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| A Comparative Multicentric Non-Inferiority Clinical Trial of WHOMBMDT with a New Monthly Chemotherapy Regime containing Rifampicin, Moxifloxacin and Clarithromycin (RMC) on Multibacillary patients from IndiaStandard Operating Procedure 2Participant Informed Consent | | | |
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**1.** **PURPOSE**

This document describes the process of screening patients for the RMC study.

### 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.

**3. Scope**

This document applies to all staff involved in the process of patient consent and enrolment. Associated materials:

* Patient information sheet (PIS)
* Informed consent form (ICF)
* Electronic Data Collection Tool (Easy Research)

**4. Responsibilities**

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| **Role** | **Responsibility** |
| RMC Principal  Investigator | * Ultimately responsible for ensuring RMC study procedures obtain ethics approval and all staff strictly adhere to both ICH GCP guidelines and this SOP. |
| Local Study researcher | * Responsible for introducing the study and inviting the participants. * Providing information to participants and obtaining informed consent at screening and enrolment. * Responsible for returning informed consent documents to the study office daily. |
| Clinical Trial Co-ordinator | * Responsible for ensuring appropriate staff members are trained on the procedures of this SOP. * Responsible for ensuring that all informed consent documents are collected, returned to the study office, and properly filed in their designated location. * Responsible for overseeing and ensuring the accurate completion of the informed consent procedure by the Local Study Researcher, along with providing sufficient oversight. * Responsible for monitoring the efficiency of the data collection process and ensuring its smooth flow. |

### 5. PROCEDURE

* 1. **Foundations of Informed Consent**
* Before any study procedures are performed, the potential participant MUST provide informed consent.
* Informed consent is a process that aims to ensure the potential participant understands why the study is being conducted, what they will be asked to do if they participate, and the benefits and potential risks of participation.
* All potential participants will be enrolled in the RMC study and will undergo screening and the enrolment informed consent process.
* The local study researcher will use an informed consent review to confirm that participants understand key messages about the study.
* Prior to the lab investigations, the study personnel will remind the participant of the information found in the RMC PIS (Appendix 1) and RMC Consent form (Appendix 2). The study personnel will proceed with written and signed consent form and ensure that ongoing informed consent is maintained throughout the duration of his/her participation.
  1. **Informed Consent Process and Screening**
* When the local study researcher identifies a potential participant, he/she will approach them, create a good rapport, explain the study and invite them to participate.
* The RMC local researcher will begin the screening process by reading the text and questions displayed on Easy Research to the prospective participant.
* The RMC local researcher will explain the two-step informed consent process. The two-step informed consent process consists of: 1) eligibility screening 2) the enrolment informed consent if the participant is eligible.
* The RMC local researcher will explain that not all patients will be able to take part in the study.
* After the explanation, the RMC local researcher will ask the potential participant if he/she has any questions or concerns and if he/she is interested in continuing with the first step of the informed consent process.
* If the participant is willing, he/she should verbally agree to continue to the eligibility determination.
  1. **Eligibility Determination Process During Screening**
* Once the screening (screening1) process has been completed, the RMC local researcher will perform an eligibility screening (screening2) to assess participant eligibility. Please refer to SOP 1 screening to more details.
* After completing the eligibility evaluation, participants who are eligible for study participation will be informed of their status and asked if they would like to learn more about the study and begin the enrolment informed consent process.

