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**Guidelines for completing CRFs used in the Inter-country operational research on all-oral shorter treatment regimens for rifampicin-resistant tuberculosis Operational Research,**

**2020-2022**

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# Acronyms

|  |  |
| --- | --- |
| AEI | Adverse events of interest |
| CRF | Case Reporting Form; p-CRF is used for printed version of CRFs; e-CRF is used for electronic version of CRFs |
| DST | Drug susceptibility testing |
| ECG | Electrocardiogram |
| GFR | Glomerular filtration rate |
| HIV | Human immunodeficiency virus |
| mSTR | Modified all-oral short RR-TB treatment regimen |
| NTM | Non-tuberculous mycobacteria |
| PMDT | Programmatic Management of Drug-Resistant TB |
| PV | Pharmacovigilance |
| RR | Rifampicin-resistant |
| SAE | Serious Adverse Event |
| TB | Tuberculosis |
|  |  |
| **Drug abbreviations:** | |
| Bdq | Bedaquiline |
| Cfz | Clofazimine |
| Dlm | Delamanid |
| Lzd | Linezolide |

# General principles

* The goal of this document is to provide detailed instructions on the completion of the Case-specific reporting forms used within the Operational Research of the modified Short Treatment Regimen (mSTR) of the Rifampicin Resistant or Multi-Drug Resistant Tuberculosis (RR/MDR-TB).
* Case-specific reporting forms (CRFs) were designed to collect data in the mSTR Operational Research. There are available two types of forms depending on how they are filled in:
* paper version - CRFs will be printed and after completed by hand (p-CRFs)
* electronic version – CRFs can be completed electronically in excel format (e-CRFs)
* In both cases, the p-CRFs and e-CRFs will be kept in the Study Centre in a secure place according to the mSTR Operational Research Protocol.
* In case when paper version of CRFs is used, all p-CRFs will be completed by hand after printing. It is encouraged to create a paper folder for each enrolled TB patient to keep all completed p-CRFs. The created folder will not contain names or other confidential patient’s information. To make it easier to work with a TB patient’s folder only the patient ID can be specified on it. All completed p-CRFs during the study will be added in the patient's personal folder. Also, as appropriate, the folders can be grouped by institutions, districts, regions, sites etc. All p-CRFs shall be stored in the locked safe, out of reach of unauthorized personnel.
* In case when the electronic version of CRFs is used, all e-CRFs can be filled in electronically. It should be noted that one e-CRFs excel file will be used for each enrolled TB patient. Thus, for one patient – one excel file. The excel file contains all the necessary e-CRFs to fill in during the entire study period, including enrolment, follow-up during the treatment, end of the treatment, and follow-up after the treatment completion. The patient ID will be used to assign a name to the excel e-CRFs file. Do not use confidential patient information (names, address, phone number etc.) to name the e-CRF file. In addition, to systematize the collected information, completed e-CRFs can be saved in computer folders grouped by institutions, districts, regions, sites etc (Figure 1). The computer where these files will be saved must have password protection.

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Figure 1. How to organize the Study folder for e-CRFs and Study centers

* For e-CRFs it is recommended to make a copy and create a back-up of the Study Folder. How to create a back-up of the Study Folder use the instruction on **Creating a back-up for study database.**
* The copy of the Study Folder shall be saved weekly in the different folder of the user’s computer and on a hard drive. Alternatively, you can save it in the cloud: (any of the following: One drive, Drop box, Google drive). First create copy of the folder with Project file then rename of as *Country Name\_studysite\_date*. E.g. *Tajikistan\_01\_20-08-2020*.
* It is encouraged to complete the e-CRFs in excel document electronically, rather than printing the form and completing it by hand
* If e-CRFs are used fields such as: **Country, Study site, Participant’s Initials, DR-TB number, Patient ID, Date of birth, Sex** are completed only in Screening Form and in other e-CRFs this is done automatically. In paper p-CRFs all fields must be completed in writing by hand.
* It is encouraged to give answers to questions, avoiding ‘**Unknown**’ answer**.**

Table 1. When and what CRFs should be completed?

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Name | Before enrolment | Baseline | During the treatment | | | | | | | | | | End of the treatment | After treatment completion | | | |
| 0  moth | 2nd  week | 1st  moth | 2nd month | 3rd month | 4th month | 5th month | 6th month | 7th month | 8th month | 9th month | 3rd month | 6th month | 9th  month | 12th month |
| Screening and enrolment logbook |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Screening |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Enrolment |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinical Evaluation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mycobacteriology results |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DST results |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SAE and AEI | Complete if appropriate | | | | | | | | | | | | | | | | |
| Treatment completion |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Follow-up completion |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

# Update of case report forms

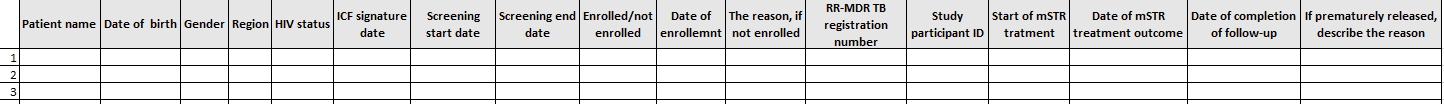
If the CRFs got updated by the WHO / national study team, do the following:

* Paper version: don’t change, reprint or amend already completed forms for previously enrolled patients. Just use updated forms for all subsequent visits of patients. Use updated version of the forms for all new patients from the beginning.
* Electronic version: don’t change or amend already completed forms for previously enrolled patients. Create a separate folder for each patient on a computer and place there: 1) Excel file with already completed forms and 2) Excel file with updated forms. Don’t copy information from the old forms into the updated ones. Just cease completion of old forms and resume completion of the updated forms from the same place you stopped in the old forms. Use updated forms for all subsequent visits. Use updated version of the forms for all new patients from the beginning.

To avoid confusion, add to the name of the old form the following: completion stopped on DD-MM-YYYY.

# Subject screening and enrolment logbook

* The **Subject screening and enrolment log** will be completed only at the Study Centre.
* Information on the patient's name will be indicated only in the screening and enrolment logbook. The identifier list, linking the identification code with the patient’s name, address and date of birth will remain strictly with study site doctor-investigator.
* Study site doctor-investigator who completes site **Subject screening and enrolment log** assigns the participant code using the instruction **Assignment of study participant code** (Annex)



# Study Screening Form

**Study Screening Form** consists of two parts. The fields **Study screening date** and **DR-TB number** fromPart II must be identically with those from the Part I. These fields in Part II are completed automatically from the Part I when the electronic version of forms is used. For the printed form it is necessary to write by hand in both parts. Here is very important to fill them in correctly so not to confuse with p-CRFs of other patients.

