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| RMC clinical trialStandard Operating Procedure 10 **ADVERSE EVENTS** | | | |
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| **Table of Contents** | **Page** |
| 1. Purpose | 3 |
| 2. Policy Statement | 3 |
| 3. Background | 3 |
| 4. Scope | 3 |
| 5. Responsibilities | 4 |
| 6. Procedure | 4 |
| 7. Definitions | 8 |
| 8. Causality | 10 |
| 9. Reporting procedures | 10 |
| 10. Admission | 11 |
| 11. Breaking the code | 12 |
| 12. References | 12 |
| 8. Appendices  Appendix 1  Appendix 2 | 12  13  21 |

**1. PURPOSE**

This document describes the process of managing and reporting side effects and adverse events.

### 2. Background

Current WHOMDT does not kill 100% bacteria even after a full course of treatment in a subset of patients harboring a large bacterial load thus continuing transmission of the disease responsible for endemicity in some countries. The duration of MDT is long and promotes noncompliance. MDT continues to be controversial with limited evidence support resulting in multiple reformulations since the last 40 years. This calls for a search for newer, more efficacious drugs with shorter duration of action evidenced with well-designed clinical trials. Relapse, advocated as the key outcome measure of efficacy of MDT, has its drawbacks. Relapse studies require long years of follow up. The gold standard test for viability was Mouse foot pad studies which is costly and time consuming. Hence, we propose Molecular Viability Assays as outcome measure of efficacy which are newer and better techniques to test viability faster.

In this study, we propose to conduct a Randomized Controlled study comparing WHO MBMDT with a monthly regime consisting of currently most bactericidal and safe drugs of Rifampicin, Moxifloxacin and Clarithromycin in MB leprosy patients.

**4. Scope**

This document applies to all staff involved in clinical assessment and clinical management of participants.

**5. Responsibilities**

|  |  |
| --- | --- |
| **Role** | **Responsibility** |
| RMC trial Principal  Investigator | * Ensure RMC trial study procedures obtain ethics approval and that ICH GCP guidelines and this SOP are adhered to by all staff. * Oversees all aspects of the trial, including participant safety and regulatory compliance. * Responsible for promptly reporting ADEs to regulatory authorities, ethics committees, and sponsors as per regulatory requirements. * Oversees the medical care and follow-up of participants experiencing ADEs. |
| Local Study researcher/  Clinician | Responsible for:   * Identify patients with adverse events or side effects and report immediately to the clinical trial co-ordinator. * Manage adverse events or side effects accordingly this SOP. |
| Clinical trial co-ordinator | Responsible for:   * Immediate reporting to the principal investigator. * Ensure thorough documentation of the ADE, including its nature, severity, timing, and any actions taken in response. * Monitor the affected participant closely, coordinating follow-up assessments, medical care, and any necessary adjustments to the study protocol or treatment plan. |

### 6. PROCEDURE

At each clinical review during the study period the participant will be closely monitored for any signs of side effects related to the study drugs, but also unrelated adverse events will be recorded as will the causality be assessed. Adverse events will be meticulously screened during history taking, general examination, and laboratory tests. A comprehensive list of specific known drug-related adverse events is provided in the table below, and it is imperative that the local RMC trial researcher/clinician conducts targeted inquiries regarding each one.

|  |  |  |
| --- | --- | --- |
|  | **Yes** | **No** |
| Fevers |  |  |
| Cutaneous (including nails) fungal infections |  |  |
| Infections |  |  |
| Infected ulcers |  |  |
| Recent tuberculosis diagnosis |  |  |
| Night sweats |  |  |
| Nausea |  |  |
| Jaundice |  |  |
| Dyspepsia |  |  |
| Gastric pain requiring antacid |  |  |
| Gastrointestinal bleeding/ Melena |  |  |
| Vomiting |  |  |
| Diarrhoea |  |  |
| Ulcers in the mouth |  |  |
| Moon face |  |  |
| Anorexia |  |  |
| Weight lost >5kg in 3 months |  |  |
| Weight gain |  |  |
| Nocturia, polyuria, polydipsia |  |  |
| Hypertension BP> 160/90 on 2 separate readings at least 1week apart |  |  |
| Other rashes |  |  |
| Hair loss |  |  |
| Pruritus |  |  |
| Acne |  |  |
| Peripheral oedema |  |  |
| Shortness of breath |  |  |
| Chronic cough |  |  |
| Chest pain |  |  |
| Easy bruising/Haematoma |  |  |
| Dizziness |  |  |
| Headaches |  |  |
| Convulsions |  |  |
| Psychosis or other mental health problems |  |  |
| Recent fractures |  |  |
| Menorrhagia |  |  |
| Amenorrhea |  |  |
| Corner Glaucoma |  |  |
| Corneal ulcer |  |  |
| Cataract |  |  |

