**Completion Guide for Operational Research Forms for All-Oral Shorter MDR-TB Regimens**

*Instructions for the forms in Package 1*

Draft Version 1.0

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# Form 1: Baseline Assessment

**REGISTRATION AND DEMOGRAPHICS**

* **EMR ID#** is a patient identifier number. The EMR ID# can be assigned by the project or automatically by the EMR. It is created as follows: Country ISO code (standard 3 letters) – Registration facility code (3 numbers assigned to the facility) – Consecutive patient code (5 numbers assigned to each patient, none repeating per registration facility). For example:
	+ Peru - facility 1 - patient 1: PER-001-00001
	+ Peru - facility 1 - patient 2: PER-001-00002
	+ Peru - facility 2 - patient 1: PER-002-00001
	+ Lesotho - facility 1 - patient 1: LSO-001-00001
* **Date of Birth:** Complete any information available from the patient. If day or month of birth are unknown but the year of birth is known, provide 01 for date and July for month. For example:
	+ Patient birth year (1980), month and day unknown: 01/Jul/1980.
	+ Patient birth year (1981) and month (Sep) known, day unknown: 01/Sep/1981.
* **Age (years):** Complete according to information provided for "Date of Birth" or to the information provided by the patient if the date of birth is unknown. Age or Date of Birth will be auto-calculated on the EMR depending on which field is updated on the form. If both are provided Date of Birth should be used for EMR and patient tracking.
* **Registration Number**: This is a treatment identifier. This number **MUST** be entered for all patients on treatment. It identifies the specific course of treatment for each particular patient. A patient identified by an EMR ID# could have more than one registration number, each one identifying a separate course of treatment within the EMR.
	+ In some countries, it is standard practice to assign a unique number when a patient enters treatment. This number can be used here, but it must be unique to each course of treatment.
	+ If it is not standard practice based on local or government regulations, a systematic numbering system should be developed internally. For example, this could be created by appending two digits to the EMR ID. These last two digits will represent the order of treatment, starting from 01 for all the patients. For example:
		- PER-001-00001-01 (Peru, Site #1, Patient #1, Treatment #1).
		- PER-001-00001-02 (Peru, Site #1, Patient #1, Treatment #2).

**SOCIAL HISTORY**

The following question regarding social history is MANDATORY:

* **Has the patient every been in prison?** Mark YES if patient reports that presently or at any time in his/her life he/she has been in prison.
	+ **If YES**: Mark CURRENTLY if patient reports being imprisoned currently.
		- Mark IN THE PAST if patient reports that he/she has been imprisoned sometime in the past (and is no longer imprisoned).

The following questions regarding social history are OPTIONAL:

* **Does the patient drink alcohol?**
	+ Mark YES if patient reports consuming alcohol currently.
	+ Mark NO if the patient does not consume alcohol currently.
	+ Mark UNKNOWN if the patient’s alcohol consumption status is unclear.
		- **If YES: How many standard alcoholic drinks does the patient drink per week?** One alcoholic drink as defined by the National Institute of Alcohol Abuse and Alcoholism (NIAAA):



* **Does the patient smoke at least 1 cigarette per day?**
	+ Mark YES if the patient smokes an estimated 1 cigarette per day.
	+ Mark NO if the patient does not report smoking.
	+ Mark UNKNOWN if the patient’s smoking status is unclear.
* **Has the patient used intravenous drugs in the past year?**
	+ Mark YES if the patient reports having used intravenous drugs at any time in the past year.
	+ Mark NO if the patient reports that they have not used intravenous drugs in the past year.
	+ Mark UNKNOWN if the patient’s intravenous drug use within the past year is unclear.
* **Has the patient used non-prescribed, non-injectable drugs in the past year?**
	+ Mark YES if the patient reports having used any non-injectable drugs, including cannabis, cocaine, prescription stimulants without a prescription, methamphetamine, inhalants, sedatives, hallucinogens, or street opioids, in the past year *without* a prescription.
	+ Mark NO if the patient reports that they have not used any of these drugs in the past year, or if they report having used any of these drugs *with* a prescription in the past year.
	+ Mark UNKNOWN if the status of the patient’s use of non-prescribed, non-injectable drugs is unclear.

**DRUGS TAKEN FOR GREATER THAN ONE MONTH**

* Circle ALL drugs in Groups 1, 2, 3, 4 and 5 that the patient has previously taken for greater than one (1) months’ time.
* If the patient has taken any anti-tuberculosis drugs for greater than one (1) month that are not listed in the table, write in the name(s) of the drug(s) in the “Other, specify” section.

**PAST MEDICAL HISTORY (CO-MORBIDITIES)**

*A trained doctor is required to collect this information.*

In general, information included in this section can be collected by asking the patient. In some cases, prior medical records for the patient may be available for review. Only current co-morbidities should be indicated in this section.

