International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB)

AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE THE TOXICITY of HIGH DOSE RIFAMPICIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS

(RIFATOX)

Protocol Version 3.1_1 June 2011

(Inclusive of PIS/IC Version 2.2_30 July 2010)

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Signature:  Date: 1st June, 2011
**General information**
This document describes the RIFATOX trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial. Clinical problems relating to this trial should be referred to the Chief Investigator.

**Compliance**
The trial will be conducted in compliance with the protocol and the principles of ICH GCP Guidelines, NHS research governance and other regulatory requirements applying in the countries in which the trial will be conducted.

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<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse reaction</td>
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<tr>
<td>ART/ARV</td>
<td>Anti-retroviral therapy/ Anti-retroviral</td>
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<td>CF</td>
<td>Consent form</td>
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<td>CI</td>
<td>Chief Investigator</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<td>DTM</td>
<td>Domiciliary Treatment Monitor</td>
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<tr>
<td>ERC</td>
<td>Endpoint Review Committee</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
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<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
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<tr>
<td>NTP</td>
<td>National Treatment Programme</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIS</td>
<td>Patient information Sheet</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious adverse reaction</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedures</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
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1. SUMMARY

1.1 Lay summary
The current treatment of tuberculosis involves taking drugs daily for 6 or 8 months. Although the drugs are free to patients in low income countries, this still involves a substantial cost, in terms of time and administration, to both the patient and the treatment services. If the length of treatment could be shortened to 3, or even, 4 months, this would be of great benefit to the patients and the treatment services. A shorter treatment could also result in greater cure rates and, perhaps, a reduction in the emergence of resistance to the drugs.

One of the drugs given in treatment is called rifampicin. Laboratory experiments suggest that increasing the dose of rifampicin results in a greater killing of the tubercle bacillus both in liquid suspensions and in animals.

In this trial, we are assessing whether giving an increased dose of rifampicin to patients receiving the standard treatment for tuberculosis is safe and does not result in greater bad effects from the higher dose. If it is found to be safe, another trial would be carried out to see if the increased dose can increase the elimination of the tubercle bacillus from the lungs and if so, whether, eventually, the treatment can be shortened to 3, or even, 4 months.

The possibility of increased side effects from the higher doses of rifampicin will be monitored closely.

1.2 Abstract and summary of trial design

Type of design
An open-label 3-arm trial to compare a standard control regimen with two alternative treatment regimens for the treatment of tuberculosis (TB).

Disease/patients studied
Patients diagnosed with TB by having 2 sputum smear specimens positive for tubercle bacilli on direct smear microscopy.
Trial interventions – research and control

All patients enrolled will receive treatment for 6 months. The duration of the study will be the first 4 months of treatment. For the last 2 months of treatment, the patients will be transferred to the National Treatment Programme to complete 6 months.

Two regimens will be compared with a standard control regimen. In the two study regimens, patients will receive a supplement of rifampicin for the first 4 months according to the allocated regimen.

Control Regimen: 2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)^A.

Study Regimen 1: The regimen as above but with an increase in the dose of rifampicin to 15mg/kg body weight daily for the first 4 months. (2EHR\textsubscript{15}Z/2HR\textsubscript{15}/2HR)^B For the first 4 months, the dose of rifampicin will be 15mg/kg.

Study Regimen 2: The regimen as above but with an increase in the dose of rifampicin to 20mg /kg body weight daily for the first 4 months. (2EHR\textsubscript{20}Z/2HR\textsubscript{20}/2HR)^C For the first 4 months, the dose of rifampicin will be 20mg/kg.

A. The dose for all drugs will be according to the WHO recommended weight bands with the dose of rifampicin of 10mg/kg body weight at start of treatment.
B. The dose of rifampicin increased to 15mg/ kg body weight for the first 4 months only.
C. The dose of rifampicin increased to 20mg/ kg body weight for the first 4 months only.

For further details see section 5.1

1.3 Outcome measures

Primary outcome measure

1. Occurrence of grade 3 or 4 adverse events during the first 4 months of chemotherapy.

Duration

Patients will be followed up for the duration of the trial, ie, the first 4 months of chemotherapy.

Data recording

Data will be recorded on paper case report forms (CRF)s and kept at the local centre.
1.4 Flow diagram

Trial entry, randomisation, treatment and analysis

Eligible Patients

Randomise

Control Regimen
(2EHRZ/4HR)

Study Regimen 1
(2EHR_{15Z}/2HR_{15}/2HR)

Study Regimen 2
(2EHR_{20Z}/2HR_{20}/2HR)

Patients seen
At 2, 4, 8, 12 and 16 weeks

Analysis of outcome measures
2. BACKGROUND

2.1 Introduction

Effective short-course regimens of chemotherapy for the treatment of pulmonary tuberculosis have been evaluated in numerous controlled trials worldwide. When adequately administered, they are capable of cure rates of 95% or more in patients with drug sensitive organisms. Moreover, the WHO recommended 6 month regimen costs approximately US$ 20.

In spite of effective and cheap regimens being available, in recent years the incidence of tuberculosis has increased dramatically due, in large part, to co-infection with HIV. The annual incidence of pulmonary tuberculosis is currently estimated to be 9 million, with 2 million deaths.

That maximum cure rates are not always achieved in the routine treatment services may, in part, be that treatment durations of 6 or 8 months are still too long. If the treatment period can be reduced to 3, or even, 4 months, this would have several important advantages. It would reduce the number of treatment doses that patients have to take, may reduce toxicity and may also improve compliance thus leading to greater cure rates.

Of the four drugs used in standard treatment, rifampicin, may, when given in larger doses, lead to treatment being shortened. The suggestion comes from laboratory investigations (in vitro and animals) which demonstrate an increased killing of tubercle bacilli with larger doses of this drug. However, larger doses in humans may lead to an increased incidence of serious side effects.

In this trial, we are seeking to determine whether an increase in the dose of rifampicin will result in an increase in serious side effects. The increased dose will be given for the first 4 months since regimens of 4 or 3 months would use a higher dose of rifampicin for the total duration of treatment.

2.2 Population

The study population will be TB patients, at the centres participating in the study, who fulfil the inclusion/exclusion criteria outlined in section 3.1 and 3.2.

Two regimens will be compared with a standard control regimen. See section 5.1 for full details.
2.3 Rationale and objectives

The principal aim of the trial is:

1) To assess whether an increase of daily rifampicin from 10 mg/Kg to 15 and 20 mg/Kg for the first four months to the standard six month regimen will result in an increase in severe (grade 3 or 4) adverse events (SAEs).

2) A secondary aim is to determine whether the increased dose would result in more rapid sterilisation of the lungs as shown by the culture conversion rate after eight weeks of treatment.

2.4 Relevant studies/trials

Tuberculosis is one of the major causes of death in the world, responsible for 1.6 million deaths annually\(^1\). In order to meet the United Nation’s Millennium Development Goals, one of the targets of the Stop TB Partnership (established in 2000) is the eradication of tuberculosis by 2050. Nine years later, it is now acknowledged that this target is unlikely to be achieved\(^2\).

Currently, the most effective form of control is treatment of clinical disease which stops transmission and saves lives. There is general agreement that shortening treatment from 6 to 4 months or less would be of great benefit\(^3\). A shorter treatment would have several advantages, including less exposure to toxic drugs and better adherence, thereby reducing both the risk of resistance emerging and health service contact as well as associated costs. A shorter treatment would also result in larger numbers of patients completing the full course of treatment and, thus, increased cure rates.

Several research groups are working on the development of new and more effective tools in the area of better vaccines, diagnostic tests and drugs. While there is hope that shortening treatment might be achieved with the development of new anti-tuberculosis drugs, the prospects for the new drugs currently in clinical development (which are at the beginning of phase II) suggest that it is likely to be many years before any treatment shortening to less than 4 months is obtained because of the limited number of drugs in the developmental pipeline\(^4\) and the time required to conduct the necessary phase II and phase III trials. The most advanced drug in the pipeline, moxifloxacin, has been shown to accelerate the elimination of tubercle bacilli from sputum in Phase II trials\(^5,6\). However, Phase III results of such a substitution will not be available for many years. No such result was obtained when it was substituted for isoniazid, despite impressive results in the mouse model\(^7\).
It is therefore essential to see whether improved results, and in particular treatment shortening, can be obtained with any of the existing drugs.

For the past 30 years, optimal treatment has been based on a six month regimen of isoniazid and rifampicin supplemented by pyrazinamide and ethambutol for the first 2 months. This regimen has been found to be highly effective in a series of clinical trials under a variety of conditions. Shorter regimens were found to have unacceptably high relapse rates. Rifampicin and pyrazinamide are the two drugs in this regimen capable of killing persisting bacilli. Could effective shorter regimens be developed by increasing the dose of either drug? An increase in the dose size of pyrazinamide is almost certain to result in unacceptable levels of liver toxicity, as demonstrated in early American studies. However, an increase in the dose size of rifampicin offers the possibility of treatment shortening. The choice of the current dose size of rifampicin of about 10 mg/kg was empirical, based on the dose size just sufficient to be effective.