**6.1 Common side effects of each medication**

Prednisolone side effects:

* Major adverse events

1. Gastrointestinal bleeding
2. Nocturia, polyuria, polydipsia
3. Diabetes mellitus
4. Psychosis or other mental problems
5. Wight loss > 5kg
6. Weight gain
7. Glaucoma
8. Cataract
9. Hypertension BP > 160/90 on 2 separate readings at least 1 week apart
10. Infections
11. Infected ulcers
12. Corneal ulcer
13. Tuberculosis
14. Night sweats

* Minor side effects

1. Moon face
2. Acne
3. Cutaneous (including nails) fungal infections
4. Gastric pain requiring antacids

**6.2 Contra-indications to Rifampicin, moxifloxacin , clarithromycin**

* Known hypersensitivity to or any component of the formulation
* Chronic liver disease
* Immunodeficiency syndromes
* Preexisting blood dyscrasias
* Several renal impairments

**Rifampicin**

Rifampicin is an antibiotic commonly used in the treatment of tuberculosis and certain other bacterial infections. Like any medication, it can have adverse effects, and it may also cause laboratory abnormalities.

Adverse Effects of Rifampicin:

1. Gastrointestinal Effects:

- Nausea

- Vomiting

- Abdominal pain

- Diarrhea

2. Hepatic Effects:

- Transient elevation of liver enzymes (AST, ALT)

- Hepatitis (in rare cases)

3. Hematologic Effects:

- Thrombocytopenia (reduced platelet count)

- Leukopenia (reduced white blood cell count)

- Hemolytic anemia (destruction of red blood cells)

4. Dermatologic Effects:

- Rash

- Pruritus (itching)

- Flushing

5. Flu-like Symptoms:

- Fever

- Headache

- Malaise

6. Other Effects:

- Fluorescent orange discoloration of body fluids (urine, sweat, tears)

Laboratory Derangements:

1. Liver Function Tests:

- Rifampicin can cause a transient increase in liver enzymes (AST and ALT). Regular monitoring of liver function is recommended during treatment.

2. Hematologic Tests:

- Thrombocytopenia, leukopenia, and hemolytic anemia are potential effects, though they are relatively uncommon.

3. Renal Function Tests:

- There may be alterations in renal function, but significant renal effects are not commonly reported.

4. Coagulation Tests:

- Altered coagulation parameters may occur in some cases.

**Clarithromycin**

Clarithromycin is a macrolide antibiotic commonly used to treat various bacterial infections. As with any medication, it can have adverse effects, and monitoring certain laboratory values may be necessary. Keep in mind that individual responses to the medication can vary, and these general guidelines should be monitored by healthcare professional.

Adverse Effects of Clarithromycin:

1. Gastrointestinal Effects:

- Nausea

- Vomiting

- Diarrhea

- Abdominal pain

2. Hepatic Effects:

- Transient elevation of liver enzymes (AST, ALT)

- Hepatitis (in rare cases)

3. Cardiovascular Effects:

- Prolongation of the QT interval (can lead to arrhythmias)

4. Allergic Reactions:

- Rash

- Itching

- Swelling (especially of the face, lips, or tongue)

5. Other Effects:

- Headache

- Changes in taste sensation

Laboratory Monitoring:

1. Liver Function Tests:

- Clarithromycin may cause a transient increase in liver enzymes (AST and ALT). A significant elevation may be defined as levels greater than three times the upper limit of normal.

2. Electrolytes:

- Clarithromycin, like other macrolides, may have a minimal effect on potassium levels. Monitoring electrolytes, especially in patients at risk of electrolyte imbalances, is advisable.

3. Cardiac Monitoring:

- Clarithromycin has been associated with QT interval prolongation. In patients with pre-existing cardiac conditions or those taking other medications that prolong the QT interval, electrocardiogram (ECG) monitoring may be considered.

4. Renal Function Tests:

- Clarithromycin is primarily eliminated through the liver, and it is not usually associated with significant renal effects. However, monitoring renal function may be necessary in certain cases.