Responses for the following co-morbidities are MANDATORY:

* **HIV serostatus:**
	+ Mark POSITIVE if the patient has been diagnosed with HIV.
		- If POSITIVE:
			* Write the date on which the patient was diagnosed with HIV.
			* Write the last CD4 count, or mark UNKNOWN if this information is unclear or unavailable.
			* Write the last RNA viral load, or mark UNKNOWN if this information is unclear or unavailable.
			* Write the date that the patient initiated ARVs and indicate whether the patient is currently taking ARV treatment (mark YES, NO or UNKNOWN).
				+ If the patient is currently taking ARVs, write the patient’s current ARV regimen.
	+ Mark NEGATIVE if the patient presents the results of a negative HIV test completed within the preceding three (3) months of the current visit date.
	+ Mark UNKNOWN if there is no written documentation or the latest negative test was done more than three (3) months prior the date of the current visit.
		- In this situation, the physician should ask for a new HIV test to be completed.
* **Diabetes (type I or II)**: Mark YES if the patient has been diagnosed with diabetes.
	+ If YES, write the latest documented HbA1c. Leave this field blank if the latest HbA1c is unknown.
* **Confirmed Hepatitis B**: Mark YES only if written documentation or test results are available to confirm diagnosis. A positive hepatitis B surface antigen (HBsAg) test is sufficient for a diagnosis of chronic hepatitis B infection.
* **Confirmed Hepatitis C:** Mark YES only if written documentation or test results are available to confirm diagnosis. A positive hepatitis C antibody test is sufficient for a diagnosis of hepatitis C infection.

Responses for the following condition is OPTIONAL:

* **Existing Neuropathy**: Mark YES if the patient has existing neuropathy.
	+ If YES, mark the appropriate neuropathy grade (1-4) at the time of the visit. Please see the *Clinical Guide for All-Oral Shorter MDR-TB Regimens* for detailed information on the severity grading scale\*.

\**Please note that this guide references severity grading scale developed by the NIAID Division of Microbiology and Infectious Diseases. If there is another scale used by your country, please use that one*.

**CASE DEFINITION**

*A trained clinician (doctor or nurse) should collect this information.*

The following questions refer to the case definition at the time of the treatment start date.

* **WHO registration group:** Patients are assigned to a registration group based on their treatment history at the treatment start date (see Treatment Initiation section for an explanation of the treatment start date). Mark the appropriate group according to definitions below:
	+ **New:** A patient who has received no or less than one month of anti-TB treatment. Patients are considered “NEW” if DST was performed within one month of the start of treatment, even if they have received more than one month of first-line drug treatment for TB by the time that DST results became available and they were registered for second-line TB treatment.
	+ **Relapse:** A patient who was previously treated for TB and whose most recent treatment outcome was CURED or TREATMENT COMPLETED, and who is subsequently diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
	+ **Treatment after loss to follow-up:** A patient who has previously been treated for TB and was declared LOST TO FOLLOW-UP at the end of the most recent course of treatment.
	+ **Treatment after failure:** A patient who has received first-line or second-line treatment for TB and in whom treatment has failed.
	+ **Other previously treated patients:** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.
* **History of past anti-TB drug use:** Mark the most suitable option based on the anti-TB regimen(s) received in the past for one month or more. "In the past" means before the treatment start date of this MDR-TB treatment—see below Treatment Start section for how to find the treatment start date.
	+ For example, in the case that new TB drugs are being started to reinforce an empiric regimen after second-line DST results show pre-XDR or XDR, "in the past" would refer to before the empiric regimen was started, not when the new TB drugs are started.
	+ If the patient has never been treated for TB in the past, do not mark any box. The EMR will automatically skip this question if NEW is marked in the previous question.
* **Disease site:** Mark the appropriate type of TB: pulmonary or extrapulmonary.
	+ Extrapulmonary TB includes lymphatic, pleural, abdominal, etc. If extrapulmonary TB is marked, please specify the exact site of disease.
	+ If the patient has both pulmonary and extrapulmonary TB, mark both boxes.
* **Detection of *M. tuberculosis*?**
	+ Mark BACTERIOLOGICALLY CONFIRMED if there is an available laboratory test positive for *M. tuberculosis*. Acceptable laboratory tests are listed in the following question.
	+ Mark NOT CONFIRMED, CLINICALLY DIAGNOSED if the patient has never had a laboratory test positive for *M. tuberculosis*.
* **What was the method of confirmation?** All of the listed methods in this section are common and acceptable methods of detection of *M. tuberculosis*. Mark all options that apply.
	+ If ‘OTHER TEST’ is marked, please specify the method used.
* **Drug resistance and subclassification of drug-resistance:** If there are several DST results, use one that reflects the pattern of resistance on the treatment start date listed in the Treatment Card.
* **Subclassification of drug resistance profile:** Select only ONE (1) profile from the list. Definitions of certain subclassifications are as follow:
	+ **Confirmed MDR:** there is a lab result that shows resistance to at least both isoniazid and rifampicin.
	+ **Confirmed pre-XDR (FQ):** there is a lab result that shows resistance to any fluoroquinolone, in addition to multidrug resistance.
	+ **Confirmed pre-XDR (Inj):** there is a lab result that shows resistance to any of the three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
	+ **Confirmed XDR:** there is a lab test that shows resistance to any fluoroquinolone, and at least one of the three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
* **MDR-TB or rifampicin resistance diagnosis date:** This is first date that the patient was diagnosed with MDR-TB.
	+ For patients that have a confirmed diagnosis of rifampicin resistance, write the date of the first such DST result.
		- If the patient has multiple DST results showing MDR, pre-XDR or XDR, write the date of the first such test.
		- An Xpert MTB/RIF positive for rifampicin resistance is often considered presumptive evidence of MDR. If an Xpert MTB/RIF positive rifampicin resistance was followed by one more complete DST showing MDR, write the date of the Xpert MTB/RIF test.
	+ For patients who were treated with an MDR regimen without bacteriological confirmation, write the first date that the patient received the MDR regimen.
		- For example, if a patient was started empirically on an MDR regimen after failure of first-line treatment but DST was not done, write the date that the MDR regimen was started.
		- This includes patients treated because they were household contacts of MDR-TB patients, and patients who could not tolerate any first-line TB drugs due to severe allergic reaction.