There are some instructions in **Study Screening Form** related to Inclusion Criteria. Follow them to assess whether the patient is eligible to be enrolled in the study and be careful which section should be filled in based on the answers received (Figure 2).

|  |
| --- |
| If all **NO**  If any **YES**  If all **NO**  If any **YES**  **YES**  **NO**  **NO**  **YES**  Discuss the study and ask if the patient is willing to consent to study participation  Discuss the study and ask if the patient is willing to consent to study participation  And mark **NO** for Enrolment  **YES**  **NO**  **Section F**  **Section E**  **Section D**  **Section C**  **Section B** |

Figure 2. Scheme for completing sections depending on the criteria for inclusion in the study

### Country and Study site

* Fill in the **country name** in the printed Screening Form, or select from the drop-down list in the electronic Screening Form. If the printed form is used country name must be typed in each p-CRFs. If the electronic form is used, the country name is selected from the drop-down list in the Study Screening Form, and in other e-CRFs this is done automatically.
* **Study site** is a numeric field. Type 01 (or 1 in e-CRF) if in the country is one focal-point site for collection all CRFs. Type 01, 02, 03 … (or 1, 2, 3) if in the country are more than one site which centralize data, accordingly.

|  |  |
| --- | --- |
| Printed Screening Form | Electronic Screening Form |
|  |  |

* **Study screening date.** Indicate the start date of screening for enrolment in the mSTR study. The study screening date should be earlier than enrolment date. It is admitted exceptions for retrospective enrolment or in other special and argumentative circumstances.
* Use dd/mm/yyyy format. Use slash to type in e-CRFs.

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| Printed Screening Form | Electronic Screening Form |
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### Section A. Patient information

* **Patient’s initials**. Indicate the first capital letter for the name, surname, and middle name of TB patient. Tape one letter in each box.
* If the patient’s initials are formed of three letters, then the letters should be typed (written) in first three boxes.
* **DR-TB Registration Number** is a specific number given to the DR-TB patients. It can contain letters or numbers or both of them.
* **Sex**. Check the appropriate box for the biological sex of the TB patient at birth for Print Form or select it from the drop-down list in the Electronic Form.
* **Date of Birth.** Indicate the day, month, and year of birth for the TB patient in format dd/mm/yyyy. For example: 26/06/1968. Use slash for fill in the date of birth in Electronic Form. A complete date of birth is required.

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| Printed Screening Form | Electronic Screening Form |
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### Section B. Non-invasive Exclusion Criteria

**Section B** contains a list of 6 questions (from B1 to B6) related to non-invasive exclusion criteria to answer Yes or No. Circle the answer in printed form or select the answer from the drop-down list in the electronic form. To answer the B6 question use Karnofsky and/or ECOG scales (Table 2). The links <https://www.mdcalc.com/karnofsky-performance-status-scale#next-steps> or <https://emedicine.medscape.com/article/2172510-overview> can be used as well.

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| Printed Screening Form | Electronic Screening Form |
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Table 2. Karnofsky and ECOG scales

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| --- | --- | --- | --- |
| Scale  % | Karnofsky performance status[[1]](#footnote-1) | Scale  Grade | ECOG performance status[[2]](#footnote-2) |
| 100 | Normal no complaints. No evidence of disease | **0** | Fully active, able to carry on all pre-disease performance without restriction |
| 90 | Able to carry on normal activity. Minor signs or symptoms of disease | **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 80 | Normal activity with effort. Some signs or symptoms of disease |
| 70 | Cares for self. Unable to carry on normal activity or to do active work | **2** | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 60 | Requires occasional assistance, but is able to care for most of his personal needs |
| 50 | Requires considerable assistance and frequent medical care | **3** | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 40 | Disabled. Requires special care and assistance |
| 30 | Severely disabled; hospital admission is indicated although death not imminent | **4** | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 20 | Very sick. Hospital admission necessary; active supportive treatment necessary |
| 10 | Moribund. Fatal processes progressing rapidly |
| 0 | Dead | **5** | Dead |

### Section C. Invasive Exclusion Criteria

* **Section C** contains a list of 4 questions (from C1 to C4) related to invasive exclusion criteria to answer **Yes** or **No**. Circle the answer in printed form or select the answers from the drop-down list in the electronic form.

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| Printed Screening Form | Electronic Screening Form |
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### Sections D – F. Enrolment status. Enrolment. Reason for non-enrolment

* After assessing eligibility, the Enrolment Status should be appreciate based on the criteria applied. Circle **Yes** or **No** in the printed form, or select **1-Yes** or **2-No** from the drop-down list in the electronic form to complete the enrolment status.

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| Printed Screening Form | Electronic Screening Form |
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* If patient is eligible to be enrolled in the study respectively the answer for enrolment status is **Yes** and the ID number must be assigned to TB patient. Study participant code is a serial number. The modality how to assign the ID number is described in the **Assignment of study participant code** document (Annex).

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| Printed Screening Form | Electronic Screening Form |
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* If patient is not eligible to be enrolled in the study respectively the answer for enrolment status is **No** and the **Section E - Reason for Non-Enrolment** should be completed. One of three reasons must be selected.

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| Printed Screening Form | Electronic Screening Form |
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* If patient declined to participate (E2) all reasons for decline should be checked. Circle all of them in in the printed form, or select **Yes** or **No** from the drop-down list for each reason in the electronic form. All fields should be fill in in the electronic form.
* If there are some additional reasons that are not listed the other reasons can be written by hand in printed form and typed in electronic form.

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| Printed Screening Form | Electronic Screening Form |
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* If site has decided to not enrol patient (E3) all reasons for site’s decision should be checked. Circle all of them in in the printed form, or select **Yes** or **No** from the drop-down list for each reason in the electronic form. All fields should be fill in in the electronic form.
* If there are some additional reasons that are not listed the other reasons can be written by hand in printed form or typed in electronic form.

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| Printed Screening Form | Electronic Screening Form |
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* If the physician has some comments regarding Study Screening, comments can be written by hand in printed form or typed in electronic form in the **Comments** rubric, at the end of **Study Screening Form**.
* **Date Form Completed** – indicate the date on which the screening was completed.