**Moxifloxacin**

Moxifloxacin is a fluoroquinolone antibiotic used to treat various bacterial infections. Like any medication, it can have adverse effects, and monitoring certain laboratory values may be necessary. It's important to note that individual responses to the medication can vary, and the following information provides a general overview. Always consult with a healthcare professional for personalized advice.

Adverse Effects of Moxifloxacin:

1. Gastrointestinal Effects:

- Nausea

- Vomiting

- Diarrhea

- Abdominal pain

2. Central Nervous System Effects:

- Headache

- Dizziness

- Insomnia

3. Tendon Rupture:

- Fluoroquinolones, including moxifloxacin, have been associated with an increased risk of tendon rupture, especially in the Achilles tendon.

4. Cardiovascular Effects:

- QT interval prolongation (can lead to arrhythmias)

- Changes in heart rate

5. Allergic Reactions:

- Rash

- Itching

- Swelling (especially of the face, lips, or tongue)

Laboratory Monitoring:

1. Liver Function Tests:

- Moxifloxacin may cause a transient increase in liver enzymes (AST and ALT). A significant elevation may be defined as levels greater than three times the upper limit of normal.

2. Renal Function Tests:

- Moxifloxacin is primarily excreted through the kidneys. Monitoring renal function may be necessary, especially in patients with pre-existing renal conditions.

3. Electrolytes:

- Moxifloxacin may cause changes in electrolyte levels, including potassium. Monitoring electrolytes, especially in patients at risk of electrolyte imbalances, is advisable.

4. Cardiac Monitoring:

- Moxifloxacin, like other fluoroquinolones, has been associated with QT interval prolongation. Monitoring ECG may be considered, particularly in patients with pre-existing cardiac conditions or those taking other medications that prolong the QT interval.

**Dapsone**

Dapsone is a medication primarily used for the treatment of leprosy and dermatitis herpetiformis, a skin condition associated with celiac disease. Like any medication, dapsone can cause side effects. It's important to note that not everyone will experience these side effects, and some individuals may tolerate the medication well. Here are some common side effects of dapsone:

1. Hematologic Effects:

- Hemolytic anemia (destruction of red blood cells), especially in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency testing is often performed before starting dapsone.

2. Dermatologic Effects:

- Rash

- Itching

- Photosensitivity (increased sensitivity to sunlight)

3. Gastrointestinal Effects:

- Nausea

- Vomiting

4. Methemoglobinemia:

- Dapsone can cause an increase in methemoglobin levels in the blood, which can reduce the ability of hemoglobin to carry oxygen.

5. Peripheral Neuropathy:

- Tingling or numbness in the hands or feet.

6. Psychiatric Effects:

- Insomnia

- Anxiety

7. Respiratory Effects:

- Shortness of breath

8. Elevated Liver Enzymes:

- Transient increases in liver enzyme levels may occur.

**Clofazimine**

Clofazimine is an antimycobacterial medication primarily used in combination therapy for the treatment of leprosy (Hansen's disease). Like any medication, clofazimine can cause side effects. It's important to note that not everyone will experience these side effects, and some individuals may tolerate the medication well. Here are some common adverse effects associated with clofazimine:

1. Gastrointestinal Effects:

- Nausea

- Vomiting

- Abdominal pain

- Constipation

2. Skin and Pigment Changes:

- Pink to brownish-black discoloration of the skin, particularly in light-exposed areas. This side effect is usually reversible upon discontinuation of the drug.

3. Gastrointestinal Disturbances:

- Gastrointestinal disturbances, such as gastrointestinal upset, have been reported.

4. Eye Effects:

- Red-brown to black discoloration of the conjunctiva and cornea, which is usually reversible upon discontinuation.

5. Lymphadenopathy:

- Enlargement of lymph nodes may occur.

6. Immune System Effects:

- Immunoglobulin changes, including reversible reduction of IgA and IgM.

7. Hematologic Effects:

- Reversible discoloration of body fluids, including urine, sweat, and tears.

