Annex 2: PICO format for assessment of new TB sample types, testing technologies, and testing strategies

Diagnostic Class	Population	Intervention	Comparison/ Reference Standards	Outcomes[1]

NPOC-NAATs for TB detection	• Adults and adolescents[2] without HIV or with unknown HIV status
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	• Persons living with HIV [3] with
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	  ○ Advanced HIV disease or seriously ill
		NPOC-NAATs for TB detection on respiratory [6] samples	1. Smear microscopy
			2. Microbiologic Reference Standard (MRS; TB culture)
			3. Composite reference standard (CRS; Decision to treat)
				Cure
				Mortality
				Pre-treatment lost-to-follow-up (pLTFU)
				Time to result (TTR)
				Time to diagnosis (TTD)
				Time to treatment (TTT)
				WRD Tested (individuals tested with initial WHO-recommended rapid diagnostic testing)[7]
				WRD-Diagnosed (individuals diagnosed with initial WHO-recommended diagnostic testing)[8]

[1] For patient-important outcomes (cure, mortality, pLTFU, TTR, TTD, TTT, WRD Tested, WRD Diagnosed) comparison with standard of care is desirable.
[2] Adults are defined as 20 years or older, while adolescents are defined as 10-19 years of age.
[3] In case recommendations are extrapolated for persons living with HIV, secondary non-inferiority diagnostic accuracy analyses will be performed using LC-aNAAT (Xpert MTB/RIF Ultra) to assess possible use of NPOC-NAAT in the WHO-recommended concurrent testing strategy for these populations.
[6] For adults respiratory samples include sputum, bronchoalveolar lavage, and induced sputum. For children respiratory samples include sputum, bronchoalveolar lavage, induced sputum, nasopharyngeal aspirates, and gastric aspirates.
[7] WHO standard on universal access to rapid TB diagnostics, Benchmark 5 absolute numbers and proportion.
[8] WHO standard on universal access to rapid TB diagnostics, Benchmark 10 absolute numbers and proportion.

	• Children[4] [5] with
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	  ○ HIV infection
				Diagnostic accuracy (sensitivity/ specificity)[9]
				Failure rate (error, invalid, other)

NPOC-NAATs for TB detection	• Adults and adolescents without HIV or with unknown HIV status
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	• Persons living with HIV with
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	  ○ AHD and/or seriously ill
	• Children with
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	  ○ HIV infection
		NPOC-NAATs for TB detection on tongue swabs, sub analyzed by:
		• self-collected swabs[10]
		• healthcare worker-collected swabs
			1. Smear microscopy
			2. MRS (TB culture on spontaneous sputum)
			3. MRS (TB culture on induced sputum for individuals unable to spontaneously produce a sample)
			4. CRS (Decision to treat)
				Cure
				Mortality
				pLTFU
				TTR
				TTD
				TTT
				WRD-Tested
				WRD-Diagnosed
				Diagnostic accuracy (sensitivity/ specificity)[11]
				Failure rate (error, invalid, other)

LC-aNAATs for TB and rifampicin resistance detection	• Adults and adolescents without HIV or with unknown HIV status
	  ○ Signs or symptoms of PTB
	  ○ Screen positive for PTB
	• PLHIV with
		LC-aNAATs for TB and rifampicin resistance (RR) detection on	1. Smear microscopy
			2. MRS for TB Detection (TB culture on spontaneous sputum)
			3. MRS for TB Detection (TB culture on induced sputum
				Cure
				Mortality
				pLTFU
				TTR
				TTD
				TTT

[4] Aged under 10 years.

[5] In case recommendation is extrapolated for children, secondary analysis of non-inferiority for diagnostic accuracy will be performed with Ultra as part of a concurrent testing strategy.

[9] Measured against TB culture as the Microbiological Reference Standard (MRS) and the decision to treat as the Composite Reference Standard (CRS).

[10] Sample obtained by use of nylon, individually packed, sterile swabs with perforated 'break' point. Can be self-collected or collected by a healthcare provider

[11] Measured against two MRS' (TB culture on spontaneous sputum and TB culture on induced sputum for those unable to produce spontaneous sputum) and one CRS (decision to treat).

	○ Signs or symptoms of PTB ○ Screen positive for PTB ○ AHD and/or seriously ill • Children with ○ Signs or symptoms of PTB ○ Screen positive for PTB ○ HIV	tongue swabs, sub-analyzed by: • self-collected swabs • healthcare worker-collected swabs	for individuals unable to spontaneously produce a sample) 4. CRS for TB Detection (Decision to treat) 5. Composite MRS for RR Detection (Phenotypic drug susceptibility testing (pDST) and whole genome sequencing (WGS))	WRD-Tested WRD-Diagnosed Diagnostic accuracy (sensitivity/ specificity)[12] Failure rate (error, invalid, other)
LC-aNAATs for TB and rifampicin resistance detection	• Adults and adolescents HIV negative or unknown ○ Signs or symptoms of PTB ○ Screen positive for PTB • PLHIV with ○ Signs or symptoms of PTB ○ Screen positive for PTB ○ AHD and/or seriously ill • Children with ○ Signs or symptoms of PTB ○ Screen positive for PTB ○ HIV	LC-aNAATs for TB and rifampicin resistance detection on pooled respiratory samples (ratios of 1:2 to 1:10)	1. LC-aNAAT on individual respiratory samples 2. MRS for TB Detection (TB Culture) 3. CRS for TB Detection (Decision to treat) 4. Composite MRS for RR Detection (pDST and WGS)	Cure Mortality pLTFU TTR TTD TTT WRD-Tested WRD-Diagnosed Incremental diagnostic accuracy (sensitivity/ specificity)[13] Failure rate (error, invalid, other)

[12] Measured against two MRS' (TB culture for TB detection in respiratory sample producers; pDST + WGS for RR-TB detection in respiratory sample producers; MRS (Culture on induced sputum) for TB detection; CRS (Decision to treat) for TB detection.

[13] MRS (Culture) for TB detection; phenotypic drug susceptibility testing and whole genome sequencing for RR-TB detection.