A compelling case for an increase in dose size of rifampicin has been made by Peloquin with some of the best evidence on efficacy coming from experimental animal tuberculosis. Mice were infected with M. tuberculosis, and treated daily at various dose levels; the surviving bacilli in the lungs were quantitatively cultured at 1.3, 3 and 4 months. In this experiment (Fig 1), the 5 mg/kg body weight dose of rifampicin had only a bacteriostatic effect. The dose size of 12.5 mg/kg, approximately equivalent to the usual 10 mg/kg dose (600 mg for a patient of 50 Kg or more) in patients, was slowly bactericidal with about $10^4$ cfu still present in the lungs after 3 months of treatment. More dramatically, when the dose was increased 2-fold to 25 mg/kg, the speed of bacterial killing was considerably accelerated and at 3 and 4 months no colonies whatsoever were obtained from most of the mice. This suggests that important acceleration of bactericidal activity might be obtained by a doubling of the current dose size; no benefit was obtained by increasing the dose from 25 to 50 mg/kg. Experiments with the guinea pig also show a significant association between dose size and the amount of residual disease (scored as a “root-index”) after treatment of established disease for 6 weeks (Table 1).
Evidence that an increased rifampicin dose would result in a faster response to treatment of pulmonary tuberculosis in humans is limited. There are, however, data indicating that some patients are failing to get adequate concentrations of rifampicin. In one of these studies, there was an improvement in response when the dose size was increased.

Additional evidence derives from studies of the early bactericidal activity (EBA) of drugs as shown by the fall in colony forming counts in the sputum caused by the drug either singly or in combination. A comparison of the therapeutic margins for isoniazid and rifampicin shows that the usual 300 mg dose of isoniazid is about 20 times the minimal effective dose size (when the EBA = 0) whereas, the corresponding therapeutic margin for rifampicin is only 4. In view of the variability in the absorption of rifampicin by individual patients, it is not surprising that a proportion of these will have inadequate dosage. In an earlier EBA study and in a recent study at Stellenbosch University, S. Africa, an

Table 1. Mean root-index of amount of visible disease in organs of groups of 6-8 guinea pigs after treatment of established disease for 6 weeks with rifampicin given daily or every 2 days

<table>
<thead>
<tr>
<th>RIF (mg/kg)</th>
<th>Daily</th>
<th>Every 2 days</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.00</td>
<td>0.79</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
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<td>0.60</td>
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<tr>
<td>40</td>
<td>0.57</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Fig 1. Count of colony forming units (cfu) cultured from the lungs of mice when established tuberculosis was treated with various dose levels of rifampicin.
Redrawn from Grumbach & Rist, 1970
increase in rifampicin dose size to 20 mg/kg (1200 mg) resulted in a substantial linear increase in EBA (Fig 2). While this is probably a measure of bactericidal activity against multiplying bacilli in cavities, it is likely to result in increased sterilizing activity against more dormant bacilli.

![Fig 2: EBA over 2 days related to rifampicin dose size](image)

Two trials, investigating the pharmacokinetics of rifampicin have been carried out in Indonesia. One was an open label phase II randomised clinical trial\(^{21}\) and the second a double blind randomised clinical trial\(^{22}\) in which rifampicin was given at doses of 450mg and 600 mg. In both trials the authors report a more than dose-proportional increase in the mean AUC-24 h and \(C_{\text{max}}\) of rifampicin without affecting the incidence of serious adverse events. Little is known about the pharmacokinetics of dose sizes above 600 mg. Acocella reported that the half-life following a single dose increased from 2.6 hr for a dose of 300 mg to 5.1 hr for a dose of 900 mg, but this difference was smaller after 6 or more doses had been given.\(^{23}\) No pharmacokinetic information is available on dose sizes as high as 1200mg.

Although the evidence of the efficacy of higher doses of rifampicin is very persuasive, very little is known about the potential toxicity of a higher dose of rifampicin. No adverse events were encountered in the treatment of 48 leishmaniasis patients given 1200 mg daily for 4 weeks\(^{24,25}\) A daily dose of 900 mg daily for 3 weeks has also been used without adverse events in 239 brucellosis patients\(^{26}\) and in staphylococcal infections\(^{27}\). In a trial of the treatment of pulmonary tuberculosis, a dose of 1200 mg was given daily or intermittently to 91 patients and no serious adverse events were reported\(^ {28}\). A dose as high as 1800 mg was also given, in this pharmacokinetic study, but intermittently\(^ {29}\). No adverse events were reported. High doses of rifampicin have been frequently given at the National Jewish Hospital, Denver without serious adverse events (personal communication).
A study on the potential toxicity of increased size doses of another rifamycin, rifapentine, has been carried out within a CDC study with 150 patients. Treatment was discontinued in 6%, 4% and 6% in the 600, 900 and 1200 mg treatment arms respectively. Only one discontinuation, in the 1200mg arm, was due to an adverse event possibly associated with the study therapy.

In summary severe adverse events due to rifampicin appear to be sporadic and not dose related (Peloquin C, personal communication) nevertheless the data are limited and the possibility of dose related adverse events cannot be excluded at this time and merits further systematic investigation.

2.5 Risks and benefits
The single most important risk is the occurrence of serious, or even fatal, side effects. Patients in the trial will be closely monitored for adverse events. All patients who enroll in the study will benefit indirectly as it is well established that the outcome for patients enrolled in clinical trials is almost always better than patients in routine care.

The Independent Data Monitoring Committee (IDMC) will review safety and efficacy data regularly. If SAEs, particularly hepatotoxicity are encountered in a significantly increased number of patients in either of the test arms, enrolment into that arm of the study will be stopped pending further investigations.

2.6 Selection of Centres
Participating centres must fulfil the following criteria:

1. They are in a country with an established National Tuberculosis Programme (NTP).
2. They have access to a laboratory capable of microscopy, culture and susceptibility testing with a system of quality assurance.
3. An uninterrupted supply of drugs and diagnostic materials, free of charge, for all patients.
4. A treatment service where directly observed treatment, whenever rifampicin is given, is routine.
5. An established recording and reporting system, following the IUATLD/WHO guidelines, providing all the information necessary for a cohort analysis.
6. Adequately trained personnel capable of supervising treatment and monitoring progress.
7. Adequately trained personnel for counselling in testing for HIV infection.
8. Agreement from their Ethics and Regulatory bodies for participation in this trial.
9. Agreement from the Ministry of Health, if required, for participation in this trial.

In addition the centre must have the following staff available locally to run the trial.

**A Medical Officer** – who would oversee the general conduct of the study. This person will be designated as the Principal Investigator of the Study in that centre.

**Treatment Supervisor(s)** - who will ensure that all patients will receive their treatment as directed, and attend for follow-up regularly. They will also be responsible for completing the study forms correctly and for despatching the forms to the Principal Investigator for signature.

**A Home Visitor** - who will be responsible for verifying the patient’s address and for tracing patients who fail to attend as directed.

The staff members concerned in the management of the study patients will form a Trial Management Committee and meet at regular intervals to discuss the progress of the study. A member of the laboratory staff will also be present. A brief report of the discussions will be sent to the Chief Investigator.

### 3. SELECTION OF PATIENTS

#### 3.1 Patient inclusion criteria

1. Newly diagnosed pulmonary tuberculosis.
2. Two sputum specimens positive for tubercle bacilli on direct smear microscopy.
3. No previous anti-tuberculosis chemotherapy.
4. Aged 18 years and over
5. A firm home address that is readily accessible for visiting and be intending to remain there or within the recruitment area for the entire treatment period
6. Agree to participate in the study and to give a sample of blood for HIV testing
7. Pre-menopausal women must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place for the duration of the treatment phase
### 3.2 Patient exclusion criteria

A patient will not be eligible for entry to the study if he/she:

1. Has any condition that may prove fatal during the study period.
2. Has TB meningitis.
3. Has pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. insulin-dependent diabetes, liver or kidney disease, blood disorders, peripheral neuritis, and severe thrombocytopenia, rash, increase of bilirubin and other diseases that are likely to be associated with rifampicin.
4. Is female and known to be pregnant, or breast feeding.
5. Is suffering from a condition likely to lead to uncooperative behaviour such as psychiatric illness or alcoholism.
6. Has contraindications to any medications in the study regimens.
7. Is HIV positive.
8. Haemoglobin <7g/l.
9. AST or ALT > 5 times the upper limit of normal (ULN) for that laboratory.
10. Creatinine clearance of < 30mls/min.
   
   Calculated as \(((140\text{-age}) \times \text{weight} \times 1.23 \times (0.85 \text{ if female})) / \text{Creat(micromol/l)}\)
11. Has glucose in urine.
12. Weight < 35kg.

Patients with initial resistance to isoniazid, and/or rifampicin are not eligible and will not be included in the analysis. However, it will not be possible to identify these patients until after randomisation, unless the Hain test is carried out at screening. When the pre-treatment susceptibility test results become available and a patient is found to be resistant to any of the drugs, they will be transferred to the NTP for the retreatment regimen recommended by NTP or institutional Guidelines.

*(For patients who are MDR, treatment should be the WHO recommended second line treatment.)*

See section 5.5 treatment regimens for initial resistance.