**CONSENT**

* **Has the Consent Form been explained and signed?**
	+ Mark YES if the patient had the consent form explained to them by study personnel and subsequently signed the study consent form.
	+ Mark NO if consent was not obtained for any reason, including that the patient refused to sign the consent form.
	+ Mark PENDING TO BE ASKED if the patient has not yet been presented with the consent form.
	+ Mark “Other” if it is not possible for the patient to sign the consent form for any reason, including that the patient died, was lost to follow-up, completed treatment, or transferred to another facility before consent could be given.

**TREATMENT START**

* **Treatment start date**:
	+ Report the treatment start date accurately. All patients enrolled in an all oral short treatment will start a new treatment regimen.
		- * .
* **In which facility did the patient start their treatment?** This is the facility in which the patient starts treatment. NOTE: this can differ from the registration facility which is the facility where the patient is registered and is not necessarily the facility where the patient receives treatment. Each country will have specific designated registration and treatment facilities. These facilities will have a code in the EMR.
	+ **Facility Patient ID #:** This ID number is a patient specific number given by some facilities (usually hospitals) where the patient is being evaluated. For example, if the patient is being evaluated in the hospital, write the number of the hospital chart. If there is no facility patient ID #, leave this field blank. This is not the registration number that is unique throughout the treatment irrespective of the treating facility.

# Form 2a: Monthly Clinical Examination Log

*Any trained study personnel can collect this information.*

This form should be filled out during the baseline visit and on a monthly basis while the patient is currently taking treatment.

* **Date**: This is the date on which the visit takes place.
* **Month of treatment**: Write in which month of treatment the patient is currently (e.g. Month 3). Baseline should be indicated as “Month 0”.

**CLINICAL EXAMINATION**

* The following tests should be conducted at baseline AND at least on a monthly basis while the patient is taking a linezolid-containing regimen:
	+ **BPNS, right and left** **sides**: Write the appropriate, subjective Brief Peripheral Neuropathy Score for both the right and left legs according to the scale outlined in the *Clinical Guide for All-Oral Shorter MDR-TB Regimens*.
		- 0 = normal
		- 1 – 10 = abnormal
	+ **Visual Acuity, right and left eyes**: Write the appropriate visual acuity score for both the right and left eyes taken at each visit.
		- Visual acuity is conducted for using a Snellen chart of equivalent. Be sure to indicate the correct scale that corresponds to the vision chart used in your country (Snellen, Golovin-Sivstev, etc.).
	+ **Ishihara Test, right and left eyes**: Write how many plates out of 11 the patient is able to read using both the right and left eyes.
* **ECG, QTcF:** An ECG should be taken for ALL patients at least on a monthly basis while the patient is taking treatment.
	+ Calculate the QTcF interval for each month using the Fridericia formula. Detailed instructions on how to calculate the QTcF using the Fridericia formula is outlined in the *Clinical Guide for All-Oral Shorter MDR-TB Regimens.*
* **Other**: Indicate any other tests conducted during each visit that are not explicitly listed in the log.

# Form 2b: Laboratory Results Log

*Any trained study personnel can collect this information.*

The primary source for data captured in this form will differ from site to site. Most sites will capture data directly from the printed report received from the laboratory that performed the test.

