World Health Organization
REGIONAL OFFICE FOR Europe

Selection of treatment regimens and specifics of patient enrollment for mSTR

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European TB Research Initiative, WHO Regional Office for Europe

Content

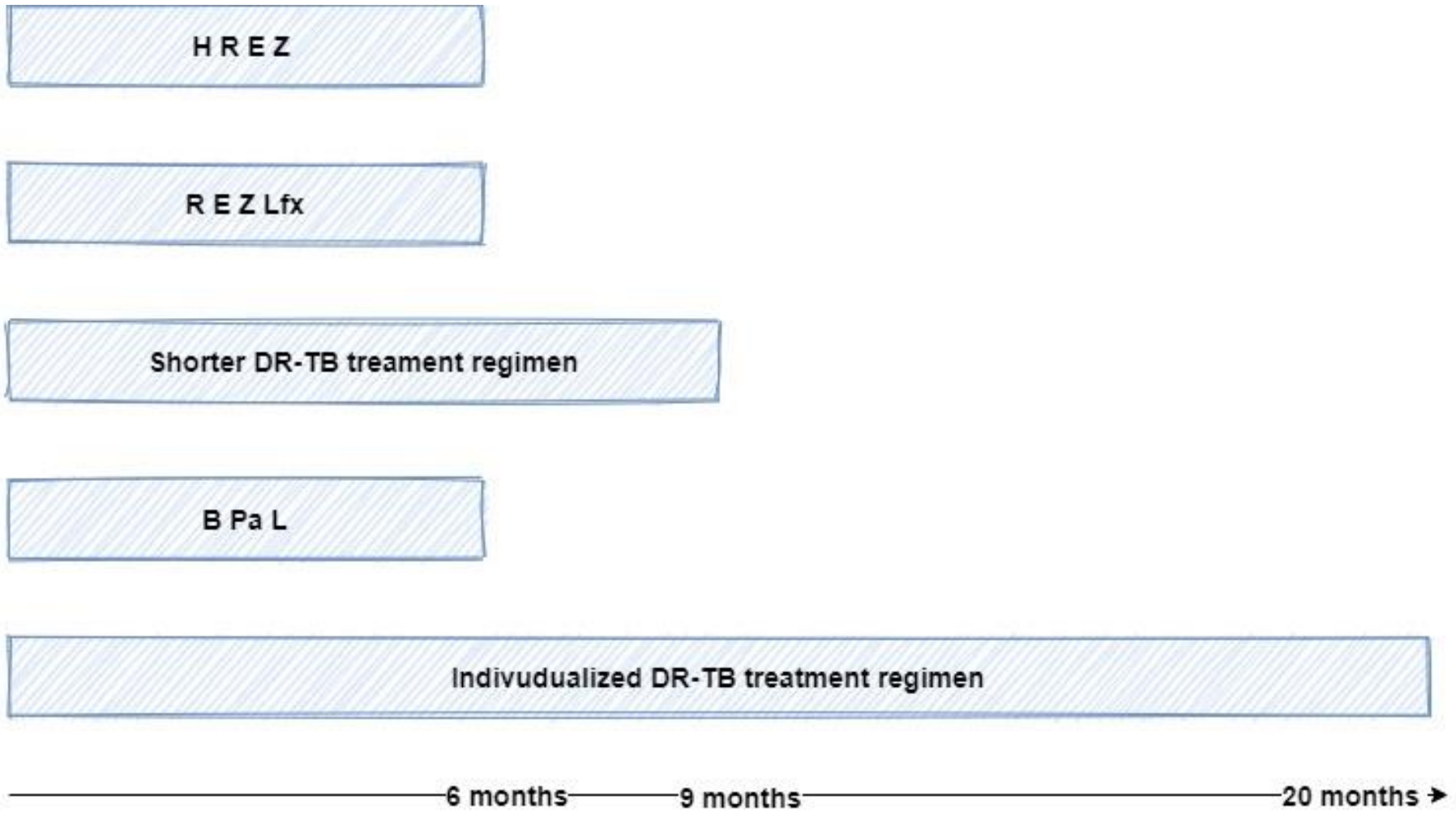
- Selection of TB treatment regimens
- Specifics of patient enrollment for mSTR
- Case presentation

Select the best regimen for each TB patient

- The most effective
- Shortest possible
- The least toxic

https://www.freepik.com/free-vector/realistic-target-composition_6479552.htm#page=1&query=archery&position=4