*Patients with concurrent illness in a mild form requiring routine treatment are eligible.*
3.3 Number and source of patients

A total of 300 patients will be enrolled. Patients will be followed for the first 4 months of treatment only. Thereafter, they will be transferred to the NTP to complete 6 months of treatment.

For selection of centres and staffing levels refer to section 2.6

3.4 Screening procedures and pre-randomisation investigations

Patients known to be direct smear microscopy positive on two sputum specimens collected at the local laboratory will be invited to be screened for inclusion in the trial. They will be given a Patient Information Sheet (PIS) about the trial and will be told that screening includes collecting blood and urine samples. Blood analysis will include testing for HIV infection. (by an agreed algorithm (Appendix 3) Patients will be encouraged to be informed of the result but this will not be mandatory. HIV seropositive individuals, who wish it, will be referred to the local HIV management services.

Patients will be told that agreeing to be screened does not mean that they have to join the trial; participation in the trial will require attendance at scheduled study visits the first 4 months of their chemotherapy. Any information entered into the database for the trial, or sent to the laboratory will be identified by a number and the patient’s initials but not by name. Patients will be told that they will be free to withdraw from the study at any time and if they do so this will not jeopardise their current or future care.

If the staff are satisfied that the patient understands the above information about the screening procedures, and is willing to continue, they will be asked to indicate their consent to be screened either by signature or by thumbprint (if the participant is illiterate) on the screening consent form. Illiterate participants will be asked to have a witness present (friend, family or another member of staff independent of the study team) to witness the discussion, thumbprint consent and confirm that there has been no coercion. Participants will be given a copy of the signed/thumbprinted consent form and an information sheet to take away.

Once a participant has signed an informed screening consent form, their details will be recorded in a Screening Register. Patients will be enrolled into the study based on the criteria of eligibility outlined in sections 3.1 and 3.2 and have signed the Consent Form for Enrolment. For those found to
be ineligible in the course of screening, the reason for non-inclusion should be recorded on the Screening Register. **For the purposes of the study data, it is most important that the Screening Register is maintained with scrupulous attention.**

Subsequent investigations (e.g., sputum culture and susceptibility tests) should be carried out only on the patients enrolled into the study and have signed the enrolment consent form.

At the screening and enrolment stage, the following forms will need to be completed.

**i) Patient’s home details:**
At screening, the Treatment Supervisor should interview the patient and make the appropriate entries in all sections of the home details form. When a patient has consented to being enrolled in the trial, it is the duty of the Home Visitor to ensure that follow-up will be possible. The addresses given on the home details form should be verified at the earliest opportunity (ideally within 1 week of enrolment) by the Home Visitor.

At enrolment, each patient will nominate their Domiciliary Treatment Monitor (DTM) who will be the person at or near the home, who will supervise and ensure that the treatment given to be taken at home is swallowed by the patient. The Principal Investigator, or recruiting physician, will interview this person and ensure that they understand their responsibility.

**ii) Pre-treatment report:**
Two pre-treatment specimens of sputum should be collected for examination in the laboratory using microscopy, culture and susceptibility testing. The first sample will be taken when the patient is seen at screening.

For collection of the second specimen, the patient should be given a sputum container and asked to return at the time agreed for the enrolment visit. At enrolment, the patient should bring the container with sputum collected that morning.

The following laboratory tests will also be carried out at screening:
- Haemoglobin, platelets (FBC)
- Either AST or ALT.
- Serum creatinine.
- HIV test *(see Appendix 4).*
- Urine dipstick test for glucose.
- Pregnancy test. Women of child-bearing age, who deny being pregnant should have a pregnancy test. If this is negative, they may be enrolled in the study but must be counselled to avoid getting pregnant during the treatment period). If a woman becomes pregnant during treatment, this should be reported on the appropriate assessment form.
- Hepatitis C antibody
- Hepatitis B surface antigen

NB: For hepatitis B and C tests, serum, taken at screening, should be stored until the patient is enrolled. These last 2 tests should be done only if the patient is enrolled.

4. RANDOMISATION & ENROLMENT PROCEDURE

Patients found to be eligible when the results of screening tests become available will be invited to enter the trial. They will be reminded that enrolment will require attendance at scheduled study visits during the first 4 months of chemotherapy. Any information entered into the database for the trial or sent to the laboratory will be identified by a number and the patient’s initials but not by name. They will be free to withdraw from the study at any time and if they do so this will not jeopardise their future care. Again, once the staff are satisfied that the patient understands the procedures, they will be required to sign the Consent Form for Enrolment consenting to participate in the trial.

A separate randomisation schedule will be provided for each centre with randomisation in blocks, e.g. blocks of 9 subjects. Sealed opaque envelopes containing the Treatment Cards will be held by the Treatment Supervisor. When a patient is found to be eligible, their details will be entered on the enrolment register by the designated member of the clinic team against the next available study number. The next Treatment Card will then be opened and the patient’s initials and Study Number entered on the Treatment Card. Treatment can be then be started. Since this is an open label trial, the patients and clinicians will be made aware of the treatment allocation.
5. TREATMENT OF PATIENTS

5.1 Introduction

Three hundred patients with newly diagnosed, smear positive tuberculosis will all receive 8 weeks of isoniazid, rifampicin, pyrazinamide and ethambutol followed by isoniazid and rifampicin for a further 18 weeks; total duration 6 months.

For the first 16 weeks, patients will be randomized to receive rifampicin at doses of 10, 15 or 20 mg/kg body weight. After randomised allocation to each arm, patients will receive the allocated regimen based on the four weight groups recommended by WHO for use when prescribing Fixed Dose Combination tablets (FDC), namely 35-39 kg, 40-54 kg, 55-69 kg and 70 or more kg (Table 2). All patients will receive the WHO recommended FDC tablets for their weight band during the first 8 weeks. This will be supplemented by rifampicin 150 mg capsules according to the treatment arm to which they have been allocated and according to their weight band. During the last 10 weeks ALL the patients will receive their remaining treatment at the standard daily rifampicin dose of 10 mg/kg.

Table 2 Range of rifampicin drug dosages per kg by patient weight

<table>
<thead>
<tr>
<th>Weight</th>
<th>Control regimen</th>
<th>Study regimen 1</th>
<th>Study regimen 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg (FDC)</td>
<td>15 mg/kg (add 2 rifampicin capsules)</td>
<td>20 mg/kg (add 3* or 4 rifampicin capsules)</td>
</tr>
<tr>
<td>35-39</td>
<td>7.7</td>
<td>8.6</td>
<td>15.4</td>
</tr>
<tr>
<td>40-54</td>
<td>8.3</td>
<td>11.3</td>
<td>14.0</td>
</tr>
<tr>
<td>55-69</td>
<td>8.7</td>
<td>10.9</td>
<td>13.0</td>
</tr>
<tr>
<td>70+</td>
<td>10.7</td>
<td></td>
<td>15.0</td>
</tr>
</tbody>
</table>

Control regimen

2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)
Study regimen 1

2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin. A supplement of 300mg of rifampicin will be given for the first four months (2EHR\textsubscript{15}Z/2HR\textsubscript{15}/2 HR).

Study regimen 2

2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin. A supplement of either 450 mg (weight bands 35-39kg and 40-54kg) or 600mg (weight band 55-69kg and 70 and more kg) of rifampicin will be given for the first four months (2EHR\textsubscript{20}Z/2HR\textsubscript{20}/2 HR).

Patients with initial isoniazid, and/or rifampicin resistance will be withdrawn when the results become available. **Patients with any resistance will be transferred to the NTP for the retreatment regimen recommended by NTP or institutional Guidelines.** (The patients found to be resistant to isoniazid alone will be treated with isoniazid and rifampicin for 4 months; those found to be resistant to rifampicin alone will be treated with isoniazid and rifampicin for 7 months. Those with MDR will be treated with a WHO recommended regimen for second line treatment (see section 5.5).)

5.2 Source of drugs

Patients will be treated with drugs supplied by the NTP. If tablets/capsules of rifampicin are needed, these will be supplied by INTERTB.

5.3 Treatment schedules

Treatment Cards

Every centre will be supplied with a batch of treatment cards. When a patient fulfilling the criteria for enrolment has signed the enrolment consent form, the Treatment Supervisor will select the next Treatment Card and enter the patient’s initials and study number on the card. The patient’s regimen and date of start of treatment will also be entered against his/her name in the Enrolment Register. The patient may then begin the treatment.
Details of Drug Dosages

ALL patients will receive the standard 6 month regimen of treatment according to their NTP supplies.

Initial intensive phase daily treatment

The doses of drugs to be given to each patient are shown below and are based on the weight of the patient at the time of starting treatment.

Table 3. Intensive phase- ALL three regimens - daily for 2 months

<table>
<thead>
<tr>
<th>MEDICATION (4FDC)</th>
<th>Number of tablets for different weights (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35-39 kg</td>
</tr>
<tr>
<td>ethambutol(275mg)</td>
<td></td>
</tr>
<tr>
<td>isoniazid(75mg)</td>
<td>2</td>
</tr>
<tr>
<td>rifampicin(150mg)</td>
<td></td>
</tr>
<tr>
<td>pyrazinamide(400mg)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Continuation phase- ALL three regimens: rifampicin and isoniazid daily for 4 months

<table>
<thead>
<tr>
<th>MEDICATION (FDC)</th>
<th>Number of tablets for different weights (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35-39 kg</td>
</tr>
<tr>
<td>rifampicin (150mg)</td>
<td>2</td>
</tr>
<tr>
<td>isoniazid (75mg)</td>
<td></td>
</tr>
</tbody>
</table>

*Doses are based on the weight of the patient at the time of starting treatment.*

Study regimen 1:

All patients will receive an additional 300mg of rifampicin for the first four months of treatment.