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| Printed Screening Form | Electronic Screening Form |
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# Study Enrolment Form

### Section A. Study Entry Enrolment

* **Study Enrolment Form** consists of two parts. The fields **Participant’s Initials,** **Participant ID** and **DR-TB registration number** must be identically with those from the **Study Screening Form** for the same patient. In electronic forms this is done automatically. In printed form is necessary to write them by hand.
* **Participant ID** and **Date participant enrolment** from Part II of Study Enrolment Form must be identically with those from the Part I. These fields in Part II are completed automatically when the electronic version of forms is used. For the printed form it is necessary to write by hand in both parts. Here is very important to fill them in correctly so not to confuse with p-CRFs of other patients.
* **Date participant signed informed consent –** participant should sign the informed consent before **Enrolment**. In some cases, the signing can be after enrolment (e.g. retrospective enrolment when participants received the mSTR regimen prior to the start of the study or other reasonable arguments)
* **Date of treatment start** – date when patient first ingested medication mSTR regimen, documented in directly observed therapy record (TB01)
* **Date of treatment start** must be later than **Study screening date**, indicated in **Study Screening Form**

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section B. Participant Demographics

* **Date of birth** and **Sex** are imported automatically from **Study Screening Form** if electronic form is used.
* **Weight** (kg) and **Height** (cm) – at the beginning of the treatment started
* For **Employment, Education** and **Marital status** check only one answer.
* Check **Unemployed** if the patient was not employed during the past 12 months prior to the TB evaluation. This should not include persons who are not seeking employment such as children and persons receiving permanent disability benefits. For these two categories mark Otherand specify them.
* Check **Other** if no answers for **Employment** are feasible.
* To appreciate **Level of education** use **Table 3**

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| Printed Enrolment Form | Electronic Enrolment Form |
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Table 3. Level of education according to educational stages

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| --- | --- |
| Level of education | Type |
| Primary | From 1st to 4th grade |
| Secondary | From 9th to 12th grade and Vocational education |
| High | University, Post-university studies |

### Section C. Participant’s social status

* Evaluate the **Patient’s Social Status** for **Homeless**, **Injecting drug**, **Alcohol** **use**, and **Employment** inthe past year (12 months prior to the TB evaluation).
* **Injecting Drug Use Within Past Year**. The purpose for collecting this information is to assess the patient's ability to adhere to anti-tuberculosis drug therapy. The intent of this question is not to require a detailed systematic interview of each patient but to identify those patients whose drug use might interfere with their ability to complete anti-tuberculosis drug therapy.
  + Check **No** if the patient has not injected drugs within the past 12 months.
  + Check **Yes** if it is known that the patient injected drugs within the past 12 months.
  + Check **Unknown** if it is not known if the patient injected drugs within the past 12 months.
* If it is marked **Not employed within the past year** in **Section C**, check the answer given in **Section B** for employment status.
* History of being **Resident of correctional facility** - a person who has ever been in detention (prison).
* **Alcohol use** - when alcohol consumption led to problems in relationships health, employment/work performance, or finances within the past year. It is not standardized; it will be subjectively evaluated by physicians.
* **History or current cigarette smoking**. Specify the number of packs of cigarettes per day that the patient smokes. If the patient smokes less than one pack, indicate 0.5 of the pack.

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section D. Tuberculosis history and treatment

* **Section D** contains information about the last previous treatment for tuberculosis.
* Specify the month and year when the last previous TB treatment started and ended. If the month is unknown specify the month of June (e.g. 06/2008) – the middle of the year.
* If there are some comments about the previous treatment, type them in the **Comments** rubric.
* **Question D3** refers to the second line drugs, excluding those used in the mSTR regimens.

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section E. Concomitant Diagnosis at the Time of TB Diagnosis

* Concomitant Diagnosis (risk factors) refers to those that are evaluated at the time of the current episode of TB. Documentation of additional TB risk factors from the medical records or a reliable source is preferred.
* If the TB patient has **Viral Hepatitis** check **Yes** and mark the type (A, B, C or B and C)
* If the TB patient has **Diabetes Mellitus** check **Yes** and mark the type (Type I or Type II) at the time of TB diagnosis
* How to assess **Peripheral neuropathy** see Table 8
* **Chronic renal insufficiency** - presence of kidney damage or loss of kidney function over 3 months or more, regardless of the cause (Table 4). GFR Calculator <https://www.mdcalc.com/mdrd-gfr-equation> can be used as well.

Table 4. Classification of chronic kidney disease stages

|  |  |  |
| --- | --- | --- |
| Stage | Description | GFR (mL/min/1.73 m2) |
| I | Kidney damage with normal or increased GFR | **˃ 90** |
| II | Kidney damage with mild decrease in GFR | **60 - 89** |
| III | Kidney damage with moderate decrease in GFR | **30 - 59** |
| IV | Kidney damage with severe decrease in GFR | **15 - 29** |
| V | Renal failure | **˂ 15** |

* **HIV Status** at Time of Enrolment in mSTR (time of TB diagnostic evaluation or at TB diagnosis).
  + HIV status is **Negative** if the patient has had a documented negative HIV test at the time of TB diagnostic evaluation or at TB diagnosis or at TB diagnosis or earlier, but not exceeding 1 year. Undocumented patient history that an HIV test result was negative is not acceptable.
  + HIV status is **Positive** if one of the following is applicable:
    - The patient is tested for HIV and the laboratory result is interpreted as **Positive**; or
    - The patient has a documented medical history of a previous positive HIV test, or a documented previous diagnosis of HIV infection or AIDS
  + HIV status is **Unknown** if it is not known:
    - if the patient has had an HIV test, was ever offered a test, or was referred for HIV testing (e.g., anonymous testing centre, private testing centre) but it is unknown whether the HIV testing was done
    - if the patient had a HIV test at the time of the TB diagnostic evaluation or TB diagnosis and the results are not known. In this case, information on HIV results will be updated when the HIV status will be known
    - if the patient was offered the test at the time of the TB diagnostic evaluation or TB diagnosis, but declined to be tested
* If **HIV status is Positive**, the most recent information on regimen and CD4 at the time of the enrolment in the mSTR study will be included
* Specify **COVID-19** only if it has been confirmed by laboratory testing (PCR).
* If the patient has other comorbidities that are not listed, type them in **Other concomitant diagnosis** rubrics.

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section F. Site of TB disease

* Check the box corresponding to the site(s) of TB disease.
* If site of disease is **Extrapulmonary** or **both** (pulmonary and extrapulmonary) mark the system organs affected (select all that apply). **Lymphatic, intrathoracic** includes hilar, mediastinal, peritracheal, and other lymph nodes within the thorax.
* If the site of TB disease is **Other**, mark the 9th answer and specify the other organ or disease site.

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section G. Chest X-ray

* Chest X-ray result obtained during the diagnostic evaluation for TB, at the time of the enrolment in the mSTR study
* Check **Normal** if the chest radiograph showed no abnormalities consistent with TB and was normal. This category can include any other abnormalities that are not consistent with TB.
* Check **Abnormal** if the chest radiograph showed any abnormalities (e.g., hilar adenopathy, infiltrate(s), cavity, scarring) associated with TB
* For **Abnormal** chest X-ray select if there are or not cavities. Evidence of cavity if there are one or more cavities
* If **Abnormal unilateral** was selected in G.1, there cannot be the second answer (Bilateral) for the Question G1.1.
* If **Normal in both** was selected in G.1, then Question G 1.1 does not need to be filled in.

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| Printed Enrolment Form | Electronic Enrolment Form |
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### Section H. Pregnancy Status at the Time of TB Diagnosis

* Complete this section only for female.

