FIND
Diagnosis for all

Request for Proposals

Assays for treatment monitoring in tuberculosis drug trials

Executive summary

- The UNITE4TB Consortium aims to upgrade current clinical trial methodology and enhance the efficiency with which new anti-tuberculosis regimens are developed. FIND, the global alliance for diagnostics, is hosting a Request for Proposals (RFP) **for assays suitable for tuberculosis treatment monitoring** in the context of UNITE4TB novel drug and regimen trials.

- The short-term areas of focus for this RFP are: (1) suitability of the assay to **accurately quantify or reflect the number of viable bacilli in a patient sample or bacterial signatures**, and (2) **readiness of the assay**, in terms of assay development, feasibility, and availability, for inclusion in phase 2 and 3 drug studies starting in 2023.

- A long-term goal of this RFP is to provide tools to **accelerate the development of new anti-tuberculosis drugs and regimens**, and ultimately replace growth-based methods for treatment monitoring, by accelerating the time to assessment of early treatment response and clinical outcome.

- A **large, innovative clinical trial platform** for drug and regimen development will be available to selected assay developers and manufacturers to generate clinical performance data for assays meeting predefined **key assay requirements**, potentially progressing selected technologies to the next readiness level and supporting regulatory filings and product registrations.

Suppliers are expected to **commit to supplying suitable assays in later stages of development for clinical trialling** in the context of novel drug and regimen trials.

* UNITE4TB is a public-private partnership with representation from academic institutions, small- and medium-sized enterprises (SMEs), public organisations, and pharmaceutical companies. Over the next 6 years, the consortium will be active in approximately 40 trial sites on four continents (Europe, Asia, Africa and South America), with the goal of delivering novel phase 2 clinical trials that will accelerate the development of new TB drugs and regimens. Achieving this goal will facilitate fulfilment of one of the main unmet needs in the TB field: better-tolerated drug regimens of shorter duration that can be deployed to tackle tuberculosis across various drug-resistance patterns and co-morbidities. The UNITE4TB project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101007873. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, Deutsches Zentrum für Infektionsforschung e. V. (DZIF), and Ludwig-Maximilians-Universität München (LMU). EFPIA/AP contribute to 50% of funding, whereas the contribution of DZIF and the LMU University Hospital Munich has been granted by the German Federal Ministry of Education and Research. See www.imieurope.eu.

BACKGROUND

This RFP aims to select suitable assays for TB treatment monitoring in clinical trials to ultimately shorten the duration of clinical trials for anti-TB drug and regimen development.

Phase 2 and 3 clinical studies of novel anti-tuberculosis drugs or combinations have been limited by reliance on culture as a growth-based monitoring method to quantify viable bacteria, describe change in bacterial load, and ultimately assess the clinical endpoint of cure vs. unfavorable treatment outcome (e.g. relapse-free cure). However, culture readouts have a long turnaround time, associated biohazard risks, and are prone to contamination, limiting their usefulness as a tool for drug development trials. Fortunately, a growing pipeline of novel tools and assays have the potential to improve the quantification of viable bacteria in sputum samples and predict relapse-free cure. However, few of these technologies have been specifically evaluated to date for either direct or indirect detection of viable bacteria in tuberculosis (TB) patients during treatment.

A TB treatment monitoring tool would improve trial feasibility/conduct by having one or more of the following advantages:

- Early: should provide informative results early after randomisation/ treatment start, making trials shorter
- Quantitative: a quantitative readout, should allow smaller trial sample sizes
- Precise: should be at least as precise as culture, but optimally be more precise, in predicting long-term outcome
- Operational feasibility: should be operationally easier to implement than culture (e.g. lower biosafety requirements, better standardisation between labs, shorter time to result, requiring fewer measurement timepoints)

This would speed up the development of novel drugs and regimens, and potentially reduce the costs of trials in general. This RFP calls for tests that generate results to accurately quantify viable bacteria within hours. These tests may ideally be performed using non-sputum samples to better ensure operator safety, with quantitative results output(s) to allow assessment of treatment response over time. Importantly, the envisioned biomarker may have relatively high cost for the purpose of drug evaluations in clinical trials (as opposed to assays signifying treatment outcome used for programmatic patient management in low-middle income countries (LMICs)).