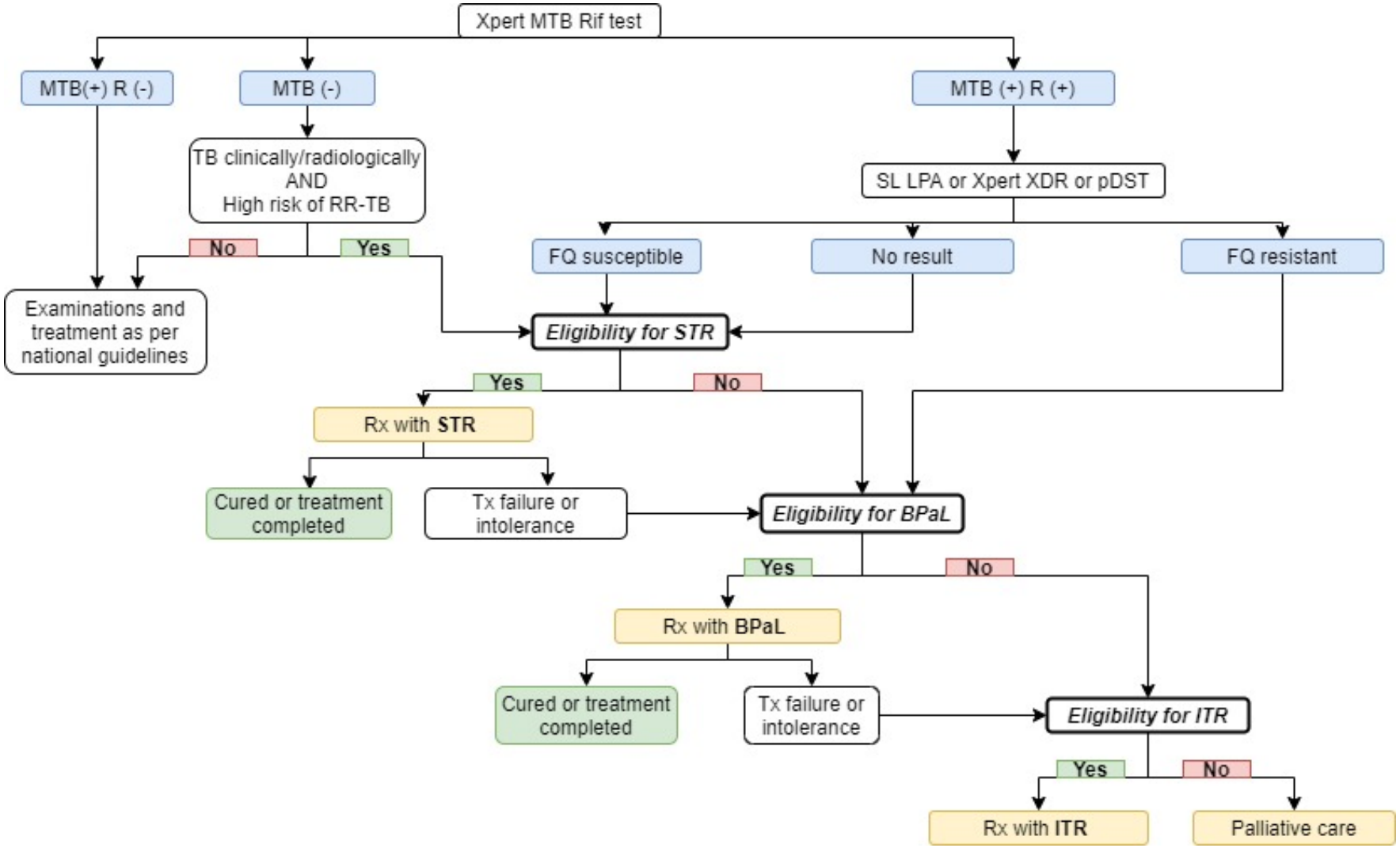
TB treatment regimens

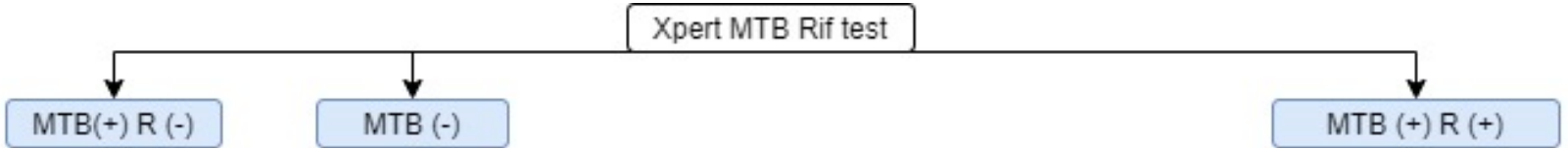


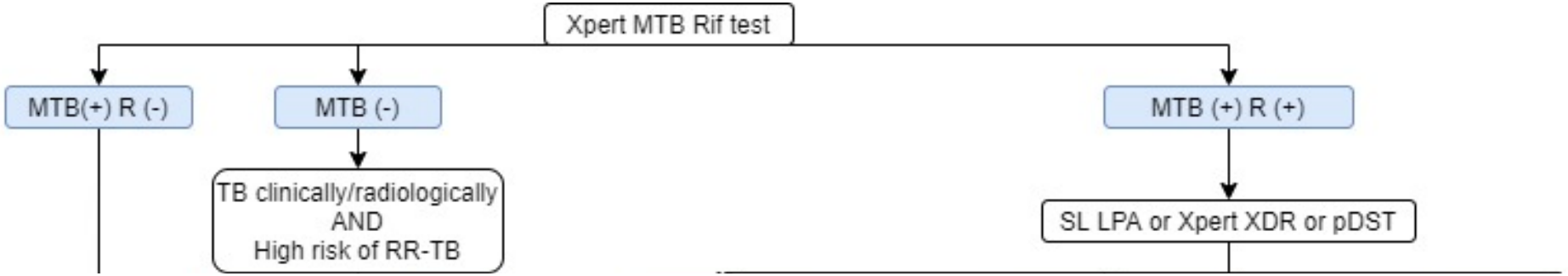
Select regimen based on:

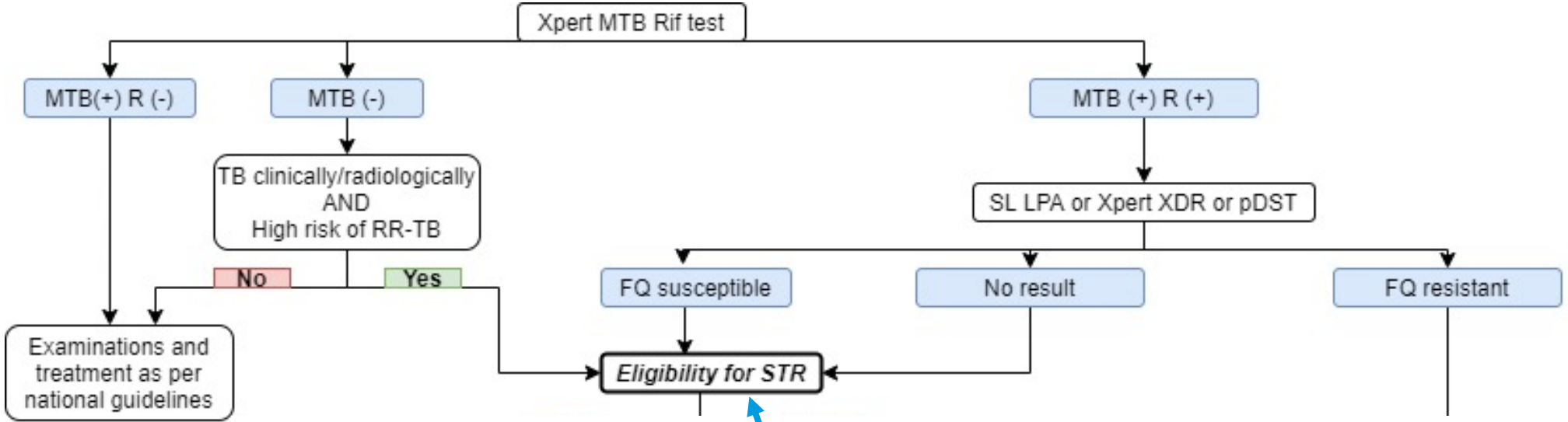
- **DST** results
- Previous **history of TB treatment**
  - Which drugs; For how long each drug
  - Tolerability and adherence to treatment
  - What and when was the outcome
- History of **contact** with infectious TB patient
  - Contact's DST pattern at the time of contact
  - Treatment status, outcome
- Other factors – underlying **illnesses**, age, **patient's preference** (if applicable)