* 1. **Informed consent Procedures for Eligible Participants**
* The RMC local researcher will proceed with informed consent process if the participant is interested in joining the study. He/she will ensure that informed consent is obtain in a setting free of coercion and undue influence.
* The RMC local researcher will highlight to the participants that the decision to participate or not is entirely theirs. They will refrain from exaggerating potential benefits and downplaying possible risks during this process.
* The RMC local researcher will stress that the participant's access to medical care and other services remains unaffected by their decision to participate or not. Additionally, they will allocate ample time during the informed consent discussion to address any questions or concerns raised by the participant.
* The RMC local researcher will read the “RMC Participant Information Sheet”, PIS, (Appendix 1) with the participant and clarify any question.
  1. **Informed Consent Procedures for Literate Potential Participants**
* If the participant is literate, ask them their preferred language. The RMC local researcher will then provide the participant with a copy of the “RMC PIS” (Appendix 1) in their preferred language (English, XXXX)
* The RMC local researcher will read the sheet to the participant word by word. Maintain frequent eye contact with the potential participant to assess their level of attention and understanding. If the potential participant appears to be inattentive, confused, upset or bored, the RMC local researcher should stop and attend to the participant.
* The RMC local researcher will highlight the main points and ask the potential participant if he/she has any questions or concerns about the information provided in each section of the form and answer all questions and discuss any concerns before moving on to the next section of the form.
* After completing the informed consent discussion, the RMC local researcher should give the participant adequate time to review the information sheet on their own and allow for further questions or concerns. The RMC local researcher should encourage the potential participant to take the time to consider their potential participation in the study.
* If the RMC local researcher confirms that the participant understands all required information, the remainder of the informed consent process will continue.
* If after all possible educational efforts are exhausted and the RMC local researcher determines that the potential participant is not able to understand all required information, the informed consent process will be discontinued.
* Participants who are willing and able will be asked to document their consent by singing on the “RMC Consent Form” (Appendix 2). The RMC local researcher will provide the participant with two copies of the consent form, then, he/she will read it together with the participant. The participant will mark “Yes, I agree” box in both copies.
* Participants who are unwilling or unable will be thanked for their time and effort. They will be provided a card with RMC study contact information and instructed that if in case, they change their mind they may contact RMC team at a later date to inquire about potential study participation.
* They will be provided a card with RMC study contact information and instructed that if they change their mind thy may contact RMC team at a later date to inquire about potential study participation.
* Participants who are unable at that moment and willing to participate will be screened in a later date.
* A witness will sign the informed consent alongside the participant. The witness can be a relative or nurse/ field worker who is not involved in the study. The witness should be present at the consent procedures and ensure the participant is not coerced to participate in the study.
  1. **Informed Consent Procedures for Illiterate Potential Participants**
* If the participant is not literate, RMC local researcher will ask them to nominate an independent witness who must be literate.
* The literate impartial witness will be present throughout the entire informed consent process for illiterate participants. Their role is to ensure, to the best of their ability, that the information presented in the consent form was accurately communicated to the potential participant and that the participant appeared to understand it. Additionally, they verify that the participant's consent was freely given. An impartial witness is someone literate in the participant's language who will not exert undue pressure on the participant to give consent. The participant’s witness will be handed a copy of the “RMC PIS” in their preferred language to read along while the RMC local researcher reads word by word.
* The process will then continue as per literate participant, except rather than reviewing the RMC PIS, on their own, the RMC local researcher will just give the potential participant adequate time for questions or concerns. The RMC local researcher worker should encourage the potential participant to take the time to consider their potential participation in the study.
* Then, the RMC local researcher will ensure that they are providing the participant adequate information from the “RMC PIS”. If the participant’s answers indicate any misunderstanding of study-related information, RMC local researcher will review and explain that information again until the potential participant demonstrates a clear understanding.
* If the RMC local researcher confirms that the participant understands all required information, informed consent process will continue.
  1. **Documentation of the Informed Consent Process** 
     1. The following are rules for signing TWO copies of the consent form:

**Literate participant**

* The participant will be required to legibly write their name on the designated line provided for the participant's name.
* Participant will sign on the signature line.
* All entries will be completed in ink.
* The witness will print their name on the witness’s name line and he/she will sign on the signature line.
* The RMC local researcher will complete his/her entry in ink on his/her respective lines (name, signature and date).

**Illiterate participant**

* The participant will place his/her thumbprint on the participant’s signature line.
* The name and date lines of the participant will be left blank.
* The witness will legibly write their name, sign and date on the witness lines.
* All entries will be completed in ink.
* The RMC local researcher will write at the bottom of the signature page that “(Participant’s name) is illiterate and consented to this form on “DD MM YY” and he/she will initial and date this entry.
* The RMC local researcher will document the process as specified for the literate participants.
  + 1. The participant will keep one copy of the “RMC SIP” (Appendix 1) and one copy of the consent form (Appendix 2), signed. The RMC local researcher will keep one copy of the consent form on the participant’s study binder.
    2. In the event that corrections are required for the informed consent, the original signature page should remain unaltered. Any necessary corrections, along with explanations, must be recorded in the bottom section of the informed consent signature page. Subsequently, the RMC local researcher is obligated to initial and date all corrections.
    3. All documentation of the informed consent process will be retained in the RMC study file. Any document bearing participant’s ID numbers such as laboratory specimen forms will be retained in participant’s study binders also identified by date of filing. All documents will be stored securely to protect participant’s privacy and confidentiality.

Informed participant consent will be signed before any study procedure takes place like blood tests and chest x-ray. Patients can verbally consent to the first part of the screening consisting of clinical questions only. Please refer to SOP 1.