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| Printed Enrolment Form | Electronic Enrolment Form |
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# Clinical Evaluation Forms

* **Clinical Evaluation Forms** contains three parts:
  + Mycobacteriology Form
  + Drug susceptibility testing (DST) Form
  + Clinical evaluation Form
* According to the Study protocol, **Clinical Evaluation Forms** should be completed at the beginning of the treatment, during the treatment, end of the treatment and after treatment completion (Table 1).
* Table 7 shows the schedule of performing bacteriological tests. According to the schedule, respective rubrics should be completed
* Fields **Country**, **Study Site** and **Participant** **ID** are imported from the **Study Screening Form** when the electronic version is used.

## Clinic Evaluation Form for Mycobacteriology results

### Section A. Visit Information

* Indicate **Baseline** if the Mycobacteriology results are at the time of diagnosis/beginning of the treatment. If the electronic version is used, then complete the sheet named **Mycobacteriology (0).**
* For recording the **Mycobacteriology results** performed during the treatment, select **Treatment evaluation** and specify for which month of the treatment are the results. In the electronic version of e-CRFs the sheets are named respectively the number of months **Mycobacteriology (1)**, **Mycobacteriology (2)** and so on.
* If the **Mycobacteriology results** are performed at the end of the treatment, select **Treatment evaluation** and specify the last month of the treatment. In the electronic version complete the sheet named **Mycobacteriology (end).**
* If the **Mycobacteriology results** are performed after treatment completion, select **Follow up after treatment completion** and specify for which month after the treatment completion are the results. In the electronic version complete the sheet named **Mycobacteriology (post-3)**, **Mycobacteriology (post-6)**, **Mycobacteriology (post-12)** depending on the month after treatment, the results are performed.
* **Date of specimen collection** - Indicate the day, month, and year (dd/mm/yyyy) the specimen was collected

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| Printed Clinical Evaluation Form - Mycobacteriology | Electronic Clinical Evaluation Form - Mycobacteriology |
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### Sections B and C. AFB Smear and Xpert MTB/RIF Test

* **Specimen Type**. Specify which specimen was taken. If it is not sputum, indicate (in writing) which sample was taken. Examples of other specimens include: tracheal aspirate, bronchial washing or lavage, urine, bone marrow, lymph node, cerebral spinal, fluid, lung, or pleura which are collected from various procedures (e.g., bronchoscopy, biopsy, gastric aspiration, pleural fluid aspiration).
* For each taken specimen - a separate **Clinic Evaluation Form for Mycobacteriology results** will be completed.
* **Smear Result**. Check **Negative** if the smear result was negative for AFB. Check **Positive** if the smear result was positive for AFB and indicate the smear count (e.g., scanty, 1+, 2+, 3+, or 4+). Check **No results** if the smear result has not been finalized or not done
* **Xpert MTB/RIF Test** will be performed once at diagnosis and the results will be entered only in the **Baseline Form**.
* Check which type of the cartridge was used
* How to check the results for Xpert MTB/RIF use Table 5

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| Printed Clinical Evaluation Form - Mycobacteriology | Electronic Clinical Evaluation Form - Mycobacteriology |
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Table 5. Xpert MTB/RIF test result

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Mycobacterium tuberculosis (MTB) | | | Rifampicin resistance | | |
| Detected | Not detected | No result/Invalid/Error | Detected | Not detected | Indeterminate result |
| MTB+ | **MTB-** | **Not done** | **RIF resistant** | **RIF susceptible** | **RIF indeterminate** |

### Sections D-F. Line-probe Assay, Solid and Liquid Culture

* Laboratory results must correspond to the specimen for which the date of collection was indicated
* How to check the results for **Culture** use Table 6

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| Printed Clinical Evaluation Form - Mycobacteriology | Electronic Clinical Evaluation Form - Mycobacteriology |
|  |  |

Table 6. Culture results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Negative  (0 colonies) | 1–9  <10 colonies (+) | 10–100  Colonies (++) | >100 colonies (+++) | Innumerable /  Confluent growth | Non-tuberculous mycobacteria | Contaminated |
| No grown | **MTB complex** | | | | **Other acid-fast bacilli (NTM)** | **Contaminated** |

## Clinic Evaluation Form for DST results[[3]](#footnote-3)

### Section G. Drug sensitivity test

* In printed version of p-CRFs – the information for DST results will be completed in a separate form - **Clinic Evaluation Form for DST results**.
* In the electronic version of e-CRFs – the rubric for DST results are part of **Mycobacteriology**.
* Check (*V*)the result of DST test in printed Form or select them from the drop-down list in the electronic Form.
* The DST results must correspond to the specimen for which the date of collection was indicated
* The results for single drug resistance (SDR) will contain all the results of sensitivity tests performed by different methods from the same sample

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| --- | --- |
| Printed Clinical Evaluation Form - DST | Electronic Clinical Evaluation Form - Mycobacteriology |
|  |  |

Table 7. Monitoring Schedule of Bacteriological tests

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Name | Baseline | During Treatment | | | | | | | | | | End of treatment | After treatment completion | | | |
| 2nd week | 1st month | 2nd month | 3rd month | 4th month | 5th month | 6th month | 7th month | 8th month | 9th month | 3rd month | 6th month | 9th month | 12th month |
| Smear |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Xpert |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Culture |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LPA |  |  |  | If smear- or culture-positive check for amplification of resistance | | | | | | | | | | | | |
| SLD-DST |  |  |  | If smear- or culture-positive check for amplification of resistance | | | | | | | | | | | | |

## Clinical Evaluation Form for Clinical results

### Visit Information

* Indicate **Baseline** if the evaluation is performed at the diagnosis/beginning of the treatment. If the electronic version is used, then complete the sheet named **FollowUpClinic (0).**
* If the evaluation is performed during the treatment, select **Treatment evaluation** and specify the number of months of treatment. In the electronic version of e-CRFs the sheets are named respectively the number of months **FollowUpClinic (1)**, **FollowUpClinic (2)** and so on.
* If the evaluation is performed at the end of the treatment, select **Treatment evaluation** and specify the number of months of treatment. In the electronic version complete the sheet named **FollowUpClinic (end)**.
* If the evaluation is performed after treatment completion, select Follow up after treatment completion and specify the number of months after treatment completion. In the electronic version complete the sheet named FollowUpClinic (post-3), FollowUpClinic (post-6), FollowUpClinic (post-9), FollowUpClinic (post-12) depending on the number of months after the treatment was completed.
* Periodicity of completing sections for clinical results in Clinical Evaluation Form is shown in Table 10.
* The **Severity Grade** will be assess using **Severity Grading Scale**.

|  |  |
| --- | --- |
| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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* **Clinical Evaluation Form for Clinical results** contains two parts:
  + Mandatory assessment of Adverse Events of Interest (AEIs)
  + Other Clinical Evaluation
* The frequency of filling in sections on clinical results in the form of clinical assessment is shown in Table 10.
* In the electronic e-CRFs version these two parts are incorporated in one Form.