DR-TB treatment regimen selection cascade

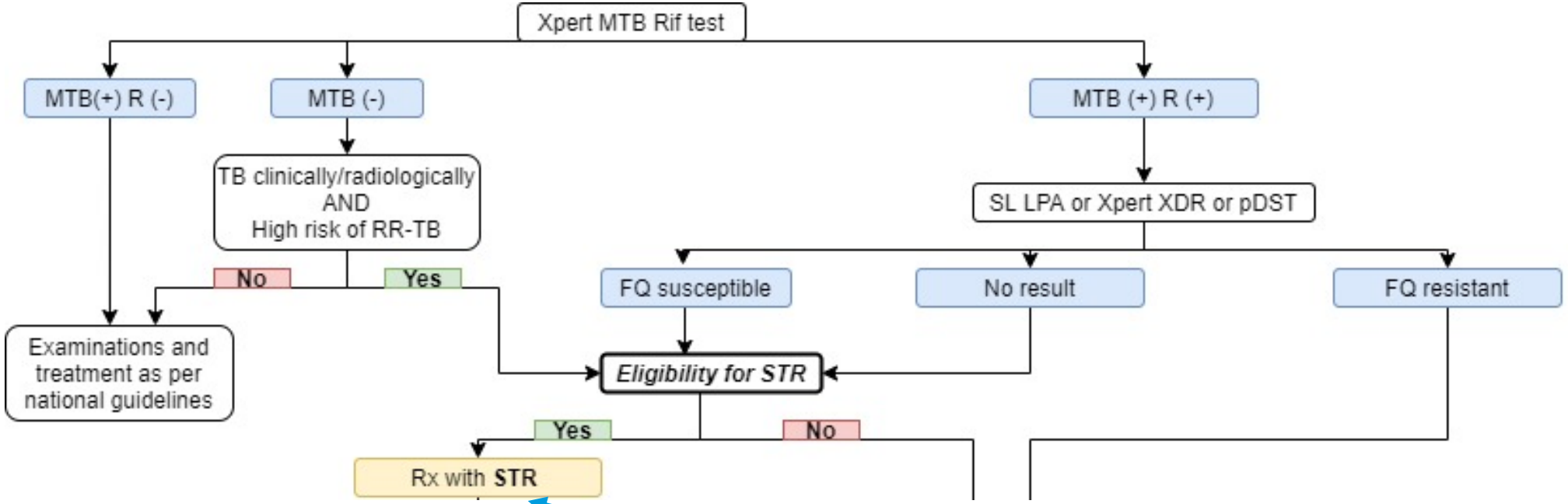



Xpert MTB Rif test
MTB(+) R (-)
MTB (-)
MTB (+) R (+)

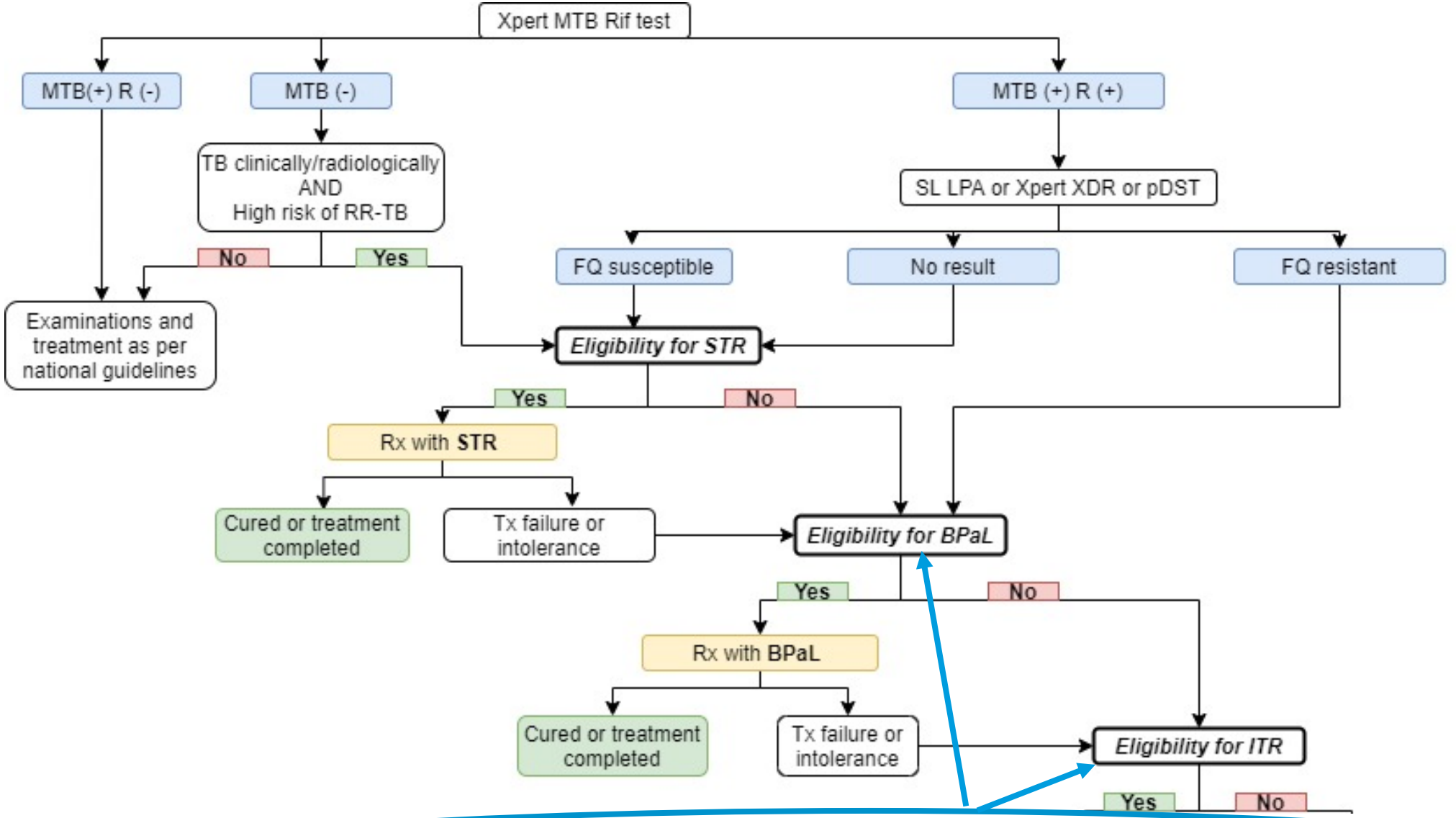

Xpert MTB Rif test
MTB(+) R (-)
MTB (-)
TB clinically/radiologically
AND
High risk of RR-TB
MTB (+) R (+)
SL LPA or Xpert XDR or pDST