Study regimen 2:

All patients will receive an additional **450** (weight bands 35-39kg and 40-54kg) or **600mg** (weight band 55-69kg and 70 and more kg) of rifampicin for the first four months of treatment.

*In addition, all patients will receive a tablet of pyridoxine daily throughout the 4 months of investigation.*
5.4 Treatment Procedures

For the first 16 weeks of treatment, every dose must be given under direct observation (DOT) by the Treatment Supervisor or the Domiciliary Treatment Monitor (DTM), who must check that the drugs have been swallowed, and record the amount taken on the Treatment Card.

Full details of the drug regimen, including drug dosages, for each patient and of the procedure to be followed are also given on each Treatment Card.

The first 16 weeks

Patients may be admitted to hospital, or be required to attend the treatment facility daily, or weekly, for the first 16 weeks of chemotherapy so that the drug ingestion can be directly observed (DOT) and the appropriate entries made in the Treatment Card. For those days the facility is expected to be closed (Saturdays, Sundays and National holidays) the ambulatory patients may be their treatment to take under the supervision of the designated DTM. However, the first 16 weeks must include at least 80 daily DOT doses (16 weeks x 5 DOT doses per week), and should not exceed 112 total doses (DOT plus self-administered doses combined).

The next 10 weeks

All the patients will be transferred to the National Treatment Programme to complete their treatment with standard dose drugs.

5.5 (Retreatment regimen for initial resistance)

When the results of pre-treatment cultures become known, patients who are found to be resistant to isoniazid and/or rifampicin (and thereby not eligible for the study) will be transferred to a standard treatment regimen shown below:

For initial isoniazid or rifamycin mono-resistance:
Treatment should continue with isoniazid and rifampicin, for 4 (isoniazid resistance) or 7 (rifampicin resistance) months:

For initial isoniazid+rifampicin resistance (MDR):
Treatment should be the WHO recommended second-line treatment:
5.6 5.5 Measures of adherence

Adherence to treatment is a measure of the number of DOT* doses of the allocated drugs the patient has taken.

*DOT doses for the first 16 weeks of all arms of the trial will include both doses supervised at the clinic and by the DTM at home. Ideally, this should be a total of 80 to 112 daily DOT doses in the first sixteen weeks of daily treatment;

The number of DOT doses missed may be made up provided this takes place within 2 weeks of the end of treatment.

The following procedure is recommended:

Treatment missed during the first 16 weeks.

Patients must receive a minimum of 80 and a maximum of 112 daily DOT doses in the first 16 weeks of treatment. Patients may also receive self-administered doses, but the total of DOT + self-administered doses may not exceed 112 doses. If patients miss some doses, they have a total of 126 days from the date of start of chemotherapy to complete their required number of daily doses. The same limits apply whether the therapy is given as an inpatient or as an outpatient.

Patients who have not adhered to the above schedule will have further treatment at the discretion of the Principal Investigator who may choose to continue with the allocated regimen. These patients will be classified as treatment failures.

5.7 5.6 Non-trial treatment

Medications permitted

Drugs not known to have any interaction with the trial drugs will be permitted (see Appendix 3).

All non-trial treatment taken by the patient will be recorded at enrolment and in the event of an SAE occurring.
6. ASSESSMENTS AND PROCEDURES

6.1 Follow-Up Schedule

When the required amount of chemotherapy (see section 5.5 entitled “Measures of Adherence”) has been successfully completed, all patients will be transferred to the National Treatment Programme for the remainder of their treatment at standard doses.

6.2 Summary of Investigations during Treatment and Follow-Up

<table>
<thead>
<tr>
<th>Visit (week)</th>
<th>Consent</th>
<th>Home details</th>
<th>Clinical form</th>
<th>Blood and urine tests*</th>
<th>Treatment phase report</th>
<th>Sputum smear+ culture</th>
<th>Susceptibility test (if culture +ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>FBC, AST or ALT, creatinine, HIV, dipstick glucose, pregnancy</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Enrolment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Hepatitis B and C,</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓(AST or ALT)</td>
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<td>✓</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓(AST or ALT)</td>
<td>✓</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓(AST or ALT)</td>
<td>✓</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓(AST or ALT)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In the Mbarara centre only, FBC, creatinine and, in women, pregnancy test will be done at each visit

6.3 Procedures for assessing safety

The primary outcome safety measures are grade 3 or 4 adverse events (serious adverse events, SAEs). Throughout this study patients will be closely monitored for signs and symptoms of drug toxicity. In order to avoid bias in the assessment of safety, an independent physician-assessor will be appointed to review symptoms and signs of possible toxicity. The Independent Assessor must not be told the allocated regimen of the patient being assessed. All toxicities leading to the study therapy being temporarily or permanently discontinued and all Grade 3 or 4 toxicity effects will require thorough investigation with relevant clinical and laboratory tests, as clinically indicated. These should be repeated as needed until final resolution or stabilization of the toxicity. All symptoms and laboratory findings will be graded according to severity using the modified Division of AIDS toxicity
criteria filed in the Trial Master File. Laboratory and other notifiable adverse events (NAEs) will be reported only if clinically significant (Grade 3 or 4). If the patient has a medical diagnosis at enrolment whose signs or symptoms worsen during the study to a Grade 3 or 4, this is a notifiable adverse event that must be reported.

SAEs and other NAEs will be reported, as they occur, to the CI as well as other bodies required to be notified in each country.

*For details of safety reporting, expected adverse events and flow chart for assessing and notifying adverse events see section 10, Appendix 3 and Appendix 4.*

### 6.4 Loss to follow-up

**Procedure on absconding:**

A patient will be deemed to have absconded if he/she does not attend the treatment centre to take the treatment as prescribed for a period of one week.

The Treatment Supervisor should ask the Home Visitor to visit the addresses given on the home details form and make every effort to persuade the patient to attend the treatment centre as directed and complete the allocated regimen.

If the patient is not found at home, every effort should be made to find him/her by interviewing relatives and neighbours, and by visiting the alternative addresses given on the home details form.

If the patient has not resumed treatment **within seven days** of absconding, i.e. if the patient has missed at least two weeks of therapy, the absconding section of the 'Loss to follow up form' should be completed and the top copy forwarded to the Principal Investigator. This procedure should be repeated every time a patient has not attended for treatment for a period of one week.

For the subsequent management of patients who abscond one or more times, see **section 5.5 Measures of adherence.**
6.5 Trial closure
The trial will be considered closed when the last patient has completed 4 months in the study and all laboratory reports have been received. Early termination could be decided by the TSC based on the suggestions from the IDMC. For details of the “Stopping rule”, please see Section 8.3 and Appendix 4.

7. WITHDRAWAL OF PATIENTS
In consenting to participate in the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes. If the patient explicitly states their wish not to contribute further data to the study, the CI should be informed in writing by the PI.

7.1 Withdrawal from trial intervention
Patients may be withdrawn from a trial intervention for initial drug resistance, severe and intolerable adverse events, inability to comply with the trial protocol, inability to attend regularly for treatment or assessment or if a patient withdraws consent. If the patient is withdrawn from the trial intervention for any reason their treatment will be changed to the standard regimen. At each visit, women of child bearing age will be asked if they are pregnant. If pregnancy is confirmed, the patient will be withdrawn from the trial but follow up will continue until the end of the pregnancy.

7.2 Withdrawal from the trial completely
For patients moving within or outside the study area, every effort should be made for the patient to be followed up if at all possible. In the event of this not being possible, the patient should be withdrawn from the study.

8. STATISTICAL CONSIDERATIONS
8.1 Method of Randomisation
A randomisation schedule will be created using randomised blocks of 9. Details of treatment allocation are shown in Section 4.
8.2 Outcome Measures

Primary outcomes

1. Occurrence of grade 3 or 4 hepatic adverse events at any time during chemotherapy.

Secondary outcomes

1. Culture conversion at the end of 8 weeks of chemotherapy
2. Per protocol analysis of the primary outcome.
3. Any adverse event graded according to the modified DAIDS criteria.
4. Rate of completion of chemotherapy according to the protocol.
5. Number of observed doses of chemotherapy ingested

8.3 Proposed stopping rule for RIFATOX study

In (Jindani 2004)\(^8\) the largest number of hepatic adverse events, defined as change of treatment or an interruption of treatment of 7 days or longer, occurred in the 2EHRZ/6HE regimen, 7 events, n=346, 2%. [Note: The other two regimens had only 2 and 1 hepatic events]. We assume that a doubling of this rate to 4% is unacceptable. Out of the sample of 300 we would expect approximately 6 Grade 4 clinical ARs due to hepatotoxicity by the completion of the study. We propose that a safety review by the DSMB be triggered if the total number of events recorded in the study reaches 7 at any point. This rationale for this figure is that if all such events had occurred in one of the study arms, the lower bound for an 80% confidence interval of the estimate of the minimum proportion of such events expected in the study would be equal to 4%. At any point further in the study, an arm would be discontinued if 5 ARs were observed since the point estimate of the minimum proportion of adverse events expected in the completed study would then be 5% and the lower bound of an 80% confidence interval would be 2.45%.

