Name of patient's resident Tabia \_\_\_\_\_
3. Name of patient's resident kushet \_\_\_\_\_
4. Anti-TB drugs and dosage prescribed during the second month of treatment:
  - Ethambutol: \_\_\_\_\_
  - RHZ: \_\_\_\_\_
5. Day the patient starts daily supervised treatment \_\_\_\_\_

The following table will be used to monitor the daily-supervised treatment of a patient. Patients will be observed every day for 28 days. Please write  $\checkmark$  and main reason given by the patient in the appropriate column in the following table.

| S/number | Day DOT should be given | The patient took the daily dose | The patient did not take the daily dose | If the patient missed appointment, please write the main reason given. |
|----------|-------------------------|---------------------------------|---|--|
| 1        |                         |                                 |   |  |
| 2        |                         |                                 |   |  |
| 3        |                         |                                 |   |  |
| 4        |                         |                                 |   |  |
| 5        |                         |                                 |   |  |
| 6        |                         |                                 |   |  |
| 7        |                         |                                 |   |  |
| 8        |                         |                                 |   |  |
| 9        |                         |                                 |   |  |
| 10       |                         |                                 |   |  |
| 11       |                         |                                 |   |  |
| 12       |                         |                                 |   |  |
| 13       |                         |                                 |   |  |
| 14       |                         |                                 |   |  |
| 15       |                         |                                 |   |  |
| 16       |                         |                                 |   |  |
| 17       |                         |                                 |   |  |
| 18       |                         |                                 |   |  |
| 19       |                         |                                 |   |  |
| 20-28    |                         |                                 |   |  |

5. The specific day of follow up visit to the respective health institution by a patient after completing the intensive phase of treatment \_\_\_\_\_
6. Anti-TB drugs and dosage prescribed during the continuation phase:
  - EH: \_\_\_\_\_

**The following table will be used to monitor the monthly treatment follow up of patients. Patients should be observed every 28 days for 6 months. Please tick  $\checkmark$  and fill the appropriate response in each column in the following table.**

| S/n | Specific day of patient monthly visit | The patient took monthly drugs | The patient did not take monthly drugs | If missed appointment, date the patient collected | If the patient did not collect drugs on time, please write the main reason given by the patient |
|-----|---------------------------------------|--------------------------------|--|---|---|
| 1   |                                       |                                |  |   |   |
| 2   |                                       |                                |  |   |   |
| 3   |                                       |                                |  |   |   |
| 4   |                                       |                                |  |   |   |
| 5   |                                       |                                |  |   |   |
| 6   |                                       |                                |  |   |   |

5. The specific day of follow up visit to the respective health institution by a patient after completing the fifth month of treatment \_\_\_\_\_
6. The specific day of follow up visit to the respective health institution by a patient after completing the seventh month of treatment \_\_\_\_\_

**Annex 1.8: Treatment follow-up and outcome assessment forms for pulmonary TB cases.**

**1. LABORATORY REGISTRATION FOR AFB**

Month(s): \_\_\_\_\_

Year: \_\_\_\_\_

| Patient number | Health unit | Date | Lab Serial number | Name and address of Patient | Age | Sex | Name and address of contact person | New patient | Follow-up | Woreda TB/Lep number | Results |   |   | Sign | Remark |
|----------------|-------------|------|-------------------|-----------------------------|-----|-----|------------------------------------|-------------|-----------|----------------------|---------|---|---|------|--------|
|                |             |      |                   |                             |     |     |                                    |             |           |                      | 1       | 2 | 3 |      |        |
|                |             |      |                   |                             |     |     |                                    |             |           |                      |         |   |   |      |        |
|                |             |      |                   |                             |     |     |                                    |             |           |                      |         |   |   |      |        |
|                |             |      |                   |                             |     |     |                                    |             |           |                      |         |   |   |      |        |