### Part I. Mandatory assessment of the Adverse Events of Interest (AEIs)

#### Section A. Peripheral Neuropathy/paraesthesia

* The Peripheral Neuropathy (paraesthesia) should be assessed at the Baseline, monthly during the treatment, at the end of the treatment and at 12th months after treatment completion (Table 10).
* To assess the peripheral neuropathy use Table 8.
* If at least one of the answers is **Yes**, then you need to assess the Severity Grade using the **Severity Grading Scale** (Neurological Disorders).

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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Table 8. Simple Screening Tests for Peripheral Neuropathy

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Normal | Mild |  | | | | | | | | Severe | | 00 | **01** | **02** | **03** | **04** | **05** | **06** | **07** | **08** | **09** | **10** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | | Symptoms | Right | Left | | Pain, aching, or burning in feet, legs |  |  | | "Pins and needles" in feet, legs |  |  | | Numbness (lack of feeling) in feet, legs |  |  |   A user’s guide to foot screening (peripheral neuropathy) can be used <https://www.woundsinternational.com/resources/details/a-users-guide-to-foot-screening-part-1-peripheral-neuropathy>   |  |  |  | | --- | --- | --- | | The perception of vibration | Results | Score | | Vibration felt for > 10 sec |  | Normal | | Vibration felt for 6-10 sec |  | Mild loss | | Vibration felt for < 5 sec |  | Moderate loss | | No felling of vibration |  | Severe loss | |

#### Sections B-D. Myelosuppression, Hepatitis, Electrolyte disbalance

* The presence or absence of **Myelosuppression** should be assessed at the Baseline, monthly during the treatment, at the end of the treatment and at 12th months after treatment completion (Table 10).
* **Liver function tests** (Hepatitis) should be evaluated at the Baseline, monthly during the treatment and at the end of the treatment (Table 10).
* **Liver function tests** will be assessed by AST and ALT. Test for Bilirubin will be performed if AST and ALT are elevated.
* **Electrolyte Disbalance** should be assessed at the Baseline, monthly during the treatment and at the end of the treatment. (Table 10).
* **Electrolyte Disbalance** will be evaluated by Serum Potassium. If decreasing will be observed additional tests (Magnesium, Sodium, Ionized Calcium) will be performed.
* The Value must be filled in whether it has been decreased or not for **Myelosuppression** and **Electrolyte Disbalance** sections and if has been elevated for **Liver function tests** (Hepatitis) section.
* All values of the tests **should be entered** in the Clinical Evaluation Form, regardless of the normality/abnormality.
* The used unit of measurement should be indicated in the same boxes where the value is indicated.
* Use **Severity Grading Scale** to assess the Severity Grade:
  + for **Myelosuppression** use rubric **Haematology**
  + for **Hepatitis** (liver function tests)use rubric **Enzymes**
  + for **Electrolyte Disbalance** use rubric **Chemistry**

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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#### Section E-F. Optic Neuritis and Colour vision

* The Optic Neuritis and Colour vision should be assessed at the Baseline, monthly during the treatment, at the end of the treatment and at 12th months after treatment completion (Table 10).
* **Visual acuity** commonly refers to the clarity of vision, but technically rates an examinee's ability to recognize small details with precision. A typical Snellen chart is frequently used for visual acuity testing.
* A guide **Test distance vision using a Snellen chart** (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2040251/>) can be used
* Different notations of visual acuity values as decimal values (<http://www.lea-test.fi/en/vistests/instruct/contrast/lowsymbo/Snellen.pdf>) (Snellen fractions) can be used
* Use Table 9[[4]](#footnote-4) to mark the results of Visual acuity in CRFs.
* Use **Severity Grading Scale** (rubric **Eye Disorders**) to assess the Severity Grade for **Visual acuity**
* Ishihara Instruction <https://www.good-lite.com/cw3/Assets/documents/730039%2024%20Plate%20Ishihara%20Instructions-web.pdf> and book <http://www.dfisica.ubi.pt/~hgil/p.v.2/Ishihara/Ishihara.24.Plate.TEST.Book.pdf> can be used.

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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Table 9. Category for Visual Acuity[[5]](#footnote-5)

|  |  |
| --- | --- |
| Visual Acuity | Category |
| 6/6 to 6/18 | Normal vision |
| < 6/18 to > 3/60 or Worse than 6/18 but better than or equal to 3/60 | Low vision |
| <3/60 or Worse than 3/60 | No light perception (no vision) |

#### Section G. QTcF Interval

* The QTcF Interval should be assessed at the Baseline, at the 2nd week of the treatment, monthly during the treatment, at the end of the treatment and at 3rd and 6th months after treatment completion (Table 10).
* Fill in the results for QT-interval and Heart rate in respectively boxes
* Use **Severity Grading Scale** (rubric **Cardiovascular Disorders**) to assess the Severity Grade for **QTcF Interval**

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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#### Section H. Acute Kidney Injury

* The presence or absence of Acute Kidney Injury should be assessed at the Baseline, monthly during the treatment and at the end of the treatment (Table 10) using Creatinine test. The used unit of measurement should be indicated in the same boxes where the value is indicated.
* Use **Severity Grading Scale** (Chemistry rubric) to assess the Severity Grade for **Acute Kidney Injury**

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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#### Section I. Serology/Blood Tests

* All serology tests (HBsAg, HCV Ab and Glucose) are mandatory at the baseline (Table 10).
* For HBsAg and HCV Ab check Seropositive or Seronegative.
* **Glycated haemoglobin** test (HbA1c) should be performed at the Baseline if results for **Glucose test** are elevated.
* **Glycated haemoglobin** test (HbA1c) should be repeated every three months during the treatment if is elevated.
* Use **Severity Grading Scale** (Chemistry rubric) to assess the Severity Grade for **Glucose.**
* The used unit of measurement should be indicated in the same boxes where the value is indicated

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| --- | --- |
| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
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### Part II. Other Clinical Evaluation

* **Chest X-ray** will be performed at the Baseline, at 6th months of the treatment and at the end of the treatment. Mark answers in printed form or select from the drop-down list in electronic form. If **Abnormal unilateral** was selected there cannot be the answer Bilateral for the Question on Cavities. If **Normal in both** was selected, then Question on Cavities does not need to be fill in.
* Pregnancy test (for female) will be performed at the Baseline and as appropriate during the treatment.
* Body weight will be evaluated at the Baseline, at 2nd week of the treatment, monthly during the treatment, at the end of the treatment and every three months after treatment completion (Table 10).