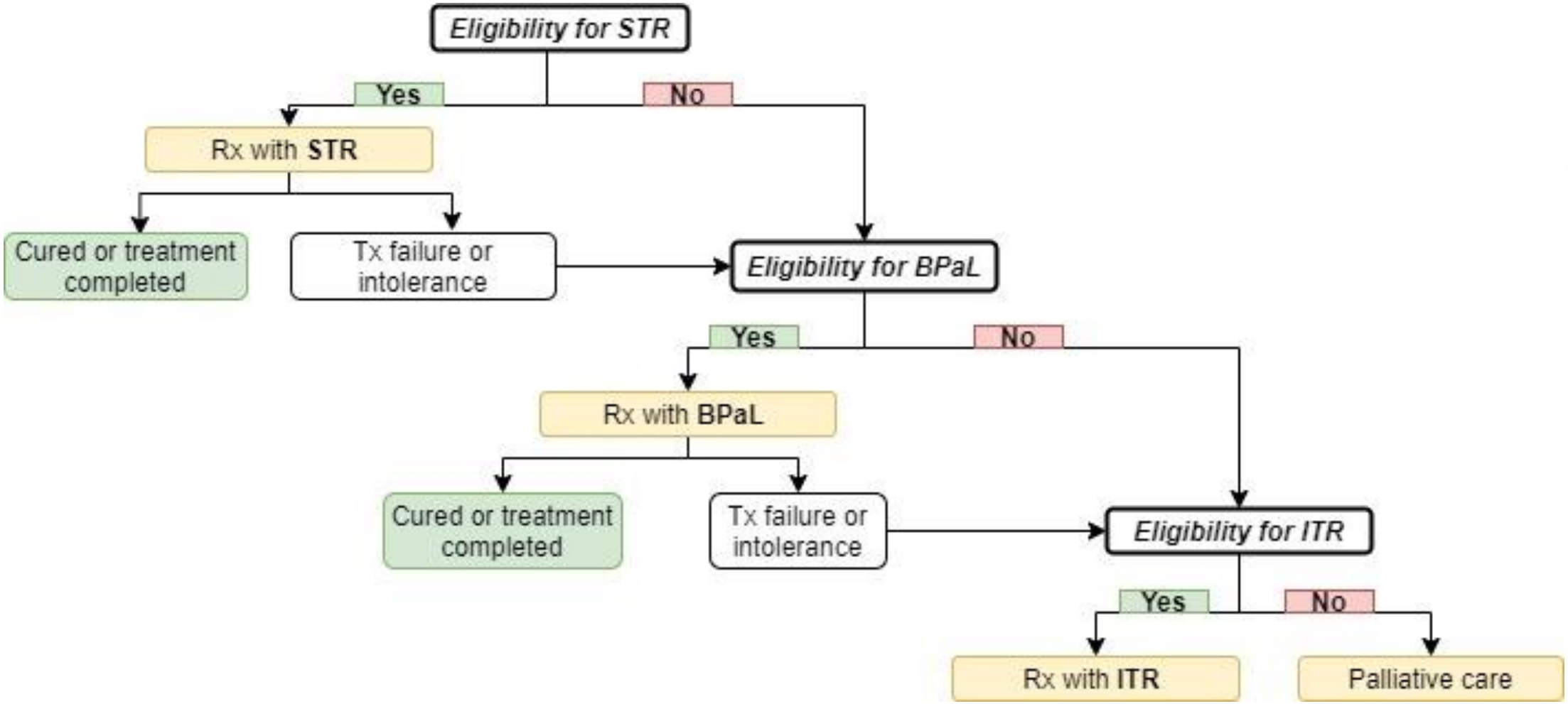
Screen every RR-TB patient for eligibility for STR



Eligible + signs informed consent = Enroll in treatment with mSTR



Select another regimen, if not eligible and/or does not sign informed consent


Eligibility for STR
Yes
No
Rx with STR
Cured or treatment completed
Tx failure or intolerance
Eligibility for BPaL
Yes
No
Rx with BPaL
Cured or treatment completed
Tx failure or intolerance
Eligibility for ITR
Yes
No
Rx with ITR
Palliative care

Screen every RR-TB patient for eligibility for STR

Non-invasive exclusion criteria for mSTR

- Did patient ever receive drugs included in mSTR for one month or more?
- Is the patient unable to take oral medication?
- Is the patient taking any medications contraindicated with the medications in the mSTR?
- Does the patient have TB meningitis, miliary TB or TB osteomyelitis?
- Does the patient have a known allergy to any medication in the mSTR?
- Is the patient in a very severe clinical condition (Karnofski scale <40 or ECOG ≥4)?

