

Position statement on innovative clinical trial design for development of new TB treatments

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Tuberculosis (TB) therapeutics is advancing rapidly, with an increasing number of new and repurposed compounds undergoing evaluation as part of novel treatment regimens. The development of new TB drugs remains complex, lengthy and costly, and the pathway to establishing the efficacy of new TB treatment regimens is fraught with numerous obstacles and uncertainties (1). Recent successes in identifying new shorter regimens for drug-sensitive TB (DS-TB) and drug-resistant (DR-TB) pulmonary TB, however, provide new hope for additional advances to be realized in TB therapeutics in the coming decade (2,3).

Research and innovation is one of the three pillars of the End TB Strategy (4). The discovery, development and rapid uptake of new tools, interventions, and strategies are critical to substantially reduce TB incidence and reach the global End TB targets. This includes shorter, safer and more effective regimens for treating DS-TB and DR-TB that can be used in all patient populations, including children, pregnant women, people living with HIV, people who inject drugs and other subgroups (4). In particular, TB therapeutic research should optimize equitable implementation and scale-up of effective innovations. In 2020, WHO published the 'Global Strategy for Tuberculosis Research and Innovation' to support the efforts of governments and other stakeholders to accelerate TB research and improve equitable access to its benefits (5). The strategy calls for greater financial investments in TB research and innovation, strengthening public-private partnerships as well as promoting and improving approaches to data sharing to advance scientific discovery. Building on this work, the WHO Global Tuberculosis Programme has developed this document to support TB regimen development by highlighting key clinical trial characteristics to help advance novel therapies.

This position statement summarises key innovations in TB clinical trial designs, ranging from pharmacokinetic-pharmacodynamic (PK-PD) modelling and new advances in biomarker development to the value of novel clinical trial design methodologies and post-licensure observational studies. For various stages along the development pathway, outstanding challenges are described alongside solutions to help overcome these issues. Beyond a welcome expansion of the TB drug pipeline, innovations in TB drug development and clinical trial design are anticipated to accelarate the development and evaluation as well as facilitate approval of novel regimens to treat all forms of TB.

This position statement focuses on the following elements to support the development and selection of novel and effective TB drugs and/or regimens for clinical trials:

- Translational PK-PD modelling for bridging preclinical and clinical development phases
- Biomarkers to support and/or accelerate decisions on suitable treatment regimens
- Adaptive and seamless Phase 2 trial designs to streamline clinical development
- New Phase 3 trial designs and how they will facilitate ultimate regimen development
- Observational data and special populations (strengthening the evidence-base post licensure)

Translational pharmacokinetic-pharmacodynamic (PK-PD) modelling for bridging preclinical to clinical development phases.

Given the recent progress in TB drug development, it is necessary to first prioritize which medicines may be best incorporated into multidrug regimens and tested in resource- and cost-intensive clinical trials. Translational modelling and quantitative pharmacology has the ability to accelerate drug selection by informing the dose rationale of bactericidal drugs and by identifying the best combination(s) with potential to accelerate sterilization, thus reducing relapse rates and limiting the emergence of resistance (6). Quantitative pharmacology and model-informed drug development have been shown to overcome the limitations of individual models and single experiments and combine data derived from multiple sources. Translation from *in vitro* and *in vivo* experiments to clinical trials involves a complex multi-scale approach that requires **data integration** from experiments investigating efficacy of single and multidrug regimens, immunology, lung and lesion penetration, intra- and extra-cellular distribution, emergence of resistance and intra-bacterial drug transport (7). Data integration platforms should include a toolbox of methods and tools capable of merging data collected across preclinical and clinical phases and describing plasma PK scaling, site-of-disease lesion PK, host immune and bacteria interplay, monotherapy PK-PD relationships, combination PK-PD relationships of multidrug regimens, emergence and impact of resistance, and relevant biomarkers for treatment monitoring and efficacy (8).

Translational platforms should complement Phase 2A, so called early bactericidal activity (EBA), studies and may also benefit Phase 2A study design optimization, rank ordering regimens, combination selection and dose rationalization, especially with inclusion of novel PD biomarkers providing dose-range information. They provide the opportunity to bring a broader range of data into the drug development process, particularly for aspects that are more difficult to study in the clinical setting due to cost, time, resource and clinical population constraints, such as modelling of drug susceptibility across bacterial populations, impact of the emergence of drug resistance, and treatment of hard-to-treat disease.

Areas of research

There is a need to better utilize and apply established translational tools to drive selection of regimens for clinical testing. Integration of animal and clinical trial data for already studied regimens into predictive platform and models is necessary so we can understand full capability and potential limitations, if any, of these tools. This includes data sharing, integration and modelling of preclinical data to predict Phase 2A monotherapy studies, Phase 2B regimen studies and ultimately Phase 3 trials. Further, it is necessary to complement all novel clinical trials with animal experiments to have informative data and understand the time component of overall antibacterial activity (i.e., time dependent PK-PD relationships) for any drug given the complicated interplay of disease pathology and immune response during treatment. In addition, it is of critical importance to apply translational modelling to study acquired resistance to prolong the utility of new drugs and associated treatment regimens. Furthermore, the focus of most translational modelling approaches has been on efficacy outcomes thus far, but further investigation is needed in the areas of drug safety, variability in disease severity and treatment response, as well as treatment adherence patterns. Finally, there is a need to incorporate interpatient variability in drug exposure in the evaluation of antibacterial activity and relapse.

Biomarkers to support and/or accelerate decisions on suitable regimens to be tested.