8.4 Sample Size

The primary outcomes of the trial are the occurrence of grade 3 and 4 hepatic side effects. Since high dose rifampicin has never been used in the treatment of tuberculosis, it is not possible to estimate the frequency of Grade 3 and 4 side effects when higher doses are given.

In a trial\(^8\) comparing 2 eight month regimens with the standard 6 month regimen, of 1355 patients in the trial, 28 patients experienced side effects which led to an interruption of treatment of longer than...
7 days. Of these 28, 10 had hepatic side effects of which jaundice was the most common. There were no deaths attributable to adverse events.

A study on the potential toxicity of increased size doses of rifapentine has been carried out within a CDC study with 150 patients. Treatment was discontinued in 6%, 4% and 6% in the 600, 900 and 1200 mg treatment arms respectively. Only one discontinuation, in the 1200mg arm, was due to an adverse event possibly associated with the study therapy.

This is a preliminary, observational study and it is proposed to enrol a total of 300 patients. A study with 100 controls and 200 test cases has 85% power to detect the difference between a major adverse event rate of 5% in controls and 15% in test cases.

8.5 Interim Monitoring and Analyses

There will be no formal interim analysis but the Independent Data Monitoring Committee (IDMC) will review all serious and notifiable adverse events regularly. On the basis of their findings the IDMC will make recommendations to the Trial Steering Committee (TSC) about the continuation of the study.

The IDMC will advise the Chair of the TSC if, in its view, the randomised comparisons in the trial have provided both:

(a) proof beyond reasonable doubt that one or other of the regimens are clearly contraindicated in terms of any serious adverse effects of treatment or vice versa.

and

(b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the results of any other studies.

If these criteria are used, the exact number of interim analyses is of little importance so no fixed schedule is proposed.

8.6 Preliminary Analysis Plan

After data cleaning, analysis will proceed according to a pre-designed analysis plan. The primary analysis will be analysed by intention-to-treat. Secondary analyses will include a per protocol analysis (i.e. excluding those who did not receive adequate chemotherapy). Inadequate treatment is defined as missing 2 weeks or more of the 16 weeks of allocated treatment.
After the crude primary analysis has been performed, an adjusted analysis will be performed including covariates (such as age, gender and microbiology and smoking status) which may influence outcome. Chi-squared tests will be used to compare crude event rates, and multiple logistic regression will be used to adjust for covariates.

A full analysis plan will be developed before the final analysis is conducted.

8.7 Analysis of adverse events:

The primary endpoint for adverse events is the occurrence of a Grade 3 or 4 hepatic adverse events.

In addition, all patients will be classified according to whether they have had an adverse event necessitating:
- An interruption of the allocated regimen of more than 7 days
- Stopping or changing one or more drug for that adverse event.

9. TRIAL MONITORING

The purposes of trial monitoring are to verify that:
- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with the applicable regulatory requirement

9.1 Extent and nature of monitoring

The sites will be visited at regular intervals in order to monitor the conduct of the trial. These visits will be made by the Trial Manager. Visits will also be made by the Chief Investigator and Assistant Chief Investigator. The frequency of monitoring visits will be determined according to site specific risk assessments and pre-defined triggers.
9.2 Site monitoring

At monitoring visits the data entered in the CRF’s will be checked against available source data according to the procedures described in the trial monitoring plan filed in the Trial Master File. Data stored will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified any data which are changed should be crossed through with a single line and initialled. Particular attention will be given to:

(a) Verifying, for the investigational products:
   (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
   (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
   (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
   (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
   (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(b) Verifying that the local investigator follows the approved protocol and all approved amendment(s), if any.

(c) Verifying that written informed consent was obtained before each subject’s participation in the trial.

(d) Ensuring that the Principal Investigator has received the current Investigator’s Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(e) Ensuring that the local investigator and the investigator’s trial staff are adequately informed about the trial.

(f) Verifying that the local investigator and the investigator’s trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the local investigator/institution, and have not delegated these functions to unauthorised individuals.

(g) Verifying that the local investigator is enrolling only eligible subjects.

(h) Reporting the subject recruitment rate.
(i) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(j) Verifying that the local investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(k) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. In particular:

   (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

   (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

   (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

   (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

   (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(l) Informing the local investigator of any CRF entry error, omission, or illegibility. Any corrections, additions, or deletions made, are dated, explained (if necessary), and initialled by the local investigator or by a member of the investigator’s trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented.

(m) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(n) Determining whether the local investigator is maintaining the essential documents

(o) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the local investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

9.3 Data collection

Essential information will be collected in Case Record Forms (CRF) on a daily basis, from pre-screening to end of patient follow up, and entered in an electronic database. Laboratory records,
notes on methodologies used, hospital records, x-rays, pharmacy notes and clinical notes will be considered source data and possibly copied to be filed inside the Investigator Files (if specifically important for the reconstruction and evaluation of the trial). Accuracy of CRF pages will be verified against source data.

9.4 Direct Access to Data
The Investigator will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents.

9.5 Confidentiality
All patient information will be kept in locked cabinets and will be available only to the treatment staff. The patient’s name and address will not be disclosed to the trial sponsor.

The patient’s data/specimens will be identified by study number and/or initials only. Individual patients will not be identified in the resulting publications and presentations from the trial. The trial will comply with the principles of the Data Protection Act of the country of the participating centre.
10. **SAFETY REPORTING**

10.1 **Safety Reporting**

**Terms and definitions for notifiable events and adverse events**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Notifiable Event</strong></td>
<td>Any of the following occurrences:                                                                ㄦ</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy</td>
</tr>
<tr>
<td></td>
<td>- New medical diagnosis</td>
</tr>
<tr>
<td></td>
<td>- Study drug discontinued</td>
</tr>
<tr>
<td></td>
<td>- Study drug dose reduced for toxicity</td>
</tr>
<tr>
<td></td>
<td>- Identification of isoniazid and Rifamycin monoresistance</td>
</tr>
<tr>
<td><strong>Adverse Event</strong> (AE)</td>
<td>Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.</td>
</tr>
<tr>
<td><strong>Adverse Reaction</strong> (AR)</td>
<td>Any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject.</td>
</tr>
<tr>
<td><strong>Serious Adverse Event</strong></td>
<td>Respectively, any adverse event or adverse reaction that:</td>
</tr>
<tr>
<td><strong>Serious Adverse Reaction</strong></td>
<td>- results in death</td>
</tr>
<tr>
<td>(SAE)</td>
<td>- is life-threatening*</td>
</tr>
<tr>
<td>(SAR)</td>
<td>- requires hospitalisation or prolongation of existing hospitalisation**</td>
</tr>
<tr>
<td></td>
<td>- results in persistent or significant disability or incapacity</td>
</tr>
<tr>
<td></td>
<td>- consists of a congenital anomaly or birth defect</td>
</tr>
<tr>
<td></td>
<td>- other important medical event(s)***</td>
</tr>
<tr>
<td><strong>Suspected Unexpected</strong></td>
<td>A serious adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:</td>
</tr>
<tr>
<td><strong>Serious Adverse Reaction</strong></td>
<td>- The Summary of Product Characteristics (SPC) for that product (for products with a marketing authorisation)</td>
</tr>
<tr>
<td>(SUSAR)</td>
<td>- The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)</td>
</tr>
</tbody>
</table>

* The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
*** Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose).

**All adverse events – Guidelines on inclusions and exclusions**

<table>
<thead>
<tr>
<th>Adverse events include</th>
<th>Adverse events do not include</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) an exacerbation of a pre-existing illness</td>
<td>a) medical or surgical procedures- the condition which leads to the procedure is the adverse event</td>
</tr>
<tr>
<td>b) an increase in frequency or intensity of a pre-existing episodic event/condition</td>
<td>b) pre-existing disease or conditions present before treatment that do not worsen</td>
</tr>
<tr>
<td>c) a condition (even though it may have been present prior to the start of the trial) detected after trial drug administration</td>
<td>c) situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery</td>
</tr>
<tr>
<td>d) continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment</td>
<td>d) overdose of medication without signs or symptoms</td>
</tr>
<tr>
<td></td>
<td>e) the disease being treated or associated symptoms/signs unless more severe than expected for the patient’s condition</td>
</tr>
</tbody>
</table>

**Institution Responsibilities**

All serious adverse events and notifiable events (SAE/NAE) will be reported immediately by the Principal Investigator by e-mail or fax to the Trial Manager on SAE/important event notification forms. The Trial Manager will then inform the Chief Investigator or the Assistant Chief Investigator by telephone, e-mail or fax. All other adverse events should be reported in the patient’s medical notes and adverse reactions in the regular progress/follow-up reports.
**Procedures**

The SAE/NAE should be completed by the responsible investigator or delegated a staff member. The investigator should assess the SAE/NAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team and e-mailed or faxed to the Chief Investigator immediately. The responsible investigator should check the SAE/NAE Form, make changes as appropriate, sign and then re-send to the Trial centre as soon as possible. The initial report shall be followed by detailed, written reports via a follow-up SAE/NAE Form.