Invasive exclusion criteria

- Does the patient have documented resistance to a fluoroquinolones?
- Does the patient have a heart rate-corrected QT (QTc Fridericia correction) interval of ≥500 msec on ECG at screening?
- Does the patient have AST or ALT > 3 times the upper limit of normal?
- Does the patient have a creatinine clearance of less than 30 ml/min per 1.73 m2 of body surface area?

Study Screening Form
mSTR WHO Euro

Annex #3

Study Screening Form (Part I)

Country _____ **Study site** ☐☐

Study screening date ____/____/_____ dd/mm/yyyy

A Patient Information

A1 Participant's Initials ☐☐☐☐

A2 DR-TB Registration Number ☐☐☐☐☐☐☐☐☐☐

A3 Sex 1 Male 2 Female

A4 Date of birth _____/_____/_____ dd/mm/yyyy

B Non-invasive Exclusion Criteria

B1 Did patient ever receive drugs included in mSTR for one month or more?	1 Yes 2 No
B2 Is the patient unable to take oral medication?	1 Yes 2 No
B3 Is the patient taking any medications contraindicated with the medications in the mSTR?	1 Yes 2 No
B4 Does the patient have TB meningitis, miliary TB or TB osteomyelitis?	1 Yes 2 No
B5 Does the patient have a known allergy to any medication in the mSTR?	1 Yes 2 No
B6 Is the patient in a very severe clinical condition (Karnofski scale <40 or ECOG ≥4)	1 Yes 2 No

If any question is answered **YES**, patient does not meet eligibility criteria. Skip to **Section D**

If all answers are **NO** - discuss study with patient

If patient provides verbal consent for additional testing, complete **Section C**

If patient does not want to discuss the study, or refuses additional testing, skip to **Section D**

C Invasive Exclusion Criteria

C1 Does the patient have documented resistance to a fluoroquinolones and/or other mSTR medicines with reliable DST results (Bdq, Dlm, Lzd, Cfz)?	1 Yes 2 No
C2 Does the patient have a heart rate-corrected QT (QTc Fridericia correction) interval of ≥500 msec on ECG at screening?	1 Yes 2 No
C3 Does the patient have AST or ALT > 3 times the upper limit of normal?	1 Yes 2 No
C4 Does the patient have a creatinine clearance of less than 30 ml/min per 1.73 m2 of body surface area?	1 Yes 2 No

If any question is answered **YES**, patient does not meet eligibility criteria. Skip to **Section D**

If all answers are **NO** - patient is **eligible** for enrollment

Discuss the study and ask if the patient is willing to consent to study participation

If patient is willing to consent, document enrollment in **Sections D and F,** complete **informed consent** process, and complete **Enrollment Form**

If patient is not willing to consent, document decline in **Section D**

If site chooses not to enroll the patient, document this in **Section D**

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Study screening form (Part I)

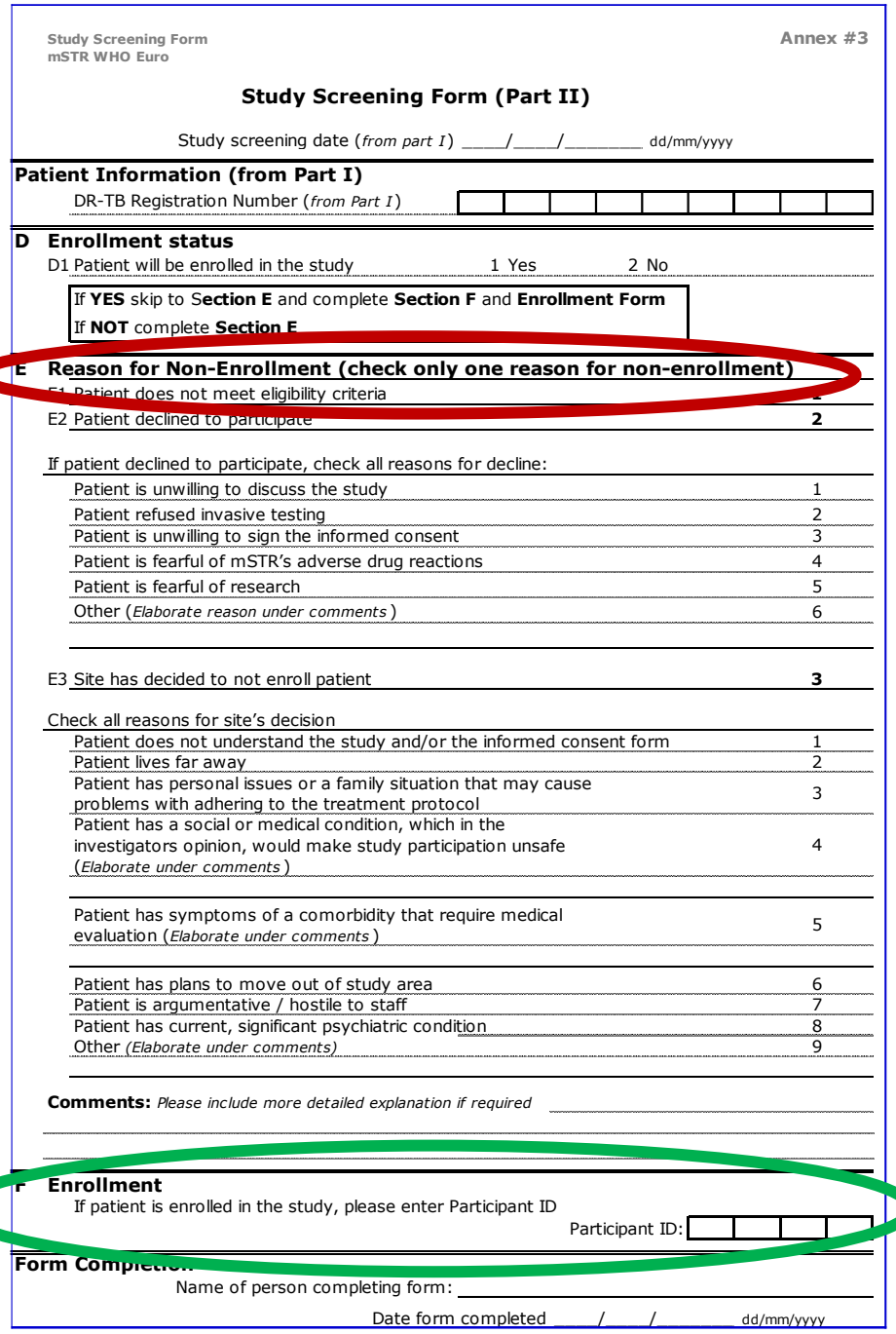
Online Drug Interaction Database to find and identify drug-drug interactions