OBJECTIVE AND SCOPE

UNITE4TB aims to **shorten the duration of anti-TB drug and regimen development** through the selection and evaluation of assays suitable as endpoints in clinical trials This RFP focuses on assays that:

- ✓ Provide quantitative results for monitoring of TB treatment response over time and prediction of long-term treatment outcome
- ✓ Suitable for use in clinical laboratories

UNITE4TB seeks assays that closely meet the key product requirements listed in the "**Technical Assessment**" sheet within the **Assessment Matrix** (see **HOW TO APPLY below** for forms and templates).

UNITE4TB will support clinical evidence generation for assays in later stages of development, with the goal of trialing selected solutions beginning end Q2 2023. Assays that are in an earlier stage of development but for which there is proof-of-concept data that suggest a very high accuracy to predict the long-term endpoint in clinical trials may still be selected for use in clinical trials. If deemed relevant and necessary by the relevant UNITE4TB governing boards, the UNITE4TB consortium may decide to perform additional activities (which may be further defined in consultation with the applicant) next to the evaluation of assay performance for TB treatment monitoring in prospective, clinical drug trials upon provision of assay kits, training materials and trial placement support by the suppliers. Please note that in any case **UNITE4TB will not support** early research and development activities, nor market access and post-launch activities (e.g. shipping logistics, procurement, implementation, user training, distributor qualification, post-market surveillance).

The UNITE4TB trials will provide the opportunity for **data generation for novel biomarker assays** and compare these against 1) Change of bacterial load in sputum measured by MGIT time-to-positivity, 2) Interim analyses based on endpoint 1 to continue or discontinue treatment arms, and/or 3) Long-term TB treatment outcomes.

The first planned trial will be a two-stage study. It will evaluate up to eight different drug regimens against one control arm in stage 1; with a primary endpoint of slope of bacterial load decline (measured by MGIT TTP), and post-treatment observation for relapse. After an interim analysis, it will be decided which regimens will be evaluated in a duration randomization design with relapse as the primary endpoint.

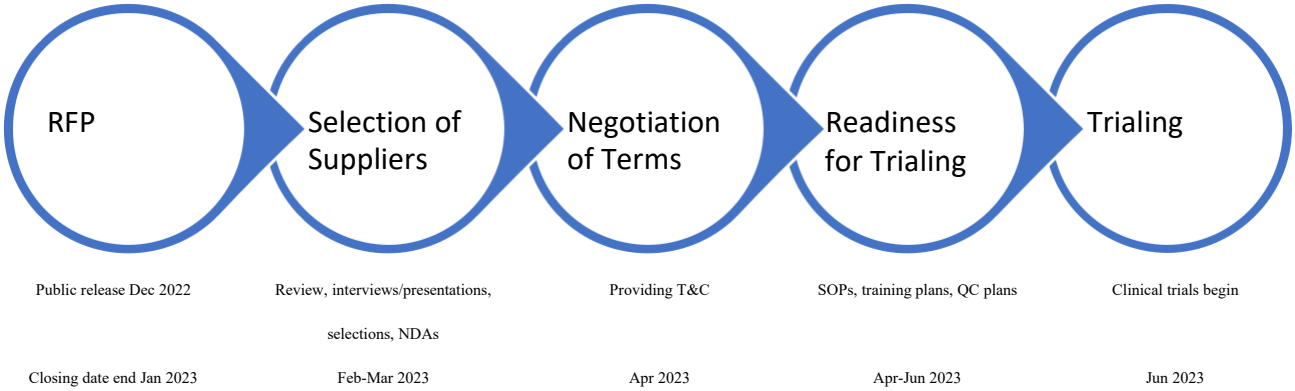
Importantly, the clinical performance data generated by UNITE4TB as a part of this RFP may also be used at a later date to secure stringent regulatory approval (e.g. FDA, EMA) of included assays.