**6.3 Laboratory tests:**

In the event of abnormalities in monitoring investigations, the following dosage modifications will be made:

|  |  |  |
| --- | --- | --- |
| **Abnormality** | **Action** | **Follow up** |
| Haemoglobin <= 7 gm % | Withdraw | None |
| Total WBC count < 3.0 x109 cells/l | Withhold trial drugs | If repeat labs  are < 3.0 x109 cells/l then withdraw participant |
| Neutrophils < 1.0 x109 cells/l  (if available) | Withhold trial drugs |  |
| AST and ALT increased by less than two times the ULN | Continue trial drugs and Repeat LFTs in 2–4 weeks | If LFTs are less than twice ULN continue trial drugs and monitor again in 4 weeks |
| AST and ALT greater than 2 but less than or equal to 3 times the ULN | Withhold;  Repeat LFTs in 4 weeks  Consider other risk factors (including alcohol consumption) | If LFTs are less than twice ULN resume and monitor again in 4 weeks |
| AST and ALT greater 3 times the normal | Withdrawal from study | Monitor until normal or cause identified |
| Creatinine > 2 × ULN | Withhold trial drugs. Repeat in 4 weeks | If repeat creatinine > 2x ULN withdraw participant |

**6.4 Managing clinical symptoms**

* Nausea and vomiting: if mild treat with anti-emetics (ondasertron), if severe, IV rehydration

### 7. DEFINITIONS

**Adverse Event (AE)**

Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences, which are not necessarily caused by or related to that product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

**Adverse Reaction (AR)**

Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

**Serious Adverse Event (SAE)**

A serious adverse event is any untoward medical occurrence that:

* Results in death
* Is life-threatening
* Requires patient hospitalisation or prolongation of existing hospitalisation
* Results in persistent or significant disability/incapacity
* Consists of a congenital anomaly or birth defect

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

**Serious Adverse Reaction (SAE)**

An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

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 the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product
* In the case of any other investigational medicinal product, in the investigator brochure (IB) relating to the trial in question.

### 8. CAUSUALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related side effects due to the drugs used in this study. The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be reported.

|  |  |
| --- | --- |
| **Relationship** | **Description** |
| **Unrelated** | There is no evidence of any causal relationship |
| **Unlikely** | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment). |
| **Possible** | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments). |
| **Probable** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| **Definitely** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |
| **Not assessable** | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

### 9. REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given in appendix 2 to aid in the reporting procedures.

### 9.1 Non serious Adverse Reaction (ARs)/ Adverse Events (AEs)

All AEs and ARs will be recorded in the electronic data collection form (Easy Research).

**9.2 Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)**

Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information. The CI (for a single-centre trial) or PI (for a multi-centre trial) must record the event with an assessment of seriousness, causality and expectedness.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

**9.3** **Suspected Unexpected Serious Adverse Reactions (SUSARs)**

All SAEs assigned by the PI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Regulatory Authority, in the UK: Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor (or delegate) will inform the MHRA, and the ethics committee of UK-relevant SUSARs within the required expedited reporting timescales (as per TLMTI Standard Operating Procedure for recording, managing and reporting of adverse events for IMP studies).

All SUSARs will be reported assuming the active compound is involved.

In the case of a suspected, unexpected, serious adverse reactions (SUSAR), the staff at the site should:

1. Contact the study coordination centre immediately by phone or email to inform them of the event.
2. Submit a completed SAE form (signed and dated) within 24 hours, together with relevant treatment forms and anonymised copies of all relevant investigations.
3. Submit any additional information promptly upon request.

### 10. ADMISSION

Participants may be admitted for the first few days to have all initials tests done and results back prior to starting the study, if this is more convenient for the participant and the study centres. Each centre will decide what is the best procedure to admit participants and for how long they must stay in hospital. However, patients will generally be treated as out-patients.

**10.1 Criteria for hospitalization:**

* Patient is too unwell to be at home
* Patient develops severe infection
* Patient develops severe nausea, vomiting and/or diarrhoea requiring i.v rehydration
* Patient is unable to travel between home and hospital, e.g. foot ulcer requiring bed rest, lives too far and is willing to be admitted.

### 11. Major adverse event necessitating hospital admission

* The patient will be withdrawn from the study.
* An adverse event form will be completed.
* The DSMB will be informed of this event.

### 12. REFERENCES

1. RMC trial protocol

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**SAFETY REPORT FLOWCHART**

**AR and AE**: record in notes and CRF

**SAE and SSAR**: report to sponsor immediately

**SUSAR**: expedited reporting!

Not expected

**SAE**

Suspected Unexpected Serious Adverse Reaction

Serious Adverse Reaction

Serious Adverse Reaction

Serious Adverse Event

Related to study drugs

Not related to study drug

Not related to study drug

ADVERSE EVENT

Not serious

Serious

*Seriousness*

Related to study drugs

*Causality*

Adverse Event

Adverse Reaction

*Expectedness*

Expected

**AE**

**AR**

*Severity grading*

**SUSAR**

**SSAR**