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| Printed Clinical Evaluation Form | Electronic Clinical Evaluation Form |
|  |  |

Table 10. Periodicity of completion Sections for Clinical Results in Clinical Evaluation Form

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Name | Baseline | During Treatment | | | | | | | | | | End of treat. | After treatment completion | | | |
| 2nd week | 1st month | 2nd month | 3rd month | 4th month | 5th month | 6th month | 7th month | 8th month | 9th month | 3rd month | 6th month | 9th month | 12th month |
| Mandatory assessment of the Adverse Events of Interest | | | | | | | | | | | | | | | | |
| Peripheral Neuropathy |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Myelo-suppression |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Liver function tests (Hepatitis) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Electrolyte Disbalance |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Optic Neuritis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Colour vision |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| QTcF interval |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum creatinine |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Other Clinical Evaluation | | | | | | | | | | | | | | | | |
| Serology Blood Tests |  |  | As appropriate | | | | | | | | | |  |  |  |  |
| *HBsAg & HCab* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *HbA1c* |  |  | Repeated every 3 months if elevated | | | | | | | | | |  |  |  |  |
| *Glucose* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chest X-ray |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy Test (female) |  | If necessary | | | | | | | | | | |  |  |  |  |
| COVID-19 |  | At baseline and then only if clinically indicated | | | | | | | | | | | | | | |
| Body weight |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

# SAE and adverse event of interest reporting form

* A **Serious Adverse Event (SAE)** is any untoward occurrence in a patient given a pharmaceutical product and that at any dose:
  + Results in death
  + Is immediately life-threatening, meaning the patient was at risk of death at the time of the event. It does not apply to an event which hypothetically might have caused death if it were more severe
  + Requires inpatient hospitalization or prolongation of hospitalization. This seriousness criterion does not apply to out-patient hospital visits.
  + Results in persistent or significant disability/incapacity meaning a substantial disruption of patient’s ability to carry out normal life activities.
  + Is a congenital anomaly/birth defect in a child whose parent was exposed to a medicinal product prior to conception or during pregnancy?
  + Is considered otherwise medically significant and requires intervention to prevent one of the outcomes listed above.
* An **Adverse Event of Interest (AEI)** as defined by the Task Force of the Operational Research (OR) are the following 7 Adverse Events (AEs) occurring at any grade of severity. These are the:

|  |  |  |  |
| --- | --- | --- | --- |
| **Peripheral Neuropathy** |  | **Optic Neuritis** |  |
| **Myelosuppression** |  | **Hypokalemia** |  |
| **Prolonged QTcF Interval** |  | **Acute Kidney Injury** |  |
| **Hepatitis** |  |  |  |

Figure 3. Type of Adverse Events

* The AEI/SAE Report Form is designed to allow for a proper case assessment and appropriate reporting in accordance with the applicable international standards (ICH E2B)[[6]](#footnote-6). The available fields must be completed as much as possible with the relevant information available at the time of reporting.
* The minimal information to be reported includes: at least one **suspected drug** (study drug in a CT/ delivered drug in a program), at least one **serious adverse event or the adverse event of interest**
* Dates should be provided in the Day/Month/Year format: dd/mm/yyyy (e.g. 06/11/2020). If the exact date is not known, a partial date can be provided and the full date completed later upon follow-up (e.g. UNK/04/2021).
* When several events are signs and symptoms grouped under a single **diagnosis**, the diagnosis should preferentially be reported.

### Section A. Visit Information

* When transmitting information on the particular AEI/SAE, visit type should be selected from **Baseline**, **Treatment evaluation** or **Follow-up.**

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| --- | --- |
| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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### Section B. AEI/SAE information

* If all signs and symptoms experienced by a patient can be grouped under a single diagnosis, diagnosis should be reported by selecting one of the Adverse Event Terms under **Section B**. In the situations, where diagnosis is not feasible at time of reporting, and/or event other than listed has occurred, the other term or the signs and symptoms should be listed under **Other** in **Section B**.
* Please note that only one AE term should be selected or listed. In case of more than one adverse event another AEI/SAE reporting form should be completed separately.
* Date of event’s onset and the date of resolution of the event should be documented.
* If the event is ongoing at time of reporting, the event end date should be left blank.

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| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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* Event should be specified as **Serious** or **Non-Serious**. If the reported event is Serious, the relevant **seriousness criteria** should be selected per defined seriousness criteria definitions provided above.
* In case of fatal adverse events, if autopsy report is available, an anonymized copy should be provided.
* Severity grading is mandatory for each AEI or SAE and should be performed using the **Severity Grading Scale** (from grade 1 to 4).
* Event outcome, when known, should be documented.
  + **Fatal/died**: the event is the cause of patient’s death or one of the causes of patient’s death.
  + **Not resolved**: the event is ongoing; no improvement is observed.
  + **Resolved**: the event is fully resolved or stabilized; return to baseline condition for chronic disorders.
  + **Resolved with sequelae**: the event is resolved, but patient has some permanent condition as a consequence of the event (e.g. mild paresthesia following transient ischemic attack).
  + **Resolving**: the event is improving, lab results returned improved results, patient’s general condition is better but not fully resolved/stabilized or returned to baseline condition.
  + **Unknown**: the reporter has no information on the event’s outcome.

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| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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### Section C. Relevant laboratory tests

* Relevant tests should be listed including test name (e.g. serum blood urea nitrogen), test date, results including units and reference range in **Section C**. Full lab results can be appended to the Report Form if relevant to the case.

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| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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### Section D. TB drugs

* Up to 6 suspected drugs can be entered in **Section D**. Information on each drug including daily dose, route of administration, batch number and administration dates should be mentioned.
* By default, all administered TB drugs are to be considered as suspected and assessed for causality.
  + As a general rule, **at least all ongoing TB treatments administered at time of event** should be listed, plus **Bedaquiline** if taken within 6 months of the reported event.
  + The causality table then allows for the evaluation of the causal relationship between each TB drug and the reported event.
* In case of drug-drug interaction (DDI), all interacting drugs have to be recorded as suspected and specified under other related drugs in the causality assessment section. For information drug interactions please refer to the mSTR clinical guideline, or use the MedScape drug checker at <https://reference.medscape.com/drug-interactionchecker>

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| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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* Action taken following the occurrence of the AEI/SAE should be documented for each drug using the possibilities presented in the table. Action taken is considered not applicable, if the drug was already stopped at time of event’s occurrence for other reason.
* Information on the appearance/disappearance of the symptoms following changes in drug administration (discontinuation, dose reduction, drug reintroduction, full dose reintroduction) should be documented for each drug. The first question is so called **De-challenge** and the second question refers to the so-called **De-challenge** in PV.

#### Causality assessment

* The reporter (the Investigator or TB doctor) should determine for each AEI/SAE the causal relationship with each suspected drug using the categories defined as follows in **Question D5**:
* **Related**: there is a reasonable possibility that the AEI/SAE may be related to the drug(s). Elements in favor of a reasonable causal relationship include (but are not limited to):
  + A favorable temporal relationship,
  + A positive dechallenge, meaning symptoms are receding when the drug(s) is withdrawn or the dose is reduced,
  + A positive rechallenge, meaning symptoms are reappearing when the drug(s) is reintroduced or the full dose is re-administered,
  + A plausible pharmacological/biological mechanism of action (whether proven or potential),
  + Previous knowledge of similar reaction with the drug(s), or
  + No other evident cause (e.g. previous disease, other drugs).
* **Not Related**: there is **no** reasonable possibility that the SAE is related to the drug(s). This implies that there is a plausible alternative cause for the SAE that better explains the occurrence of the SAE or that highly confounds the causal relationship between the drug(s) and the SAE.
* In the situations where there is insufficient information to evaluate the causal relationship, ‘related’ should be conservatively selected by default.
* Any other causal factor including pre-existing conditions, risk factors, trial procedure, etc., should be mentioned as ‘free-text’ field. Drug(s) Interacting with the related TB drug(s) should be specified in the ‘Other drugs’ field.