* **Collection date**: This is the date on which samples were collected .
* **Month of treatment**: Write in which month of treatment the patient is currently (e.g. Month 3). Baseline should be indicated as “Month 0”.
* Enter all applicable results from the lab report in the box that corresponds to the appropriate visit column/date.
	+ Make sure that the units for each test correspond with the units stated in the form. If the results taken from the lab results report are not in the correct units, convert the numbers to the appropriate units stated in the form.
* **Baseline and at least monthly**: All tests included in this section should be conducted at baseline and on a monthly basis once treatment has been started. These tests include:
	+ Hemoglobin (Hb)\*
	+ White blood cell count (WBC)\*
	+ Platelets\*
	+ ALT
	+ AST

***\*For patients that are taking a linezolid-containing regimen, Hb, WBC and platelets should be taken at least monthly***.

* **Baseline and if clinically indicated**: Tests included in this section should be conducted at baseline and may be conducted at any time after treatment has been started if clinically indicated. These tests include:
	+ Creatinine
	+ Potassium
	+ Pregnancy testing
* **Other baseline or clinically indicated**: Tests included in this section should be conducted at any time during treatment if clinically indicated. It is not mandatory to conduct these tests on a monthly basis:
	+ HbA1c
	+ Albumin
	+ Other
		- For OTHER tests that are not listed in this form, write the test name in the blank fields provided. Include the result(s) and the appropriate unit.

# Form 3: Severe Adverse Event Form

*A trained doctor is required to collect this information. Each country will determine whether severe adverse events will be collected for operational research purposes. The following instructions serve as general guidelines for filling out a severe adverse event 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 the 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: other situation such as important medical events that may not immediately be life threatening or result in death or hospitalization, but jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above, should also be considered serious (e.g. treatment in an emergency room for allergic bronchospasm). Medical judgement should always prevail in the assessment of medically significant events.

Many NTPs require any SAE as defined above to be reported within a specific timeframe, typically within 24 hours of awareness, to a designated pharmacovigilance (PV) unit. If appropriate, countries participating in operational research on the all-oral, short treatment regimens may use a SAE Report Form similar to the template provided here to report these SAEs.

In some studies or programs, other types of events may require notification (e.g. AEs of special interest, medication errors). When no dedicated form is planned per study protocol or the program’s PV guidelines, the SAE Report Form may be used for this purpose.

**GENERAL INSTRUCTIONS**

The SAE Report Form is designed to allow for a proper case assessment and appropriate reporting in accordance with the applicable international standards (ICH E2B). 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:

1. Name of any identifier of a reporter (e.g. a function such as ‘nurse’ is acceptable),
2. Any identifier of the patient (e.g. patient number, initials, date of birth),
3. At least one suspected drug (study drug in a study/delivered drug in a program),
4. At least one serious adverse event (or overdose or any other safety information to be collected as per study protocol/program’s PV guideline).

As a general medical guideline, the following points should be considered:

* When several events are signs and symptoms grouped under a single **diagnosis**, the diagnosis should preferentially be reported. Relevant signs and symptoms can be described in the free-text field allowing for the event’s description.
* In the case of **several reportable events** occurred at the same time in a single patient, it is upon the Investigator’s/physician’s judgement to report these on one SAE Report Form or on separate SAE Report Forms.
	+ Example 1: a patient is hospitalized with concomitant fever and nausea of unknown origin 🡪 it is advised to use a single SAE Report Form mentioning fever and nausea.
	+ Example 2: a patient experienced a life-threatening anaphylactic shock during drug infusion and his lab data revealed a grade 4 thrombocytopenia 🡪 it is advised to report anaphylactic shock on one SAE Report Form and to report the grade 4 thrombocytopenia on a second, separate SAE Report Form.
* Anonymized copies of relevant hospital records (e.g. discharge summary), additional lab results, list of concomitant drugs or therapies, may be requested as attachments. In addition, for fatal cases, an autopsy report if available should be provided.

The seriousness criteria for each reported event should be selected as appropriate (see above definitions). In some studies/programs/therapeutic areas, further specifications are added; the study protocol or program’s PV guideline should be strictly followed (e.g. in some studies, hospitalization for elective surgery is not serious).

* In the case of fatal adverse events, death date and autopsy status (yes/no) should be documented. If an autopsy report is available, an anonymized copy should be provided.
* Hospitalization dates should be documented. In the case that the patient was hospitalized several times for the same SAE, the Event Description section should be used to capture all admission and discharge dates.
* The Event Description section should additionally be used to add details such as description of the type of disability/incapacity (if applicable).
* For overdoses without associated SAEs or for other non-serious events requiring expedited reporting (e.g. AEs of special interest) as specified in the study protocol or program’s PV guideline, the box “Non-serious reportable information” should be marked.

**SEVERITY**

Severity grading is mandatory for each SAE and should be performed using the available severity grading scale (from grade 1 to 4). Generally, details on the severity grading system are available in the study protocol or program’s PV guidelines.