Each participant will have a participant’s study binder to be kept in local site. This file will hold important documents such as a copy of the consent form, contact information, next to kin, hospital number, participant’s labels and recorded logs. This file will be storage in a locked location and only the local study manager will have access to.

1. **DEFINITION**

Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a study, having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. [Source: ICH Consolidated Guidance for Good Clinical Practice (ICH-E6)]

Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1. **REFERENCES**
2. WMA DWMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. World Medical Assocation. Available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
3. Guideline for Good Clinical Practice. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Available at: <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf>
4. RMC protocol

**10. Appendices**

Appendix 1: RMC Participant Information Sheet

Appendix 2: RMC Consent Form

**Appendix 1**

**Participant Information Sheet**

###### *A Comparative Multicentric Non-Inferiority Clinical Trial of WHOMBMDT with a New Monthly Chemotherapy Regime containing Rifampicin, Moxifloxacin and Clarithromycin (RMC) on Multibacillary patients from India*

**Introduction**

*We would like to invite you to take part in a research study. Joining the study is entirely up to you. Before you decide, you need to understand why the research is being done and what it would involve. One member of our team will go through this information sheet with you, and answer any questions you may have. Ask questions if anything you read is not clear or you would like more information. Please feel free to talk to others about the study if you wish. Take time to decide whether or not to take part*.

**What is the purpose of the study?**

*Current WHOMBMDT does not kill 100% bacteria even after a full course of treatment in a subset of patients harbouring 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.*

**Why have I been asked to take part?**

*You have been invited because you were diagnosed with Multibacillary leprosy and have never been treated for it.*

**Do I have to take part?**

*No. It is up to you to decide to take part or no. If you don’t want to take part, that’s ok. Your doctor will still care for you and your decision will not affect the quality of care you receive. We will discuss the study together and give you a copy of this information sheet. If you agree to take part, we will then ask you to sign a consent form.*

**What will happen to me if I take part?**

*If you are willing to take part in this study, we will first ask you to sign a consent form which is your indication that you understand the study and agree to take part.*

*Then you will be evaluated, do a clinical examination with blood tests that include complete blood count, haemoglobin, random blood sugar (RBS) and creatinine. Along with this urine samples will be taken and samples for bacterial index (BI), biopsy, molecular viability assay and mouse foot pad will also be taken.*

*If you meet the study’s criteria, and you wish to participate, you will be treated with either WHOMBMDT OR RMC, the treatment we are testing. The treatment will be chosen by chance by a computer. It is really important that the two groups for this study have a similar mix of patients in them. Having a similar mix means that we know that if one group of patients does better than the other, it is very likely to be because of the treatment and not because there are differences in the types of patients in each group. You will have an equal chance of receiving either WHOMBMDT OR RMC. You will be treated properly for MB leprosy.*

*It is important that you realise that treatment is not always effective and the symptoms can get worse.*

*If you agree to take part of this study, you will be seen by a member of the research team for the next 12 months. The follow up will be similar to a regular leprosy treatment. We will also ask you to do blood tests and give samples for BI, biopsy and MVA at the beginning of the study and then at 6months and 12 months.*

**What will I have to do?**

*You will be expected to take the medication as directed by your doctors and they will advise you on whether you can continue to take other medication. An important part of this study is the information we gain from the questions we will ask you, examination and laboratory tests. It is important you answer all the questions and attend to the appointments, so that we have a complete set of data for you.*

**What are the possible risks and disadvantages?**

*The current treatment with WHOMBMDT has common side effects like nausea, vomiting, diarrhoea, rash, fluorescent orange discolouration of body fluids (urine, sweat, tears), anaemia, change in taste sensation, insomnia, photosensitivity, anxiety, shortness of breath, pink or brownish to black discolouration of skin, abdominal pain etc. The treatment we are testing that is RMC is usually well tolerated. The most common side effects are nausea, vomiting, diarrhoea, abdominal pain, anaemia, discoloration of body fluids, headache, dizziness, insomnia etc. There may sometimes be side effects that are not listed, if you notice anything unusual and are concerned then should contact your study team.*

**What are the possible benefits?**

*We cannot promise but we anticipate you may receive a more effective treatment for leprosy. Your participation will contribute to improving leprosy treatment for.*

*other patients like you.*

**What if something goes wrong?**

*If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions*

*Dr Joydeepa Darlong, Phone number 91 9434885198* [*joydeepa.darlong@leprosymission.in*](mailto:joydeepa.darlong@leprosymission.in)