https://reference.medscape.com/drug-interactionchecker

https://www.druginteractions.org/

Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead



Study Screening Form
mSTR WHO Euro

Annex #3

Study Screening Form (Part II)

Study screening date (*from part I*) _____/_____/_____ dd/mm/yyyy

Patient Information (from Part I)

DR-TB Registration Number (*from Part I*)

D Enrollment status

D1 Patient will be enrolled in the study 1 Yes 2 No

If **YES** skip to **Section E** and complete **Section F** and **Enrollment Form**
If **NOT** complete **Section E**

E Reason for Non-Enrollment (check only one reason for non-enrollment)

E1 Patient does not meet eligibility criteria **1**

E2 Patient declined to participate **2**

If patient declined to participate, check all reasons for decline:

Patient is unwilling to discuss the study	1
Patient refused invasive testing	2
Patient is unwilling to sign the informed consent	3
Patient is fearful of mSTR's adverse drug reactions	4
Patient is fearful of research	5
Other (*Elaborate reason under comments*)	6

E3 Site has decided to not enroll patient **3**

Check all reasons for site's decision

Patient does not understand the study and/or the informed consent form	1
Patient lives far away	2
Patient has personal issues or a family situation that may cause problems with adhering to the treatment protocol	3
Patient has a social or medical condition, which in the investigators opinion, would make study participation unsafe (*Elaborate under comments*)	4
Patient has symptoms of a comorbidity that require medical evaluation (*Elaborate under comments*)	5
Patient has plans to move out of study area	6
Patient is argumentative / hostile to staff	7
Patient has current, significant psychiatric condition	8
Other *(Elaborate under comments)*	9

Comments: *Please include more detailed explanation if required*

F Enrollment

If patient is enrolled in the study, please enter Participant ID

Participant ID:

Form Completion

Name of person completing form:

Date form completed ____/____/_____ dd/mm/yyyy

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Study screening form (Part II)

Fill out the enrollment form

Study Enrollment Form (Part I)

Country _____ **Study site** ☐☐

A Study Entry Enrollment

A1 Participant's Initials ☐☐☐☐

A2 DR-TB Registration Number ☐☐☐☐☐☐☐☐☐

A3 Participant ID ☐☐☐☐

A4 Date participant signed informed consent _____/_____/_____ dd/mm/yyyy

A5 Date of treatment start _____/_____/_____ dd/mm/yyyy

A6 Treatment regimen *1 Lfx+Bdq+Lzd+Cfz+Cs* *2 Lfx+Bdq+Lzd+Cfz+Dlm* *3 Lfx+Dlm+Lzd+Cfz*

B Participant Demographics

B1 Date of birth _____/_____/_____ dd/mm/yyyy B3 Sex *1 Male* *2 Female*

B4 Weight (kg) ☐☐☐ B5 Height (cm) ☐☐☐

B6 Employment *1 Employed* *2 Unemployed* *3 Student* *4 Retired* *5 Other*

B7 Education *1 No education* *2 Primary* *3 Secondary* *4 Higher* *9 Unknown*

B8 Marital status *1 Single* *2 Married/cohabitation* *9 Unknown*

C Participant's social status

C1 Homeless within the past year *1 Yes* *2 No* *9 Unknown*

C2 Injecting drug use within the past year *1 Yes* *2 No* *9 Unknown*

C3 History of being resident of correctional faci *1 Yes* *2 No* *9 Unknown*

C4 Alcohol use led to problems in relationships, health, employment/work performance or finances within the past year *1 Yes* *2 No* *9 Unknown*