**SAE OUTCOME**

Event outcome, when known, should be documented. For events considered resolved with sequelae, a description of these is expected in the Event Description section.

* **Fatal**: the event is the cause of the patient’s death or one of the causes of the patient’s death.
* **Not resolved**: the event is ongoing, no improvement is observed.
* **Resolved**: the event is fully resolved or stabilized; a return to baseline condition for chronic disorders is observed.
* **Resolved with sequelae**: the event is resolved, but the patient has some permanent condition as a consequence of the event (e.g. mild paraesthesia following transient ischaemic attack).
* **Resolving**: the event is improving, with lab results indicating improved results. The 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.

**CAUSAL FACTORS**

The reporter (the Investigator or co-Investigator in studies) should determine for each SAE the causal relationship with each suspected drug using the categories defined as follows:

* **Related**: there is a reasonable possibility that the 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 situations where there is insufficient information to evaluate the causal relationship, RELATED should be conservatively selected by default.

Any other causal factor(s) including pre-existing conditions, risk factors, trial procedure, etc. should be mentioned as ‘free text’.

# Form 4: End of Treatment Outcome Form

This form is filled out whenever the patient ends treatment and there is an outcome, including:

* When a patient dies;
* When a patient is judged to be lost to follow-up;
* When it is decided to stop treatment because of treatment failure; or
* On the last day of treatment in the case of when a patient is cured or completes treatment.
* **Date of the end of treatment.** This is the last day the patient received treatment. This date is always relevant no matter what the treatment outcome is.
	+ If the patient **died**, write the last day that the patient ingested treatment; this may not be the same date as the date of death.
	+ If the patient was **lost to follow-up**, write the last known date that the patient ingested treatment before becoming lost to follow-up.
	+ If the patient is deemed to be **cured**, write the date on which the patient was declared as cured.
* **Date of the end of treatment decision.** This is the date that the outcome was decided. This date is often after the date of the end of treatment.
	+ For example, a patient will be declared CURED if all culture results are negative, but this cannot be known until several weeks or months after the patient has finished treatment.

**END OF TREATMENT OUTCOME**

Once a patient stops treatment, ONE (1) of the following end of treatment outcomes should be selected:

* **Cured**. A patient is assigned an outcome of CURED if treatment is completed as recommended by the national policy without evidence of failure AND three (3) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase\* of treatment.
* **Completed**. A patient is assigned an outcome of treatment COMPLETED if treatment is completed as recommended by the national policy without evidence of failure BUT there is no record that three (3) or more consecutive cultures taken at least 30 days apart are negative after the intensive phase\* of treatment.
* **Died**. A patient is assigned an outcome of DIED if death occurs before treatment is completed.
	+ If the outcome is DIED,
		- Write the date of death, which may not be the same as the last day that the patient received treatment.
		- Mark ONE (1) suspected primary cause of death:
			* TB is immediate cause of death
			* TB is contributing cause of death
			* Surgery-related death
				+ If this choice is selected, write the type of surgery the patient underwent
			* Cause other than TB
				+ If this choice is selected, write the suspected cause of death
			* Cause related to TB treatment
				+ If this choice is selected, write the suspected cause of death
			* Unknown
* **Failed**. A patient is assigned an outcome of FAILED if treatment is terminated or it is necessary to permanently change at least two anti-TB drugs in the treatment regimen.
	+ If the outcome is FAILED, choose the reason(s) for treatment failure. Multiple reasons for treatment failure may be marked:
		- Lack of conversion\*
		- Bacteriological reversion after conversion to negative
		- Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs
		- Adverse drug reactions
		- Other. Please specify any OTHER reasons in the indicated space.
* **Lost to follow-up**. A patient is assigned an outcome of LOST TO FOLLOW-UP if treatment was interrupted for two (2) consecutive months or more.
	+ If the outcome is LOST TO FOLLOW-UP, choose the reason(s) for why the patient’s treatment was interrupted. Multiple reasons for why the patient became lost to follow-up may be marked:
		- Adverse events
		- Patient refused follow-up
		- Substance abuse
		- Social problem: family, financial, complex social situation
		- Left region, country
		- No confidence in treatment
		- Unknown
		- Other. Please specify any OTHER reasons in the indicated space.
* **Not evaluated**. A patient is assigned an outcome of NOT EVALUATED when no treatment outcome is assigned. This includes cases that transferred to another treatment unit and whose treatment outcome is unknown.
	+ If the patient transferred to another facility, write the name of the health center to which the patient was transferred and the district in which the health center is located.
	+ If the patient was not transferred to another facility but is still assigned an outcome of NOT EVALUATED, indicate the reason that this patient was assigned this outcome.