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| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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### Section E. Concomitant medications (Including the drugs taken within 2 weeks prior to the event and drugs with the long half file)

The **Section E** aims at capturing all relevant concomitant drugs, including herbals/complements or self-medications.

|  |  |
| --- | --- |
| Printed AEI and SAE Report Form | Electronic AEI and SAE Report Form |
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#### Special situation – Parent/Child Foetus reports

* Any SAE occurring in the mother or the foetus/child has to be recorded using an AEI/SAE Report Form.
* In the event of an SAE in the mother (e.g. late miscarriage), the SAE Report Form should mention the mother as the patient and the serious mother’s event (e.g. late miscarriage) as the SAE. In the event of an SAE in the foetus/child (e.g. spina bifida), the SAE Report Form should mention the foetus/child as the patient and the serious foetus/child event (e.g. spina bifida) as the SAE.
* If both the mother and the foetus/child experienced SAEs (e.g. vaginal hemorrhage and foetal distress), 2 SAE Report Forms should be completed (1 for vaginal hemorrhage in the mother and 1 for foetal distress in the baby).

# Treatment completion form

* Treatment completion Form must be completed after treatment has been stopped. This can be at the end of the treatment or earlier depending on the reasons for discontinuation of TB treatment
* In addition, Clinical evaluation Forms (Clinical evaluation including evaluation for any adverse events that may have occurred, X-Ray, Mycobacteriology and DST) should be completed as appropriate (Table 1)

### Section A. Study Treatment Completion

* **Total number of study treatment doses** – number of doses taken by patient during the study period
* The **completed study treatment** will be considered if:
  + the patient took 273 daily doses in the period of 39 weeks (39 weeks x 7 days = 273 days/doses). According to Study protocol, in some special cases, it is allowed to take 273 doses up to 43 weeks. If patient took all 273 doses, check **Yes** for Question A2.
  + If the patient took less or more doses than 273, check **No** for Question A2 on study treatment completion

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| Printed Treatment Completion Form | Electronic Treatment Completion Form |
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| --- |
| NB: If the patient was not bacteriologically confirmed but had clinical TB and had been in close contact with an index-patient with active RR/MDR-TB, please elaborate under comments (record resistance profile of the index-patient).  *Comments*: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ *Comments*: |

* **Record resistance profile of the index-patient, if** the patient was not bacteriologically confirmed, but had clinical TB and had been in close contact with an **index-patient with active** RR/MDR-TB

### Section B. Reason for Not Completing the Study Treatment as Per Protocol

* **Section B** will be completed only in cases when patient will not complete study treatment according to protocol
* From 10 reasons listed one of them should be selected. Use the specification from Table 11.
* If one of the answer **Participant determined ineligible after enrolment** or **Physician judged it no longer advisable for participant to continue the study treatment** or **Failure to complete required number of study treatment doses within 43 weeks** or **Other**, the reasons will be specified in written
* If patient took more than 273 doses, check **Other** and specify the reasons in written.

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| Printed Treatment Completion Form | Electronic Treatment Completion Form |
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Table 11. Reasons for Not Completing the Study Treatment

|  |  |
| --- | --- |
| Reasons | Specification |
| Participant died | The patient died during treatment for any reason |
| Participant has *M. tuberculosis* resistant to at least one drug in the study regimen | For patients started on treatment based on fluoroquinolone susceptibility by molecular test, whose culture-based second-line DST showing fluoroquinolone resistance come after treatment has started. If resistance to drugs in the mSTR is discovered after treatment is initiated |
| Participant withdrew consent | The participant gave his/her consent to be enrolled in the Study, started treatment (or was assigned a treatment regimen), but after withdrew his/her consent but started TB treatment out of study |
| Participant determined ineligible after enrolment | It will be determined based on Non-invasive and Invasive Exclusion Criteria if they were not correctly applied something were missed during the Screening |
| Study treatment not started | The participant was eligible, but for some reasons, the treatment was not initiated (e.g. lack of drugs etc.) |
| Participant developed adverse events requiring permanent discontinuation of the treatment regimen | The participant developed adverse events and the mSTR treatment cannot be continued |
| Physician judged it no longer advisable for participant to continue the study treatment | Other reasons from the physician side or medical that do not fall within the other descriptions |
| Failure to complete required number of study treatment doses within 43 weeks | That refers to the number of doses |
| Lost contact with participant | The connection with the participant was lost after several attempts to be contacted |
| Other | Other reasons not listed |

### Section C. Interim Treatment Outcome (Sputum Culture Conversion)

* Date of conversion is considered the date when the specimen was taken. To appreciate Conversion, use the definition in Table 12

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| Printed Treatment Completion Form | Electronic Treatment Completion Form |
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Table 12. Definitions of conversion and reversion

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| --- | --- |
| Name | Definition |
| Conversion (to negative) | Culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion. |
| Reversion (to positive) | Culture is considered to have reverted to positive when after an initial conversion two consecutive cultures taken at least 30 days apart are found to be positive. |

### Section D. End of Treatment Outcome

* Date of end of treatment outcome should be the date when participant took the last doses for TB treatment
* Check (in printed version) or select from drop-down list (in electronic version) the outcome. Use the definitions from Table 13.
* If Withdrawn was marked the reason should be specified in written.

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| Printed Treatment Completion Form | Electronic Treatment Completion Form |
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Table 13. Definitions of Treatment Outcomes

|  |  |
| --- | --- |
| Name | Definition |
| Cured | A patient with bacteriologically confirmed RR-TB who has completed treatment as recommended by Study Protocol without evidence of failure AND at least three or more consecutive cultures taken at least 30 days apart are negative at the end of treatment. |
| Treatment Completed | Treatment completed as recommended by Study Protocol without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative at the end of treatment |
| Treatment Failed | Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:   * lack of sputum culture conversion after 4 months of treatment, or * bacteriological reversion of sputum culture after 5 months of treatment in a patient with previous culture conversion to negative, or * evidence of additional acquired resistance to fluoroquinolones, Bdq, Dlm, Lzd, Cfz, or adverse drug reactions (leading to the change of at least two anti-TB drugs in the regimen) |
| Died | A patient who dies for any reason during the course of treatment |
| Lost to follow-up | A patient whose treatment was interrupted for 2 consecutive months or more |
| Withdrawn | A patient is taken off the mSTR for any reason other than treatment Failure or Lost to follow-up:   * baseline resistance to the mSTR regimen drugs is discovered after treatment was initiated * withdrawn patient informed consent * transferred out to another treatment unit without supervision or contact with patient was lost * not evaluated * or other argumentative reasons   and referred to the PMDT program for routine care |

# Follow-up completion form

* **Follow-up Completion Form** will be filled-in for all patients enrolled to study, unless the patient died during the treatment, was withdrawn due to *M. tuberculosis* resistance to at least one drug at the mSTR or patient withdrew consent
* In addition, Clinical evaluation Forms (Clinical evaluation including evaluation for any adverse events that may have occurred, X-Ray, Mycobacteriology and DST) should be completed as appropriate (Table 1).

