Terms of Reference

Systematic review of the diagnostic accuracy of targeted next-generation sequencing technologies for detection of drug resistance among people diagnosed with TB

1. Background

In preparation for an upcoming Guideline Development Group (GDG) meeting focused on targeted next-generation sequencing technologies for detection of drug resistance among people diagnosed with TB, tentatively planned for December 2022, there is a need to perform a systematic review and meta-analysis of the data on diagnostic accuracy of this class of technologies.

2. Objectives

- To perform a systematic review of the published and unpublished literature on diagnostic accuracy of targeted next-generation sequencing technologies for detection of drug resistance among people diagnosed with TB, compared to phenotypic drug susceptibility testing (DST) and / or whole genome sequencing;
- To conduct a quality assessment of the identified evidence, following the GRADE framework, to summarize the results in the format of the Evidence table/Evidence-to-decision framework (GRADEpro software 2020), and to prepare a presentation and a descriptive report summarizing the methods and findings for the Guideline Development Group members.

3. Research questions to guide GDG policy-making process

Should targeted next-generation sequencing technologies be used as an alternative to phenotypic DST to detect drug resistance among individuals diagnosed with TB disease (bacteriologically confirmed *Mycobacterium tuberculosis*)? **(PICO question)**

Sub-populations:

- Children <15;
- Adults ≥15 years;

- People living with HIV;
- Previously treated TB patients;

Index test:

- Targeted next-generation sequencing solutions for detection of genetic markers of drug resistance

Comparison:

- Microbiological reference standard: Phenotypic DST
- Composite reference standard: Phenotypic DST and Whole genome sequencing

Outcomes:

- Sensitivity/specificity for detection of resistance to:
    - RIF
    - INH
    - FQ
    - AMK
    - PZA
    - EMB
    - ETH
    - SM
    - LZD
    - BDQ
    - CFZ
- Negative predictive value of tNGS technologies for ruling out resistance for the new and re-purposed drugs

4. Deliverables

- Technical protocol for conducting systematic review and meta-analysis (SR/MA), including search strategy, inclusion/exclusion criteria, plan for evidence quality (certainty) assessment and statistical analysis plan;
- Draft written report of findings of SR/MA results ahead of Guideline Development Group meeting;
- Completed online GRADE profiles, based on PICO question, including judgements about the certainty of evidence and explanations for judgements;
- Completed online Evidence-to-decision table, summarizing diagnostic accuracy information on use of respective class of technologies
- Final systematic review report incorporating edits, and revisions suggested by WHO technical officers and GDG committee members as appropriate.
- Presentation (ppt) of SR/MA results for Guideline Development Group meeting;

5. Timeline

- Draft systematic review and evidence assessment protocol – 1 June 2022

- Presentation of preliminary results to GDG – 1 October 2022
- Draft written report of findings and online Evidence-to-decisions tables in GRADEpro software – 1 November 2022
- Final report incorporating revisions based on feedback from WHO and GDG – 1 December 2022

6. Qualifications, experience, skills and languages

- Educational Qualifications:
    - Essential: Advanced postgraduate degree (at least Masters level) or equivalent in epidemiology, biostatistics, quantitative social science or relevant fields;
    - Desirable: Medical degree or training in infectious diseases, preferably tuberculosis.
- Experience.
    - Essential: At least 10 years' experience in epidemiological data analysis, and monitoring and evaluation skills; Documented experience in conducting systematic reviews of the medical or public health literature; Documented experience in managing and analyzing a wide range of public health data, including data from clinical trials and/or other studies; Theoretical and practical knowledge of infectious diseases' epidemiology, prevention, control and public health interventions; Strong skills in analyzing and drawing conclusions based on information presented; Experience of working in TB.
    - Desirable: Excellent planning and facilitation skills; Ability to handle multiple tasks simultaneously and flexibly.
    - Skills/Knowledge: Excellent oral and written communication skills; Excellent epidemiological data analysis skills; Ability to research, analyze and present complex information/data; Strong analytical and presentations skills as demonstrated by past work experience; Proven ability to work as part of a multicultural and multidisciplinary team.
    - Languages and level required: Excellent level of English (reading, writing, speaking); proficiency in other languages will be an advantage. Other essential: Available for the assignment ideally from 15th May 2022 until 15th December 2022

7. Remuneration and Budget

- The remuneration will be in accordance with the WHO remuneration scales for international consultants. The number of working days needs to be defined as per submitted proposal.
- Payments will be made following satisfactory completion of a set of deliverables. In line with WHO norms, payment will be made in instalments on satisfactory completion of a set of deliverables:
    - 30% upon submission of a systematic review and evidence assessment technical protocol by 1 June, 2022

- 30% upon submission of an advanced draft of the systematic review report + GRADE profiles in GRADEpro by 10 November, 2022
- 40% upon completion of final systematic review and presenting at the GDG meeting by 9 December, 2022

- Other terms and conditions of employment will be in accordance with WHO policy on the employment of consultants (details available upon request).