1. **Send** the form by fax (within 24 hours or next working day) to the **Chief Investigator**
   
   **Fax Number:** +44 20 8725 0137

Or **scan the form and send as e-mail attachment to the Chief Investigator**

2. **Follow-up of SAEs/NAEs:** In the case of an SAE (or relevant NAE) the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information is noted on another SAE/NAE Form by ticking the box marked ‘follow-up’ and faxing to the Trial Manager as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient **must** be identified by study number, date of birth and initials only. The patient’s name **should not** be used on any correspondence.

The Chief Investigator (or a delegate) will evaluate all SAEs/NAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported as necessary. The causality assessment given by the PI at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report. All evaluated SAE/NAEs will be sent back within agreed timescales to the PI at the site from where it originated.

All SAEs, SARs, NAEs, and SUSARs will be reported within an agreed timescale by the PI or delegated person to the necessary regulatory and ethics authorities for that site as laid out in the approvals and/or corresponding regulations and RIFATOX site specific working practice documents.
10.2 Severity/grading of adverse events
This will be according to the modified DAIDS Classification filed in the Trial Master File.

10.3 Relationship to trial treatment
When reporting on serious adverse events, the Trial Doctor will state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship. They will also state whether the adverse event was expected and what, if any, action was taken (see Form E).

10.4 Follow-up after adverse events
Patients may be either admitted to hospital or seen at intervals to monitor the progress, recovery and investigations of the adverse events.
If treatment is interrupted, attempts should be made to identify the drug concerned. After complete recovery, treatment may be gradually re-introduced until the allocated regimen has been re-instituted.
In the event that treatment needs to be modified or changed, the Principal Investigator should inform the Chief Investigator and agree on the new treatment.
Women who become pregnant will be withdrawn from the trial but continue to receive standard treatment. They will be followed up until the end of pregnancy.

For details of safety reporting, expected adverse events and flow chart for assessing and notifying adverse events see section 10.1, Appendix 3 and Appendix 8.

11. ETHICAL CONSIDERATIONS AND APPROVAL

11.1 Ethical considerations
The patients will, before being enrolled into the study, have the conditions of the study, as set out in the Patient Information Sheet (Appendix 1) explained to them. The information contained in the PIS will be translated into the local dialect. Literate patients will be asked to read the PIS and the illiterate patients will have the contents explained to them by the Principal Investigator or a senior treatment supervisor. The patient will have the opportunity to discuss the PIS with the medical
officer/treatment supervisor. Once this person is satisfied that the patient has understood the PIS and the consent form, the patient will be asked to sign the screening consent form. The top copy should be filed in the patient’s study folder and the duplicate, together with a copy of the PIS, given to the patient.

This process will be repeated after the pre-treatment investigations show that the patient fulfils the eligibility criteria and at each amendment to the protocol.

The right of the patient to refuse to participate in the trial without giving reasons will be respected.

After the patient has entered the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient will remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

11.2 Ethical approval

The protocol has been approved by the Oxford Tropical Research Ethics Committee of the University of Oxford.

The protocol will also be submitted to the Medical Ethics Committee of each participating clinical site and/or country and enrolment to the study will start only after receiving the written agreement of the relevant body(ies).

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki from the World Medical Association.

http://www.wma.net/e/ethicsunit/helsinki.htm

12. REGULATORY APPROVAL

Principal Investigators will be expected to obtain, in writing, approval to participate from their Regulatory Authority.
13. INDEMNITY
The sponsor of the trial is St. George’s, University of London. Patients will be indemnified for harm as a result of participation in the study, through a separate policy taken out by the trial sponsor. All personnel involved in the trial will be expected to be indemnified by their employing authority.

14. TRIAL COMMITTEES

14.1 Trial Management Group (TMG)
A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical). The TMG will be responsible for the day-to-day running and management of the trial and will meet at regular intervals.

14.2 Trial Steering Committee (TSC)
The Trial Steering Committee (TSC) will be constituted. The Chairman will be independent of the running of the trial.

Its terms of reference will be:
1. to monitor and supervise the progress of the trial towards its interim and overall objectives;
2. to review at regular intervals relevant information from other sources (e.g. other related trials);
3. to consider the recommendations of the Independent Data Monitoring Committee;

The role of the TSC is to provide overall supervision for the trial and provide advice through its Independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

14.3 Independent Data Monitoring Committee (IDMC)
There will be an Independent Data Monitoring Committee whose terms of reference will be as follows:

1. To review safety data regularly, in particular all serious adverse events possibly attributable to the trial drugs, such as local reactions or unexpected deaths.
2. To monitor the conduct of the trial with respect to the ethical aspects of the trial.
3. To assess the results of the formal analyses with the possibility of advising the Trial Steering Committee (TSC) that the trial should be modified or discontinued.
15. PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications.

The names of all the investigators will be included in any publication either in the authorship or listed in the article. Any authorship policy will be agreed by all the investigators before any publication. The members of the TSC and IDMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

Publications will include any public presentation of the data emerging from the trial. In order to manage the strategy, a publications committee will be set up which will include the Chief Investigator, the Principal Investigators and others, such as the Trial Statistician, involved in the trial. Additional individuals may be involved as necessary with the agreement of the group. This publications group will agree and circulate the publication strategy. The use of the data for the purposes of publication must first be approved by the group. It is anticipated that this group will meet at intervals as necessary and will communicate by e-mail and teleconferences as necessary.

Written publications will be through international peer reviewed journals. Updates on the progress of the trial will be presented at the annual EDCTP Meeting of Investigators. The results of interim analyses, if significant, will be presented at the EDCTP Investigators Meeting and at other international scientific conferences. If they concern policy decisions, dissemination will be through the press, national governments at meetings and international organisations at conferences.

16. PROTOCOL AMENDMENTS

1. Pretreatment haemoglobin AND platelet count will be done
2. HIV positive patients will not be included in the trial
3. All Appendices dealing with HIV management have been deleted
4. Page 37, change of Fax number to +4420 8725 0137
5. For all initial drug resistance, treatment should be according to national and institutional recommendations. Section 5.5 “Retreatment for initial resistance” has been deleted.
6. Section 6.1 “Follow up Schedule”. Additional tests will be done at Mbarara only.
7. Section 8.3, see “Stopping Rule for the trial” on page 30.
17. REFERENCES


18. Mehta JB, Shantaveerapa H, Byrd RP jr., Morton SE, Fountain F, Roy TM. Utility of rifampin blood levels in the treatment and follow up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. Chest 2001; 120: 1520-1524.


APPENDICES

APPENDIX 1 - PIS version 2.2

RIFATOX TRIAL
AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE THE TOXICITY
of HIGH DOSE RIFAMPICIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS

PATIENT INFORMATION SHEET

Part 1.
You are being invited to take part in a research trial. Before you decide to take part in the trial, it is important
for you to understand why the research is being done and what it will involve. Please take time to read the
following information carefully. Talk to others about the study if you wish.
1. Part 1 tells you the purpose of this study and what will happen to you if you take part.

2. Part 2 gives you more detailed information about the conduct of the study.
Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether
or not you wish to take part. Initially we only need your permission to assess whether you are eligible for the
study. You will have a further opportunity to decide if you wish to take part.

1. What is the purpose of the trial?
The usual treatment for tuberculosis of the lungs is either six or eight months long. One of the drugs used is
called rifampicin. The usual dose of rifampicin is 10mg/Kg daily for 6 months. We believe that if the dose can
be increased to 15mg/Kg or 20mg/kg daily, in the first 4 months, it may be possible to reduce the treatment
length from 6 months to 4 or even 3 months. However, we first have to be sure that an increase in the dose is
safe and will not increase the bad side effects of the drug.

2. Why you have been chosen?
We are inviting you to join this study because you have tuberculosis of the lungs. This is an infection which is
caused by a germ which can affect any part of the body. It is curable if you take your treatment as directed.
We will be asking 300 patients with TB in Delhi, Kathmandu and Santa Cruz to join this study.

3. Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to
keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a
reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care
you receive.
4. What will happen to me if I take part?
Before letting you join in this study, we will examine you to be sure you are suitable for the study. We will do a sputum test, blood tests, and a urine test. You must also agree to have an HIV test. This is a blood test to detect if you have been infected with the human immunodeficiency virus which is most commonly transmitted by sexual intercourse with an infected person. You will be given the result of the HIV test from a trained counsellor if you wish. You do not have to get the result of the test if you prefer not to but we would encourage you to do so, so that further treatment can be administered if necessary.

You will receive one of three treatments. It will be decided by chance (like flipping a coin) which treatment you will receive. The possible treatments are standard TB treatment for six months; you may also be selected to receive a higher dose of rifampicin, either 15mg/Kg or 20mg/Kg daily for the first four months of the treatment.