**2. UNIT TB REGISTRATION**

| Unit TB Number | Name and Address of patient | Sex M/F | Name and address of contact person | Smear result     | Category N.R.F.D.T.O | Intensive phase |      | Intensive phase monitoring chart |   |   |   |   |   |   |   |   |   |
|----------------|-----------------------------|---------|------------------------------------|------------------|----------------------|-----------------|------|----------------------------------|---|---|---|---|---|---|---|---|---|
|                |                             |         |                                    |                  |                      | Drug            | Dose | Days (1-29 days):                |   |   |   |   |   |   |   |   |   |
| Woreda TB num. |                             | Age     |                                    | Lab.no<br>weight | P/pos,p/neg<br>EP    |                 |      | mt                               | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|                |                             |         |                                    |                  |                      |                 |      |                                  |   |   |   |   |   |   |   |   |   |
|                |                             |         |                                    |                  |                      |                 |      |                                  |   |   |   |   |   |   |   |   |   |

| Sputum results         |                       |                       | Continuation phase |      | Continuation phase treatment monitoring chart |     |     |     |     |     |     |     |     |     |     |     | Date treatment stopped (enter data in appropriate column): |                     |      |         |         |              |  |
|------------------------|-----------------------|-----------------------|--------------------|------|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|---------------------|------|---------|---------|--------------|--|
| Lab.name,serial no.&wt |                       |                       | phase              |      | 4-weekly attendance:                          |     |     |     |     |     |     |     |     |     |     |     | Cure   | Treatment completed | Died | Failure | Default | Transfer Out |  |
| 2nd Month              | 3 <sup>rd</sup> Month | 7 <sup>th</sup> month | Drug               | Dose | Month:  |     |     |     |     |     |     |     |     |     |     |     |  |                     |      |         |         |              |  |
| h                      |                       |                       |                    |      | Ha  | Neh | Pag | Mes | Tik | Hid | Tah | Tir | Yek | Meg | Mia | Gin | Sen  |                     |      |         |         |              |  |
|                        |                       |                       |                    |      |   |     |     |     |     |     |     |     |     |     |     |     |  |                     |      |         |         |              |  |
|                        |                       |                       |                    |      |   |     |     |     |     |     |     |     |     |     |     |     |  |                     |      |         |         |              |  |
|                        |                       |                       |                    |      |   |     |     |     |     |     |     |     |     |     |     |     |  |                     |      |         |         |              |  |

### 3. District TB Registration

| Date of registration | Woreda TB number | Name of patient | Sex (M/F) | Name of treatment unit |           | Date treatment started and regimen | Classification: P/POS, P/NEG, E.P. | Category of patient N.R.F D.T.O |
|----------------------|------------------|-----------------|-----------|------------------------|-----------|------------------------------------|------------------------------------|---------------------------------|
|                      |                  |                 | Age       | Starting               | Finishing |                                    |                                    |                                 |
|                      |                  |                 |           |                        |           |                                    |                                    |                                 |
|                      |                  |                 |           |                        |           |                                    |                                    |                                 |
|                      |                  |                 |           |                        |           |                                    |                                    |                                 |
|                      |                  |                 |           |                        |           |                                    |                                    |                                 |
|                      |                  |                 |           |                        |           |                                    |                                    |                                 |

| Sputum examination results (incl.lab name & serial no.) |                       |                       |                       | Date treatment stopped |          |      |         |         |              | Remark |
|---|-----------------------|-----------------------|-----------------------|------------------------|----------|------|---------|---------|--------------|--------|
| Pre-treatment   | 2 <sup>nd</sup> month | 5 <sup>th</sup> month | 7 <sup>th</sup> month | Cure                   | Complete | Died | Failure | Default | Transfer out |        |
|   |                       |                       |                       |                        |          |      |         |         |              |        |
|   |                       |                       |                       |                        |          |      |         |         |              |        |
|   |                       |                       |                       |                        |          |      |         |         |              |        |
|   |                       |                       |                       |                        |          |      |         |         |              |        |

## Annex 2: Ethical clearance letter

Reference No. 25A3/1-21/2003  
Date 12, February 2003

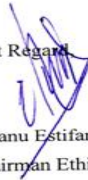


### Re: Notifying Ethical clearance

The regional Ethical clearance committee for Biomedical Research reviewed the study protocol under the title "A randomized control trial on the effectiveness of three modalities of tuberculosis treatment supervision under the Dots strategy in Ethiopia" presented by Dr. Mengiste Mesfin (Primary investigator).

The trial protocol was found to be consistent both with the National and international guidelines pertaining to the involvement of human beings as study subjects. We hereby acknowledge that your study is ethically accepted.

Best Regards

  
Kidanu Estifanos MD,  
Chairman Ethical clearance committee  
Tigray Health Research Council