### Sections A-D. Follow-up after ending the study treatment

* **Follow-up Form** should be completed at 3, 6, 9 and 12 months after ending the Study treatment
* **TB recurrence** (definition from Study protocol) - cure or treatment completion with two consecutive positive cultures during posttreatment follow-up, or one positive culture with clinical signs and symptoms or radiographic deterioration, but without genotyping information on baseline and recurrent strain.
* Check **Not evaluated** if the patient has not been evaluated at the indicated period.

|  |  |
| --- | --- |
| Printed Treatment Completion Form | Electronic Treatment Completion Form |
|  |  |

### Section Study Follow-up Completion

* Check Yes if participant complete 12-months study follow-up
* If participant did not complete 12-months study follow-up select one of the reasons, use Table 14

|  |  |
| --- | --- |
| Printed Treatment Completion Form | Electronic Treatment Completion Form |
|  |  |

Table 14. Reasons for Not Completing 12 months Follow-up

|  |  |
| --- | --- |
| Name | Definition |
| Lost to follow-up after treatment | A patient who is lost to follow-up during the course of 12 months follow-up period |
| Withdrawn after treatment | A patient withdrew informed consent or other argumentative reasons |
| Died after treatment | A patient who dies for any reason during the course of treatment and 12 months follow-up period |

* If Participant Died during the 12 months Follow-up, complete the information concerning death
* To complete information concerning death use information from Medical Certification of Death

|  |  |
| --- | --- |
| Printed Treatment Completion Form | Electronic Treatment Completion Form |
|  |  |

**Annex**

## Assignment of study participant code

## Decentralized data entry

### Site enrollment

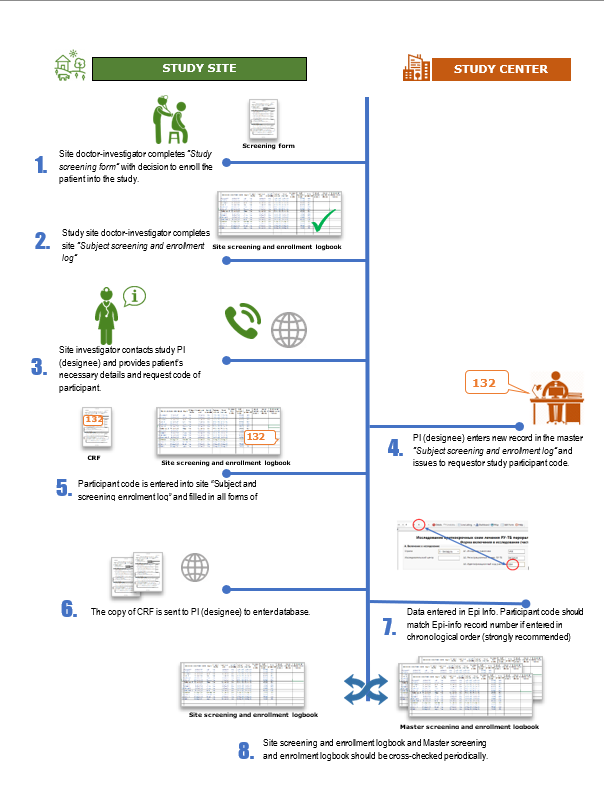
* Site doctor-investigator completes **Study Screening Form** with decision to enroll the patient into the study.
* Study site doctor-investigator completes site **Subject Screening and Enrollment Logbook** and assign the participant code. This is composite code consisting from one-digit site code and 3-digit subject code, indicating the consecutive number of the patient in the **Subject Screening and Enrollment Logbook**.
* Participant code is entered in CRFs.
* CRFs is entered into Epi-Info. Participant code should match to the record number generated by EpiInfo.
* Site investigator within 24 hours contacts by e-mail to Principal Investigator (designee) and provides the details of newly enrolled subject (participant code, initials and date of birth).
* Principal Investigator (designee) records the details in the **Subject Screening and Enrollment Master Logbook**.
* The same participant code shall not be assigned to another study participant.

### Enrollment at the referral hospital

* Doctor-investigator at the referral hospital completes **Study Screening Form** with decision to enroll the patient into the study.
* Doctor-investigator shall check with the patient where he/she is planning to complete the treatment after the discharge from the referral hospital.
* Doctor-investigator contacts the site investigator of the from the catchment area indicated by patients, provides the details and agrees the participant code.
* Site investigator complete the participant code in the site **Subject Screening and Enrollment Logbook**.
* Principal Investigator (PI, designee) records the patient and his details in the **Subject Screening and Enrollment Master Log**.
* Partially completed CRF is sent to site investigation site and entered at the site database.
* At the end of the month Principal Investigator and site investigators cross-check Master and site log-books to ensure that both of them are complete and match to each other.

## Centralized data entry

* Site doctor-investigator completes study screening form with decision to enroll the patient into the study.
* Study site doctor-investigator completes site **Subject Screening and Enrollment Logbook.**
* Site investigator contacts study PI (designee) and provides patient necessary details and request code of participant.
* PI (designee) enters new record in the master **Subject Screening and Enrollment Logbook** and issues to requestor new study participant code.
* Participant code is entered into site **Subject and Screening Enrolment Logbook** and filled in all CRFs.
* Available data is entered into Epi-Info by PI (designee). Upon availability of the data, the rest of data is entered into database.
* Participant code should match to the record number generated by EpiInfo. The same participant code shall not be assigned to another study participant.
* The copy of CRF and monitoring data are sent to PI (designee) to enter into the database. In addition, the database could be completed during the site monitoring visits.



1. Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205. [↑](#footnote-ref-1)
2. Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. Journal of Chronic Diseases; 1960:11:7-33. [↑](#footnote-ref-2)
3. If a patient was not bacteriologically confirmed, but had clinical TB and had been in close contact with an index-patient with active RR/MDR-TB, please, reflect index-patient resistance profile in the relevant comment section of Treatment Completion Form [↑](#footnote-ref-3)
4. The classification will be updated after CRF are tested under field conditions. [↑](#footnote-ref-4)
5. https://apps.who.int/iris/bitstream/handle/10665/58719/WHO-PBL-95.48-book1-eng.pdf?sequence=9&isAllowed=y [↑](#footnote-ref-5)
6. ICH E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 27 October 1994.

   ICH E2B(R2) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. 5 February 2001. [↑](#footnote-ref-6)