If you are taking any other medicines, including birth control pills or injections, you should tell the doctor. If you are a pre-menopausal woman you must use a barrier form of contraception or be surgically sterilised or have an IUCD in place during the course of the trial.

5. What do I have to do?
In the study, you must come to clinic to receive the medicine every day or every week for the first two months. Then you must come to clinic, at intervals required by your doctor, for the next two or four months. After you finish the medicines, you will no longer be required to attend the clinic.

If a woman who is participating in the study becomes pregnant she must inform her doctor immediately. She will be withdrawn from the study treatment and given standard TB therapy (which is known to be safe in pregnancy) but will be seen in the study clinic until she delivers.

6. What are the side effects of any treatment received when taking part?
Increased dosage of rifampicin may increase the risk of side effects that you would normally expect from the standard treatment. These may be skin rash, yellow eyes, change in urine colour, problems with eye-sight, stomach pain or vomiting and pain in the legs. If you have bad side effects and need to go to hospital, we will pay the hospital. Before you enter the trial you should tell the doctor if you are taking any other medicines including birth control pills or injections.

7. What are the other possible disadvantages and risks of taking part?
There is a small risk that you will develop resistance to the drugs. In such a case, we will treat you with drugs to which you will respond. If you are a pregnant woman, you cannot participate to this trial. If you become pregnant while in the trial, the treatment could harm the unborn child; therefore you will be withdrawn from...
the study and treated according to the guidelines of the National TB programme for treatment of TB in pregnant women.

8. What are the possible benefits of taking part?
There will be no direct benefit to you from taking part however your progress will be monitored frequently and the information we get might help to improve the treatment of people with TB.

9. What happens when the treatment stops?
After the treatment has been completed, it is expected that your TB will be cured. You will not be required to attend the clinic any more. However, if your symptoms return, you should consult the trial doctor immediately.

10. What if there is a problem?
If you have questions, or if you are having any problem from any medicines, you should talk to the study nurse or doctor.

11. Will my taking part in the trial be kept confidential?
Your medical record will be kept safe and only your doctor or nurse can see it. We will not use your name in any study report.

Contact details:
Dr.
Dr.
Nurse

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.
Part 2.

12. Travel expenses
You will be reimbursed for travel expenses connected with the study

13. What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue appropriately. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

14. What will happen if I do not carry on in the trial?
You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

15. What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number). If you remain unhappy and wish to complain formally, details of complaints procedures can be obtained from the hospital.

Compensation will be paid for reasonable medical expenses incurred as a result of study-related injury or illness. St George’s University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. We would not be bound to pay compensation where:
- The injury resulted from a drug or procedure outside the trial protocol and/or
- The protocol was not followed.
These arrangements do not affect your right to pursue a claim through legal action.
16. Will my taking part in the trial be kept confidential?
If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring and/or the company organising the research. They may also be looked at by people from the company, by representatives of regulatory authorities and by authorised to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

17. What will happen to any samples I give?
Any samples that you give will be used only for the evaluation of this trial unless you have given separate written consent allowing them to be used for other tests (e.g. the measurement of drug levels). Your samples may be sent to the Department of Medical Microbiology, St. George’s, University of London for parallel testing for susceptibility to the drugs being given to you. If they are required for any other evaluations, you will be asked for your permission to use any stored samples and will be asked to sign a separate consent form.

18. Will any genetic tests be done?
No, there will be no genetic tests

19. What will happen to the results of the trial?
The results of the trial will be published so that they are available to the medical profession throughout the world. However, no patients will be identified individually.

20. Who has reviewed the trial?
The trial has been reviewed by the Trial Steering Committee and the Ethics Committee of St. George’s, University of London. It has also been reviewed by the Ethics Committee of your country and has received approval.

*One copy of this form to be given to the patient to keep.
APPENDIX 2 – CONSENT FOR SCREENING AND ENROLMENT – VERSION 2.2

RIFATOX TRIAL
AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE THE TOXICITY of HIGH DOSE RIFAMPICIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS

CONSENT FORM FOR SCREENING

(TO BE PRESENTED ON LOCAL HEADED PAPER)

Screening No.: ______________

Date and version: _____/____/____ dd/mm/yyyy, Version 2.0 [Local date and version]

Please initial box to agree

1. I confirm that I have read (or had read to me) and understand the information sheet dated 25 Feb 2010 (version 2.0) for the above study and have had the opportunity to ask questions and have these answered satisfactorily. □

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. □

3. I understand that being screened for possible participation in this study does not mean that I have agreed to be enrolled in the study. □

4. I agree to sections of any of my medical notes being looked at to assess my eligibility for this study □

5. I agree to being screened for eligibility to take part in the above study □

6. I agree to have an HIV test □

7. I agree to be informed of the result of the HIV test □

8. I agree if I am a pre-menopausal women, I must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place for the duration of the treatment phase. □

________________________ ______________________ ______________
Name of Patient Signature or thumbprint Date

________________________ _________________________ ______________
Name of witness Signature Date

(if patient is illiterate)

__________________________ _________________________ ______________
Name of Person taking consent Signature Date

2 copies: 1 for patient, 1 for the patient’s confidential records.

Rifatox Protocol Version 3.1 – PIS/IC Version 2.2
RIFATOX TRIAL
AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE THE TOXICITY of HIGH DOSE RIFAMPICIN IN THE TREATMENT OF PULMONARY TUBERCULOSIS

CONSENT FORM FOR STUDY ENROLMENT

(TO BE PRESENTED ON LOCAL HEADED PAPER)
Study No.: _______________
Date and version: _____/____/____, Version 2.0 [Local date and version]

Please initial box to agree
1. I confirm that I have read (or had read to me) and understand the  
   information sheet dated 25 Feb 2010 (version 2.0) for the above  
   study and have had the opportunity to ask questions and have had these  
   answered satisfactorily.  

2. I understand that my participation is voluntary and that I am free to  
   withdraw at any time, without giving any reason, without my medical care  
   or legal rights being affected.  

3. I understand that sections of any of my medical notes may be looked at  
   by responsible individuals involved in the running of the trial or from regulatory  
   authorities where it is relevant to my taking part in research. I give permission  
   for these individuals to have access to my records.  

4. I agree to take part in the above study.  

________________________ ______________________ ______________
Name of Patient Signature or thumbprint Date

________________________ _________________________ ______________
Name of witness Signature Date
(if patient is illiterate)

__________________________ _________________________ ______________
Name of Person taking consent Signature Date

2 COPIES: 1 FOR PATIENT, 1 FOR THE PATIENT’S CONFIDENTIAL RECORDS.
APPENDIX 3: MANAGEMENT OF EXPECTED ADVERSE EVENTS AND DRUG INTERACTIONS

SECTION A : MAJOR TOXIC REACTIONS

If any one of the major reactions listed below occurs, all anti-tuberculosis treatment should be stopped immediately. If the toxic reaction requires the patient to be admitted to hospital, the International Coordinator should be notified within 24 hours.

1. Hypersensitivity Reactions:
These are characterised by the sudden onset of fever often accompanied by headache and vomiting as well as the appearance of an itchy red rash. When the fever and rash have subsided, proceed to confirm hypersensitivity and identify the causative drug (if such re-challenge is not contraindicated by the severity of the reaction) or drugs to which the patient is hypersensitive. The steps to be followed are described below:

To identify the drug causing the reaction:

NB: In all cases test for hypersensitivity to all the drugs in use at the time of the hypersensitivity reaction. This testing must be done with the patient admitted to hospital and never on an out-patient basis.

First, test for isoniazid; then, for the other drugs in any order.

To test for hypersensitivity to a drug;

a. Give the drug at the usual dose.

b. If there is no reaction to a., repeat the same dose for another two days.

c. If there is no reaction to b., test for another drug in the same way until the offending drug has been identified.

d. If a reaction occurs after any of the tests, it should be allowed to subside completely before starting to test the next drug.

Once the offending drug(s) has been identified, it should never again be given to the patient.
2. Other Cutaneous Reactions

Isoniazid: A pellagra-like reaction may very rarely occur. It should respond to nicotinic acid 50 mg three times daily or a vitamin B compound.

Rifampicin: Thrombocytopenic purpura may rarely occur due to a fall in the blood platelet count, within three hours of a dose. The drug should be stopped and never given again. It is most important to warn the patient of the possibility of this reaction during the maintenance phase of the control regimen.

3. Hepatitis

Hepatitis occasionally occurs in patients receiving isoniazid, rifamycins or pyrazinamide. In all cases where there is any manifestation of liver toxicity, all treatment should be stopped, and supportive therapy be given while waiting for the liver function tests to return to normal. Once the tests are normal, treatment can be resumed but the liver function tests should be regularly monitored. It may be necessary to stop the offending drug.

4. Neurotoxicity

Ethambutol: Loss of visual acuity due to optic neuritis is dose-related and reversible if the drug is stopped promptly. This complication is uncommon at doses used in TB therapy.

Headaches, dizziness, mental confusion, hallucinations and peripheral neuritis have all been reported infrequently. The drug should be stopped immediately and never given again.

Isoniazid: Peripheral neuritis and mental confusion may occur. Pyridoxine 10 mg daily or a vitamin B compound containing pyridoxine should be tried. Because peripheral neuritis is common among those with HIV infection, malnutrition and alcoholism, pyridoxine is given routinely as part of the study regimen.