TIMELINE

The expectation is that this RFP will enable suppliers to submit their assay for trialing by the UNITE4TB consortium by end Q2 2023. **Priority will be given to applicants who demonstrate a high likelihood to achieve readiness for trialing, including provision of a sufficient supply of assays by end Q2 2023.** You will enter into a supply agreement with Radboud University Medical Center, who is responsible for contracting of partners for the related activities within the UNITE4TB consortium. The anticipated timeline for this initiative is as follows (may vary depending on applicant):

1. Selection of suppliers and non-disclosure agreements (2 months)
2. Negotiation of terms (1 month)
3. Clinical readiness (2-3 months)

Selection and Supply of Assays for Trialing (6 months)



WHAT'S IN IT FOR YOU

Clinical trialing of selected assays for TB treatment monitoring will be performed by the UNITE4TB consortium. Further, as part of the overall UNITE4TB initiative, this programme can facilitate connections and networking opportunities with a broad ecosystem of partners, working towards support for additional evidence generation to ensure that your assay (tool kit) is suitable for regulatory submissions.

A single lead entity shall be designated for each applicant and shall assume responsibility of the application. Formal written authorizations from partners will only be required of applicants invited to full contract development with Radboudumc. UNITE4TB consortium partners reserve the right to request additional information confirming the validity of specific agreements, i.e., that specific and appropriate contractual agreements are in place that show that applicant has the required controlling rights over the assay and biomarker to enter into a supply agreement as contemplated under this RFP.

ADDITIONAL CONDITIONS

For this RFP, applicants who are selected for final awards are expected to:

- Commit to undertake activities that enable product supply for clinical trialing (volume and details to be negotiated).
- Provide SOPs, QC plan and training tools for submitted solutions for clinical trialing.
- Sign a supply agreement with Radboudumc (currently being drafted) for provision of materials and resources for trialing.

SELECTION AND AWARD PROCESS

The deadline for receipt of submissions is 30 January 2023 A commitment to a compressed timescale is required, and we anticipate contract execution within 6 months from posting of this RFP. The selection process is designed to be objective, independent, and transparent to ensure that the most suitable technologies are supported, and potential conflicts of interest are avoided. Candidates will be evaluated by a review panel comprised of subject matter experts from the UNITE4TB consortium with backgrounds in technical R&D including IVD development, drug development, clinical evaluation, product launch, and implementation. The review panels will use information submitted in the application (see **Application Requirements** section below) as well as publicly available information. The review panels may request additional information or clarifications, if needed, in writing. Applications will be evaluated in stages, as follows (see Table below):

- **Stage 0.** All applicants' eligibility will be verified and those that are "out of scope" will be excluded. Out of scope applications may include, but are not limited to, early-stage assays with little/no verification or performance data or no evidence of quantitative assessment of viable *M. tuberculosis* complex bacilli or bacterial signatures. Applicants should also verify that they will be eligible to sign a supply agreement in line with trialing timelines. A long list of eligible candidates will advance to Stage 1.
- **Stage 1.** This first evaluation will down select the long list of candidates to a short list of candidates. An internal review panel will evaluate long-listed candidates using the submitted application materials (See **Application Requirements**). More specifically, candidates will be evaluated on existing product specifications, scored in the sheet titled **"Technical Assessment"** in the **Assessment Matrix.** The internal review panel will then score the candidate's alignment to the goals of the RFP (see sheet titled **"Alignment Criteria"** in the **Assessment Matrix**). The **Applicant's Total Score** will then be calculated as a weighted sum of the scores from the Technical Assessment (cell J17) and Alignment Criteria (cell C10). Short listed candidates will be selected in a consensus call of reviewers and will advance to Stage 2.
- **Stage 2.** This second evaluation will down-select short-listed candidates to a list of finalists. Candidates will be evaluated using:
    - o Follow-up Questions and Answers (by email and/or teleconference): Short-listed candidates will be invited to address a set of questions provided to the candidates in advance.
    - o Applicant Presentation, which details specific topics described in the Application Requirements.
    - o Scores from the Technical Assessment (Stage 1) will also be provided to the secondary review panel.

The secondary review panel will score the candidate's alignment to the goals of the RFP (see sheet titled **"Alignment Criteria" in the Assessment Matrix**) – this scoring will be conducted *independently of the candidate's score in the Alignment Criteria from the internal review panel during Stage 1.* Lastly, the **Applicant's Total Score** will be calculated. Finalists will be selected in a consensus call of reviewers and will advance to contract negotiation. Final awards and contract execution is expected to be completed by end February 2023. Note: Applicants not selected will be notified.