C5 Not employed within the past year *1 Yes* *2 No* *9 Unknown*

C6 History or current cigarette smoking *1 Yes* *2 No* *9 Unknown*

C6.1. If YES, specify nr. of packs/day ☐ C6.2. how many years has patient been smoking ☐

D Tuberculosis history and treatment

D1 Was the participant ever treated for active TB prior to this episode?

1 Yes *2 No* *9 Unknown*

If **NO** or **UNKNOWN**, proceed to the **Section E**

If **YES**

D1.1. Enter the most recent month and year of treatment initiation _____/_____ mm/yyyy

D1.2. Enter the most recent month and year of treatment outcome _____/_____ mm/yyyy

D2 What was the outcome of the most recent TB treatment?

1 Cured
2 Treatment Completed
3 Treatment Failed
4 Lost to follow up
5 Not evaluated
6 Unknown

Comments:

D3 Has the participant ever received treatment with second-line anti-tuberculosis drugs for ≥1 month prior to this episode?

1 Yes
2 No
9 Unknown

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Study Enrollment form (Part I)

Study Enrollment Form
mSTR WHO Euro

Annex #4

Study Enrollment Form (Part II)

Study Entry Enrollment (from Part I)

Participant ID *(from Part I)* [ ][ ][ ][ ]

Date participant enrollment *(from Part I)* _____/_____/_____ dd/mm/yyyy

E Concomitant Diagnosis at the Time of TB Diagnosis

E1 Viral hepatitis — *1 Yes* *2 No* *9 Unknown*
E.1.1. If **YES** specify — *1 A* *2 B* *3 C* *4 B and C*

E2 Diabetes — *1 Yes* *2 No* *9 Unknown*
E2.1. If **YES**, specify type — *1 Type I* *2 Type II* *9 Unknown*

E3 Peripheral neuropathy — *1 Yes* *2 No* *9 Unknown*

E4 Chronic renal insufficiency — *1 Yes* *2 No* *9 Unknown*
E.4.1. If **YES**, specify the grade — *1 I* *2 II* *3 III* *4 IV* *9 Unknown*

E5 Ischemic heart disease — *1 Yes* *2 No* *9 Unknown*
E 5.1. If YES specify _____

E6 HIV — *1 Yes* *2 No* *9 Unknown*
E6.1. If **YES,** is patient on ART? — *1 Yes* *2 No*
E6.1.1.Specify the ART regimen at enrollemnt — *1 With Efavirenz* *2 With Dolutegravir* *3 Other*
E6.1.2.Cotrimoxazole — *1 Yes* *2 No* *9 Unknown*
E6.1.3. CD4 [ ][ ][ ][ ]

E7 COVID-19 (lab. conf) — *1 Yes* ___/___/_____ *2 No* *9 Unknown*
dd/mm/yyyy

E8 Other concomitant diagnoses _____
E9 Other concomitant diagnoses _____
E10 Other concomitant diagnoses _____

F Site of TB disease

F1 Site of disease — *1 Pulmonary* *2 Extrapulmonary* *3 Pulmonary and Extrapulmonary*

F1.1. If **Extrapulmonary** or **Pulmonary and Extrapulmonary**, specify the system organ class for each extrapulmonary site
1 Pleural
2 Lymphatic, intrathoracic
3 Lymphatic, extrathoracic
4 Genito-urinary
5 Osteo-articular
6 Disseminated
7 Peritoneal and Digestive
8 Central nervous system
9 Other, specify: _____

G Chest X-ray

G1 Chest X-ray — *1 Abnormal unilateral* *2 Abnormal bilateral* *3 Normal in both*
G1.1. Cavities — *1 Unilateral* *2 Bilateral* *3 No* *9 Unknown*

H Pregnancy status (for female patients only) at the time of TB diagnosis
for male patients proceed to ***section G***

H1 Is the patient pregnant? — *1 Yes* *2 No* *9 Unknown*
H1.1 If **YES**, estimated date of delivery _____/_____/_____ dd/mm/yyyy

Form Completion

Name of person completing form: _____

Date form completed _____/_____/_____ dd/mm/yyyy

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Study Enrollment form (Part II)

Chronic kidney insufficiency

Assign GFR category as follows:

GFR categories in CKD

Category	GFR ml/min/1.73 m^2	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

https://www.kidney.org/professionals/explore-your-knowledge/how-to-classify-ckd

Success with the enrollment!

https://www.freepik.com/free-vector/realistic-target-composition_6479552.htm#page=1&query=archery&position=4

Thank you!

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Organisation mondiale de la Santé
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