\*The intensive phase of an all-oral shorter MDR-TB regimen is generally considered to be a minimum of 4 months (depending on the protocol).

* At 4 months, the patient has not culture converted, the patient should be reviewed for clinical progress (improved symptoms, increase in weight), reduction in bacillary load on smear microscopy, adherence and radiology (signs of cavities).
	+ If there is any doubt of clinical progress then failure should be declared at 4 months and a new longer individual regimen designed. A full analysis of the patient’s resistance profile, adherence, comorbidities, extensiveness of disease and other factors that could affect treatment effectiveness should be performed.
	+ If good progress at 4 months but culture conversion is not yet documented, the intensive phase may be extended by a month at a time to a maximum of 6 months.
* If 6 months of treatment is completed without evidence of culture conversion, then the treatment should be declared a failure.

# Form 5: Quarterly Post-Treatment Follow-Up Form

This form is filled out during the follow-up period after the patient ends treatment. Post-treatment follow-up should be conducted on a quarterly basis at 3, 6, 9 and 12 months after the patient has finished treatment and has been assigned an end of treatment outcome.

There are four columns in this form, one for each month during which post-treatment follow-up may be conducted. This form should be filled out after each follow-up visit.

* **Month post end-of-treatment**. This field should indicate which month of follow-up the encounter took place (i.e. month 3).
* **Date of visit**. This is the date on which the follow-up encounter took place.
* **Type of assessment**. ONE (1) type of assessment should be chosen for each follow-up encounter. It is recommended that follow-up encounters conducted at six (6) and twelve (12) months post end-of-treatment be in-person visits.
	+ Telephone call
	+ Telephone text message
	+ Email
	+ Physical meeting in TB clinic or other facility
	+ Physical meeting elsewhere
* **Person with whom the information is provided or the assessment made**. Choose ONE (1) choice indicating who provided the information collected during the post-treatment follow-up encounter.
	+ If the encounter took place with someone who is NOT the patient, be sure to answer the question **“**Indirect information if patient not seen in person**”** ” and choose ONE (1) choice:
		- Patient well
		- Patient has left and no contact
		- Patient died
		- Patient has symptoms
		- Patient has been diagnosed with TB and re-enrolled in TB treatment
	+ If the encounter took place with the patient, be sure to answer the questions under “**Clinical questions to patient only**”.

**CLINICAL QUESTIONS TO PATIENT**

If the encounter takes place with the patient, the patient should be asked about the following symptoms:

* Cough for more than two (2) weeks
	+ If YES note:
		- Whether the patient’s cough is productive
		- If there is blood in the patient’s sputum
* Fever
	+ If YES, indicate for how long the patient has had a fever
* Night sweats
* Unexplained weight loss

**MEDICAL VISITS AND MEDICATIONS**

* **Any current medications being taken?** If YES, list all medications currently being taken by the patient.
* **Any contact with a medical practitioner since completing TB treatment?** If YES,
	+ Indicate the purpose of the visit to the practitioner, and
	+ Indicate the outcome of the visit to the practitioner

**HOUSEHOLD CONTACTS**

* **Any household contact being treated for TB?**
	+ Mark YES if any household contacts of the patient are currently being treated for TB.
	+ Mark NO if no household contacts of the patient are currently being treated for TB.
	+ Mark UNKNOWN if information on the patient’s household contacts is unavailable.
* **Any household contact symptomatic for TB?**
	+ Mark YES if any household contacts of the patient currently exhibit any of the following symptoms (also listed in the clinical questions for the patient):
		- Cough for more than two (2) weeks
		- Productive cough for more than two (2) weeks
		- Blood present in sputum
		- Fever
			* If fever present, indicate for how long the household contact has had a fever
		- Night sweats
		- Unexplained weight loss

**ACTION AT END OF ASSESSMENT**

* **Is patient a possible TB relapse?**
	+ Mark YES if information gathered during the encounter indicates that the patient has potential relapse.
	+ Mark NO if information gathered during the encounter does not indicate a possibility of relapse.
	+ Mark UNKNOWN if there is not enough information gathered during the encounter to determine whether there is a possibility of relapse.
* **Was culture ordered?**
	+ If YES, indicate the date on which the patient submitted culture for testing.
* **List all diagnostic tests ordered**: If any diagnostic tests were ordered during the encounter, please list all tests in this field.
* **Date of next appointment**:
	+ Mark YES if the patient is scheduled to have an additional follow-up encounter. Write the date of the next visit.
	+ Mark NONE if the patient is not scheduled to have an additional follow-up encounter. For example, patients who have completed a 12-month post end-of-treatment follow-up encounter will not have further follow-up.

# Form 6: Final Post-Treatment Outcome Form

This form is completed ONLY ONCE for patients who successfully completed treatment (had treatment outcomes of CURED or TREATMENT COMPLETED), and after a treatment outcome has been assigned according to your protocol. This form is typically completed at 12 months post-treatment, or prior to 12 months if an outcome is reached in the case of relapse or death.