3. Other reactions specifically associated with Rifampicin

Gastrointestinal

Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps, and diarrhoea have been noted in some patients. Although Clostridium difficile has been shown in vitro to
be sensitive to rifampicin, pseudomembranous colitis has been reported with the use of rifampicin (and other broad spectrum antibiotics). Therefore, it is important to consider this diagnosis in patients who develop diarrhoea in association with antibiotic use. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported.

Hematologic
Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
Rare reports of disseminated intravascular coagulation have been observed. Leukopaenia, hemolytic anemia, and decreased hemoglobin have been observed. Agranulocytosis has been reported very rarely.

Central Nervous System
Headache, fever, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, pains in extremities, and generalized numbness have been observed. Psychoses have been rarely reported.

Ocular
Visual disturbances have been observed.

Endocrine
Menstrual disturbances have been observed. Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Renal
Elevations in BUN and serum uric acid have been reported. Rarely, haemolysis, haemoglobinuria, haematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental
interruption of a daily dosage regimen, and are reversible when rifampicin is discontinued and appropriate therapy instituted.

**Dermatologic**

Cutaneous reactions are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. More serious cutaneous reactions which may be due to hypersensitivity occur but are uncommon.

**Hypersensitivity Reactions**

Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed. Anaphylaxis has been reported rarely.

**Miscellaneous**

Rare reports of myopathy and muscular weakness have also been observed. Oedema of the face and extremities has been reported. Other reactions reported to have occurred with intermittent dosage regimens include “flu syndrome” (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The “flu syndrome” may also appear if rifampicin is taken irregularly by the patient or if daily administration is resumed after a drug free interval.

**SECTION B : MINOR TOXIC REACTIONS**

*Rifampicin:* The urine may be coloured red; this is normal and no action is necessary.

*Pyrazinamide:* Anorexia and nausea may occur and be of no importance. It should be remembered, however, that these symptoms may be fore-runners to hepatitis (see above).

Arthralgia and swelling of one or more joints (gouty syndrome) may occur in patients who are receiving pyrazinamide – due to increased serum uric acid levels. Treatment with aspirin or ibuprofen may be successful without interruption of the regimen.
SECTION C: RIFAMPICIN - DRUG INTERACTIONS

ENZYME INDUCTION:

Rifampicin is known to induce certain cytochrome P-450 enzymes. Administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of co-administered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampicin.

Rifampicin has been reported to accelerate the metabolism of the following drugs: anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide), oral anticoagulants, antifungals (eg, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (eg, ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, nortriptyline, progestins, quinine, tacrolimus, theophylline tricyclic antidepressants (eg, amitriptyline, nortriptyline) and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampicin.

Patients using oral or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control during rifampicin therapy.

Rifampicin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. In patients receiving anticoagulants and rifampicin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Diabetes may become more difficult to control.
OTHER INTERACTIONS
When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both drugs. Concurrent use of rifampicin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

Probenecid and cotrimoxazole have been reported to increase the blood level of rifampicin. When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored close for hepatotoxicity.

Plasma concentrations of sulfapyridine may be reduced following the concomitant administration of sulfasalazine and rifampicin. This finding may be the result of alteration in the colonic bacteria responsible for the reduction of sulfasalazine to sulfapyridine and mesalamine.

The "Flu" Syndrome. This is associated almost exclusively with the intermittent administration of rifamycins. It is characterised by episodes of fever, chills, headaches, dizziness and bone pain most commonly during the third to sixth month of treatment. The symptoms start one to two hours after each dose and last for up to eight hours. Symptoms can almost always be arrested by changing from intermittent to daily administration. This can be done by giving one capsule (150 mg) on the first day, two on the next and increasing the dose by a capsule a day until the normal daily dosage is reached – usually in three to four days.
Appendix 4: Stopping rule for a treatment arm or the whole trial

The primary outcomes of the trial are the occurrence of grade 3 and 4 hepatic side effects. Since high dose rifampicin has never been used in the treatment of tuberculosis, it is not possible to estimate the frequency of Grade 3 and 4 hepatic side effects when higher doses are given.

In a trial comparing 2 eight month regimens with the standard 6 month regimen, of 1355 patients in the trial, 28 patients experienced side effects which led to an interruption of treatment of longer than 7 days. Of these 28, 10 had hepatic side effects of which jaundice was the most common. The distribution of these 10 events was as follows:

2EHRZ/6HE: 7 (Study regimen 1)
2(EHRZ)3/6HE: 1( Study regimen 2)
2EHRZ/4HR: 2 (Control group)

Five of the hepatic events occurred in the intensive phase and 5 in the continuation phase.

Of all 10 events, 6 occurred in patients on rifampicin and 4 in patients not on rifampicin.

There were no deaths attributable to adverse events.

Thus, the trial showed no evidence of increase in toxicity when rifampicin is included in the treatment combinations.

In another trial, during the first 12 weeks, hepatic toxicity was reported in 8 (1%) patients (3 HR3, 3 H6 and 2 Pl) but only 1 (H6) had symptomatic hepatitis. The serum alanine aminotransferase concentrations during chemoprophylaxis were higher in the HR3 and H6 series than in the R3 series (p<0.001); there was no significant difference between the R3 and Pl series. The authors concluded that rifampicin on its own carries a very low risk of hepatic toxicity.

In the first trial, the largest number of hepatic adverse events, defined as change of treatment or an interruption of treatment of 7 days or longer, occurred in the 2EHRZ/6HE regimen, 7 events, n=346, 2%. [Note: The other two regimens had only 2 and 1 hepatic events]

If we assume that a doubling of this rate to 4% is unacceptable

Out of the sample of 300 we would expect approximately six Grade 4 clinical ARs due to hepatotoxicity.
If we saw 7 at any point in the study without knowing the allocation......
A) If it happened that all were in one study arm, the point estimate would be 7% which we think is unacceptable and we would also be (more than) 80% confident that the true “rate” of hepatotoxicity in that arm was equal to or greater than 4% in that arm viz.

> binom.exact(7,100,conf.level=0.80)
  x n proportion lower upper conf.level
1 7 100 0.07 0.0394 0.1149 0.8

And B) the current overall estimate in the study arms would at that point remain consistent with a true “rate” less than 4% overall viz
> binom.exact(7,300,conf.level=0.80)
  x n proportion lower upper conf.level
1 7 300 0.023 0.01305 0.0389 0.8

So the occurrence of 7 ARs would seem to be a good moment to review the data. And at any point further in the study if we saw 5 ARs in any arm that would be a reason to discontinue that arm since we would then know that the “rate” was
> binom.exact(5,100,conf.level=0.80)
  x n proportion lower upper conf.level
1 5 100 0.05 0.0245 0.0908 0.8

i.e. the point estimate would be 5% and we can be 80% confident that it is not 2%.

In summary, the data would be reviewed if the number of hepatic events in the total sample reaches 7. If at review, 5 or more events had occurred in one arm of the study, there would be a reason to discontinue that arm.
APPENDIX 5: FLOW CHART OF ASSESSING AND SERIOUS ADVERSE EVENTS AND NOTIFYING IMPORTANT EVENTS

**Adverse Event**
(Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment)
Assessed for causality, seriousness and expectedness

**Serious**
- Resulted in death
- Life-threatening
- Required in-patient hospitalization/prolongation of existing hospitalization
- Congenital abnormality/birth defect
- Other medically important condition

Assess causality

**Not Serious**

Assess causality

**Notifiable Events**
- Pregnancy
- New medical diagnosis
- Study drug discontinued
- Study drug dose reduced for toxicity
- Identification of isoniazid and Rifamycin mono-resistance

Rifatix Protocol Version 3.1 – PIS/IC Version 2.2

Notify **immediately** Sponsor and Chief Investigator via Trial Manager notification –
Principal Investigators will notify relevant bodies in their own country according to local guidelines

**Notifying Important Events**

**Adverse Event (AE)**
Causal relationship to protocol drugs:
- Unlikely
- Not related

Details of all AEs to be recorded in the patient’s medical notes.

**Serious Adverse Reaction (SAR)**
Drug-Related
Causal relationship to protocol drugs:
- Definitely
- Probably
- Possible

Assess expectedness

**Expected**
- Listed in protocol, SPC, IB
- SSAR/SAR (Suspected/Serious Adverse Reaction)

**Unexpected**
- Not listed in protocol, SPC, IB
- SUSAR (Suspected Unexpected Serious Adverse Reaction)

**Adverse Reaction (AR)**
Drug-Related
Causal relationship to protocol drugs:
- Definitely
- Probably
- Possible

Assess causality

**Adverse Event (AE)**
Causal relationship to protocol drugs:
- Unlikely
- Not related

Details of all AEs to be recorded in the patient’s medical notes.

**Serious Adverse Event (SAE)**
Causal relationship to protocol drugs:
- Unlikely
- Not related

Assess causality

**Expected SAE**
- Listed in protocol, expected SAE

**Unexpected SAE**
- Not listed in protocol, unexpected SAE

**Notify Sponsor /Chief Investigator as per protocol via CRF pages**