Stage 0	Stage 1	Stage 2
Initial screening of all applicants to a set of long-listed candidates	*First evaluation to select a short-list of candidate assays*	*Second evaluation to select a final list of candidate assays*
• Verification that the contents of the application are in-scope. Applicants that are out of scope will be excluded. • Verification of applicant eligibility. Applicants that are not eligible will be excluded.	• Evaluation of long-listed candidates will be performed by an internal review panel consisting of members of the UNITE4TB biomarker work package. • Candidates will be evaluated based on: o Score on the "Technical Assessment" within the Assessment Matrix o Applicant Presentation • The internal review panel will score the candidate's overall alignment with the goals of the RFP (see sheet titled "Alignment Criteria" within the Assessment Matrix).	• Evaluation of short-listed candidates will be performed by a second review panel consisting of selected members from the UNITE4TB Steering Committee and invited external international experts. • Candidates will be evaluated based on: o Scores on the "Technical Assessment" completed in Stage 1 o Applicant Presentation o Follow-up questions and answers • The second review panel will score the candidate's overall alignment with the goals of the RFP (see sheet titled "Alignment Criteria" within the Assessment Matrix).

APPLICATION REQUIREMENTS

Applications should include the following:

1. **Applicant Presentation**
   - Applicants shall provide a slide deck of **no more than 25 slides** that must include the following information, and must use the provided PowerPoint template (see **HOW TO APPLY** for templates and forms):
     - Overview of the assay/platform.
     - Current performance of the assay: evidence of the assay performance, including but not limited to any existing verification and/or validation studies demonstrating performance (published or internal), especially in regard to quantification of viable *M. tuberculosis* bacilli.
     - Alignment with Product Requirements. Provide evidence to support performance claims, particularly for requirements denoted with a Weight of '3' in the sheet titled "Technical Assessment" in the **Assessment Matrix.**
     - Development roadmap, including current stage of development and any proposed activities to meet the design requirements, where the existing specification does not meet either the Optimal or Acceptable specification (in sheet titled "Technical Assessment" in the **Assessment Matrix**).
     - Description and timeline of activities proposed under this award for supply of assays by the applicant.
     - Plans and timelines for stringent regulatory approval, if any.
2. **Assessment Matrix**
   - Applicants are to complete the Technical Assessment portion of the provided spreadsheet titled "Assessment Matrix" (see **HOW TO APPLY** for templates and forms), specifically:
     - Please describe the system's **existing** Design Specifications (column F), and provide supporting evidence and/or data (column G) to support the claims in column F.
     - If the Existing Specification does not fall within the Acceptable and Optimal Specifications, please use the Applicant Presentation to briefly describe the expected activities and timeline required to modify the existing specification into a proposed acceptable specification.
3. **Supporting Documents**
   - Aside from the 2 forms listed above, the only additional documents allowed for submission are registration/regulatory certificates, QMS/ISO certificates, instructions for use/product inserts for existing or relevant products, if available, and CVs from relevant team members and management.
   - There will not be public opening of awards, or separate technical and financial bidding documents.

HOW TO APPLY

Submit applications via the FIND's Technology Scouting Submission Webform. Please select Tuberculosis as the Disease Area, and **'RFP: UNITE4TB TB Rx Monitoring'** as the 'Disease Area Subtype' and proceed with the online submission. Templates for the Applicant Presentation and Assessment Matrix can be downloaded from the submission portal. Please upload your completed **Applicant Presentation** and **Assessment Matrix,** along with any supporting documents by **30 January 2023**.

QUESTIONS & FURTHER INFORMATION

Please email questions to U4TB_RxMonitoring.ch@finddx.org, Jan.Heyckendorf@uksh.de and ikontsevaya@fz-borstel.de Questions will be accepted and responded to expediently until 26 January 2023.

CONFIDENTIALITY

FIND considers any application and supporting documents received under the RFP as confidential. FIND will not disclose the proposal to third parties without the prior written agreement of the proposal submitter but will be allowed to share with members of the review panel who have entered in a confidentiality agreement with FIND for these review purposes and shall be recused if found to have a potential conflict of interest (which they are obliged to disclose). Any specific questions concerning confidentiality should be addressed to FIND.