At 12 months post-treatment, a formal assessment for all patients who do not yet have a post-treatment outcome should be completed with relevant tests, including culture. This form will be filled out only once results are available (culture and/or X-ray).

* **Date of post-treatment outcome decision:** This is the date that one of the below outcomes was decided.

**FINAL POST-TREATMENT OUTCOME**

Only ONE (1) final post end-of-treatment outcome should be chosen from the following outcome options.

* **No recurrence:** This outcome is assigned when the patient continues to be considered as CURED or TREATMENT COMPLETED, and continues to be culture negative with no signs of relapse after 12-months of post-treatment follow-up.
	+ Mark “Clinically without TB symptoms and culture negative” if this outcome is assigned based of off clinical evidence in addition to negative culture results
	+ Mark “Clinically without TB symptoms and no culture done” if this outcome is assigned based solely off of clinical evidence but no new culture was collected.
* **Died post-treatment**: This outcome is assigned if the patient died during the follow-up period after a treatment outcome was assigned at the end of the patient’s treatment.
	+ If the patient is assigned an outcome of DIED,
		- Write the date of death
		- Mark only ONE (1) suspected primary cause of death:
			* TB was immediate cause of death
			* TB contributed to death
			* Surgery-related death
				+ If chosen indicate the type of surgery
			* Cause other than TB
				+ If chosen, indicate the suspected cause of death
			* Cause related to TB treatment
			* Unknown
* **Recurrence**: This outcome is assigned when the patient originally had a treatment outcome of CURED or COMPLETED but has since been diagnosed again with TB by a clinician. Mark ONE (1) of the following definitions indicating recurrence:
	+ **Two positive cultures irrespective of the presence of the clinical signs or symptoms of TB**. This option should be chosen if the patient has two (2) positive cultures taken on different days, regardless of whether the patient is exhibiting signs and/or symptoms of TB.
	+ **One positive culture with clinical signs or symptoms of TB or radiographic deterioration.** This should be chosen if the patient has one (1) positive culture in addition to signs and/or symptoms of TB, or radiographic deterioration. An isolated positive smear or culture without clinical or radiographic deterioration after treatment completion does not provide sufficient evidence to define recurrent TB.
* **Lost to follow-up after finishing treatment**. This outcome is assigned to patients who have been unreachable in the months after a treatment outcome was assigned. Multiple reasons for why a patient became lost to follow-up may be marked:
	+ Adverse event(s)
	+ Patient refused follow-up
	+ Substance abuse
	+ Social problem (family, financial, complex social situation)
	+ Left region, country
	+ No confidence in treatment
	+ Unknown
	+ Other. Please specify any OTHER reasons in the indicated space.
* **Not evaluated**. This outcome is assigned to patients for whom no post-treatment outcome is assigned. This includes cases who transferred to another treatment unit for post-treatment follow-up and those for whom the treatment outcome is unknown.
	+ Did the patient transfer out?
		- If YES, write the name of the health center to which the patient was transferred and the district in which it is located.
		- If NO, write the reason that this patient was assigned this outcome.

# Optional Forms

## Adverse Event Forms

*A trained doctor is required to collect this information. Each country will determine which, if any, adverse events will be collected for operational research purposes. The following instructions serve as general guidelines for filling out an adverse event form.*

An adverse event (AE) is defined as a new event that occurs during treatment or an existing medical condition that worsens during treatment. Pre-existing AEs (at the start of treatment) are medical conditions associated with previous treatment and should not be reported through the AE form.

One AE form should be completed per event. For Serious Adverse Events (SAE), complete the SAE form instead of the AE form and submit to the appropriate pharmacovigilance (PV) body within 24 hours (see section on Serious Adverse Events).

* **AE ID #:** Each AE should be numbered in numerical order based on the chronological order in which they occur. Write this number at the top of the AE form in the designated field.
* **Date of onset of event**:
	+ If AE is a symptom, enter the date when the symptom was first noticed.
	+ If AE is an abnormal test, enter the date of medical evaluation.
* **Date of reporting the event**: This should be the date on which the AE becomes known to the treating physician. This date is generally the date on which the form is filled out.
* **Were all anti-TB drugs suspended due to this AE?**
	+ Mark YES if the patient's TB treatment regimen was suspended for any length of time due to a severe AE.
		- For example, if the patient developed a severe drug-induced hepatitis and all drugs were suspended until liver enzymes returned to normal, mark YES.
	+ Mark NO if none or only one or some drugs (but not all) were suspended due to the AE.