*Dr. Itu Singh*

*Dr. Reeta Devi*

*Dr. Anamika Haldar -Purulia*

*Dr. Neeta Maximus / Dr Ajay Menon - Barabanki*

*Dr. Vandana Elkana - Chandkhuri*

*Dr. Rajiv Joy Nathan - Shahdara*

**Can I change my mind about taking part?**

*Yes. You can withdraw from the study at any time. You just need to tell your doctor that you don’t want to be in the study anymore. Your doctor will still care for you.*

*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, or will continue to be stored for further research.*

**What will happen to information collected about me?**

*All information collected about you will be kept private. Only authorized study personnel and regulatory authorities responsible for ensuring the proper conduct of the study will have access to your information.*

*At the end of the project, the study data will be archived at TLMTI. The data will be made available to other researchers worldwide for research and to improve medical knowledge and patient care. Your personal information will not be included and there is no way that you can be identified.*

**What will happen to the results of this study?**

*The study results will be published in a medical journal so that other doctors can learn from them. Your personal information will not be included in the study report and there is no way that you can be identified from it.*

**Who is organising and funding this study?**

*Indian Council of Medical Research is the sponsor for the research and they have full responsibility for the project including the collection, storage and analysis of your data.*

**Who has checked this study?**

*All research involving human participants is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Research Ethics Committee.*

**What happens when the research study stops?**

*As a MB leprosy patient, you will continue to be reviewed in the Leprosy clinic as needed, so your follow up will be as normal.*

**Further information and contact details**

*Thank you for taking time to read this information leaflet. If you think you will take part in the study please read and sign the consent form.*

**Appendix 2**

**RMC clinical trial in MB leprosy:**

**Study number: | | | | Patient Initials: | | | |**

Study Center:

**CONSENT FORM FOR PARTICIPATION IN RMC clinical trial in MB leprosy**

1. I understand that doctors at are involved in research into alternative treatments for leprosy. Currently treatment for leprosy is for 12 months, and the medications are 3 in number which have to be taken monthly and daily. This study will look at whether rifampicin, moxifloxacin and clarithromycin is more efficacious than MDT the management of Multibacillary leprosy .We are hoping to find a way of reducing the number of days of medication taken and reduced duration of treatment and less adverse effects.
2. The study has been explained to me.
3. I confirm that I am 18 years old or above.
4. I shall be randomly assigned to RMC regimen consisting of Rifampicin 600 mg, Moxifloxacin 400 mg and clarithromycin 1000 mg monthly once or WHO MDT consisting of Rifampicin 600 mg and Clofazimine 300 mg once monthly followed by Dapsone 100 and clofazimine 50 mg daily for 12 months.
5. I agree to regular review visits, at first fortnightly, then monthly for the duration of my treatment.
6. I also agree to return for follow-up at during the course of this study.
7. I understand that I will have to have regular blood tests to monitor for any side effects if any. The maximum amount of blood drawn at any time will be 20ml (this is the equivalent of 4 teaspoons). It is possible that I may experience some side effects as explained on the information sheet and that I will be treated for these freely and appropriately.
8. I agree to have a Slit skin smears taken as directed by the treating physician.
9. I agree to have skin biopsy taken twice , once at the start and later at the time of completion of treatment .
10. Some of the samples taken (skin biopsy and blood) may be kept in a laboratory for up to 5 years to allow future studies. Please tick the box if you agree to follow up studies to be conducted on stored materials.
    1. **□ Yes, I agree □ No, I don’t agree**
11. I can decide to leave the study at any time for any reason and will still receive other treatment from the hospital for my disease.
12. I understand that my name will not be revealed in any published material concerning this study. I understand that my notes will be treated with maximum confidentiality and will only be accessed by staff directly involved in the Study or the monitors of the Study.
13. I have received enough information about the study in a language I understand. I had the opportunity to discuss it and ask questions, and my questions have been answered to my satisfaction. I understand that participation is voluntary and that I am free to withdraw my consent at any time.
14. I freely consent to participate in this research study and to allow treatment and tests to be performed on me as explained.
15. I understand that I can be requested anytime to terminate my participation in the trial if the need arises. I will be given full explanation of the reason and will still receive standard treatment.

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| --- | --- | --- | --- |
|  | Printed Name | Signature | Date |
| Patient |  |  | / /20\_ |
| Witness |  |  | / /20\_ |
| Doctor |  |  | / /20\_ |