Common adverse events (AE) that may occur during treatment include the following. Choose ONE (1) AE term from the following list per form.

|  |  |  |  |
| --- | --- | --- | --- |
| **Organ System** | **Common Adverse Events** **(choose one)** | **Organ System** | **Common Adverse Events** **(choose one)** |
| *Cardiovascular disorders* | * Cardiac rhythm
* Prolonged (corrected) QT interval
 | *Immune disorders* | * Allergic reaction
 |
| *Chemistry* | * Hypokalemia (K ≤ 3.4 mEq/L)
* Hypomagnesemia (Mg ≤ 1.4 mmol/L)
* Lactate (serum lactate greater than ULN)
 | *Musculoskeletal disorders* | * Arthralgia
* Arthritis
* Myalgia
* Tendinopathy
 |
| *Ear disorders* | * Hearing impairment (hearing loss)
* Tinnitus
* Vestibular disorder
 | *Neurological disorders* | * Dysgeusia
* Headache
* Peripheral neuropathy (neurosensory disorder or paresthesia)
* Seizure
 |
| *Endocrine disorders* | * Hypothyroidism
 | *Reproductive system and breast disorders* | * Gynecomastia
 |
| *Enzymes* | * Increased liver enzymes (ALT increased or AST increased (≥ 1.1 x ULN))
 | *Psychiatric disorders* | * Anxiety
* Depression
* Psychosis
* Suicidal ideation
 |
| *Eye disorders* | * Optic nerve disorder (optic neuritis)
 | *Renal and urinary disorders* | * Acute kidney injury (acute renal failure)
 |
| *Gastrointestinal disorders* | * Diarrhea
* Dyspepsia
* Nausea
* Oral discomfort/dysphagia
* Pancreatitis
* Vomiting
 | *Skin disorders* | * Mucocutaneous symptoms (includes rash)
* Pruritus
* Skin hypo- or hyper-pigmentation
 |
| *Other* | A symptom, abnormal exam finding, condition or test not listed above.  |

**SEVERITY**

* Mark the severity grade assigned to the AE. If the AE being reported consists of more than one abnormal test, symptom or condition, choose the highest grade assigned according to the Severity Grading Scale\*.

\**A severity grading scale is provided in the Clinical Guide for All-Oral Shorter MDR-TB Regimens for operational research on all-oral, short treatment regimens. In some countries, the central regulatory or PV body may have a different grading scale that should be used when reporting adverse events*.

**ADVERSE EVENT OUTCOME**

This section of the form should be completed when an AE is closed, meaning that the AE is resolved or stable.

* **Date of AE outcome:** This is the date that the AE was closed. This is typically the same date on which this section of the form is completed.
* **Outcome of this AE**: Choose the ONE (1) best outcome:
	+ **Fatal**: the AE is the direct cause of the patient's death or one of the causes that contributed to the patient's death.
	+ **Not resolved**: the AE is ongoing with no observed improvement.
		- An outcome of NOT RESOLVED should generally not be selected as it indicates that the AE should not be closed. One of the few times it is appropriate to select this outcome is if the patient died in the hospital of another cause but still had the active AE unrelated to the patient's death.
	+ **Resolved**: the AE is fully resolved or stabilized and the patient has returned to their baseline condition for chronic disorders.
	+ **Resolved with sequelae**: the AE is resolved, but the patient has some permanent condition as a consequence of the event (e.g. mild paraesthesia following transient ischaemic attack).
	+ **Resolving**: this outcome may be selected when:
		- the AE is improving
		- lab results indicated improved results
		- the 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.

**MAXIMUM SEVERITY**

* Mark the maximum severity grade that the AE reached over the course of the event.

**CAUSAL FACTORS: ANTI-TB DRUGS**

* **Is this adverse event related to any of the TB drugs in the patient’s regimen?**
	+ Mark YES if the AE is possibly related to any of the drugs included in the patient’s regimen.
		- If YES is marked, list the drug name, whether it was possibly related to the AE and the final action taken in corresponding fields.
		- A drug is considered to be "related" to an AE if there is a reasonable possibility that the AE may have occurred because of said drug. Elements in favor of a reasonable causal relationship include (but are not limited to):
			* A favorable temporal relationship;
			* A positive de-challenge, meaning symptoms are receding when the drug(s) is withdrawn or the dose is reduced;
			* A positive re-challenge, 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).
		- For each related drug, choose only ONE (1) **final action taken**. These are final actions, not the actions taken immediately after the AE. For example:
			* Mark DOSE MAINTAINED (NO CHANGES) if the related drug was stopped temporarily (i.e. two weeks) but eventually the patient was able to tolerate the original dose
			* Mark DOSE REDUCED if the related drugs was stopped temporarily (i.e. two weeks) but eventually the patient was able to tolerate a reduced dose
			* Mark DRUG PERMANENTLY WITHDRAWN if the drug was stopped and never restarted, or if the patient was never able to tolerate the full or reduced dose of the drug.
			* Mark UNKNOWN if the final action is unavailable.