Novel biomarkers that accurately predict treatment outcome and guide treatment duration decisions would greatly accelerate drug development by enabling prioritized evaluation of the most promising regimens within innovative, adaptive trial designs. Recently there have been substantial advances in this area, such as the ribosomal rRNA synthesis ratio, PET/CT imaging, enzyme-linked immunosorbent assay (ELISA) to measure concentrations of lipoarabinomannan (LAM) in sputum, and the molecular bacterial load assay (9-12).

One of the most critical challenges when evaluating regimens for TB treatment is lack of validated, reproducible and reliable biomarkers that provide quantitative data to differentiate bactericidal potency and possibly sterilizing capability better than current culture techniques. Further, biomarkers that are applicable across *in vivo*, murine, and human studies, permit maximal knowledge integration to select the best TB treatment regimens. Novel biomarkers with real-time quantitative readouts further support innovative clinical trial designs, such as adaptive protocols incorporating rank ordering and prioritization of regimens for clinical evaluation. Furthermore, biomarkers should help identify the presence of organisms that cause relapse, providing qualitative as well as quantitative results.

Areas of research

Since it is unlikely that a single biomarker will be identified that fully characterizes TB disease and predicts each phase of clinical development, research efforts should focus on identifying an array of integrated biomarkers that successfully select the most potent and promising regimens to move forward through the development pathway.

Given the diversity of biomarker candidates, research on potential combination / integration of biomarkers should identify complementarity markers. These biomarkers must be evaluated across a broad range of regimens and in many different settings in order to confirm their validity across different use cases. Thus, a crucial priority is to embed evaluation of investigational biomarkers in future clinical trials, particularly across Phase 2A through 2C trials, as these can allow correlation with early sputum culture endpoints as well as long-term clinical endpoints. In addition, nesting biomarkers within the protocols of multiple trials will provide important diversity and statistical power to support their use.

It is important to distinguish biomarkers that predict an individual patient's response to therapy (which can, in principle, be evaluated in cohort studies with a single regimen) from biomarkers that predict the average treatment response at the regimen- or trial-level. The latter depends on evaluation in the broadest possible range of treatment regimens and durations.

Additionally, more research is needed on the definition of microbiological outcomes. Phase 3 trials are usually designed with composite unfavourable outcome definitions including both microbiological and clinical outcomes, but biomarker assessment requires a microbiologically driven outcome. Moreover, as microbiologic unfavourable outcomes in contemporary Phase 3 trials become uncommon, the standardized integration of biomarker substudies into trial protocols, and the subsequent pooling of data and biospecimens to support biomarker validation efforts becomes even more critically important.

Lastly, for the current portfolio of biomarkers that could provide early and rapid indication of treatment response, it is important to assess variations in dosing and rotation of the drugs within the regimen to limit adaptive response by the bacilli.

There is a need to develop Target Product Profiles to define the suitable characteristics of 'ideal' biomarker(s) as well as to define a clear biomarker strategy in multi-country TB trials based on an updated biomarker landscape analysis. Definitions and standardization of integration of biospecimen collection and biomarker substudies in TB clinical trials protocols is also needed. Ideally, this will require an international forum for biomarker development, to enhance study coordination and collaboration that will compare recent advances and define the key design components and outcomes of biomarker studies.

Adaptive and seamless Phase 2 trial designs to streamline clinical development.

The exploration of the drug/regimen development triad (i.e. drugs, dose, and duration) is ideally addressed in Phase 2 trials in order to minimize uncertainties going into large Phase 3 trials as much as possible. Methods for transitioning TB drugs and regimens through Phase 2 to Phase 3 clinical development stages have evolved significantly in the last decade, with the better integration and use of PK-PD modelling, the use of adaptive trial designs and the novel Phase 2C trial design to facilitate the transition to confirmatory Phase 3 trials. With these new PK-PD modelling and quantitative pharmacology approaches, Phase 2A and 2B studies can provide relevant data on the effect of drug doses and/or plasma concentrations on bacteriological response. Approaches combining preclinical and clinical data have the potential to guide early phase clinical development decisions with greater efficiency, reduced risk of misadventures entering Phase 3, and offer a more reliable clinical development pathway perspective, including dose-finding and rational selection of the components and duration of the treatment regimens to be studied. The number of trials and their designs within the treatment development pathway may differ according to overall objectives (e.g. licensure for regulatory agencies, rapid deployment of regimens for programmes), as well as the characteristics of the regimen and the target population (13). Shortened pathways consisting of fewer trials will require careful consideration of potential trade-offs, i.e. the potential gains in accelerated development should be weighed against additional complexities in trial design and risk. When designing clinical development pathways, it is essential that necessary data are gathered not only for regulatory purposes but also for rapid deployment of treatment in public health programmes and TB-affected communities recognizing,

for example, the central role of the multi-component GRADE framework for WHO guideline development.

There are several promising innovative approaches to middle stage development. **Enrichment for patients with 'hard-to-treat' disease** will increase relapse rates and thus increase the power for regimen comparisons, hence requiring smaller sample sizes. However, this will carry a risk of missing a regimen potentially effective in patients with 'easy-to-treat' disease, and makes predictions to a less selective patient population in Phase 3 more challenging, so attention should be given on how best to minimize these risks. It is also not clear how best to define 'hard-to-treat' disease, to what extent trials should be enriched, and whether the level of enrichment should be linked to the overall disease severity profile of patients initiating treatments in high burden countries. **Risk stratification** is an attractive alternative to enrichment designs as it can define the best durations for patients with 'hard-to-treat' disease, and the shortest possible duration for patients with 'easy-to-treat' disease, provided that the full breadth of disease severity is included (14). However, introducing risk stratification in Phase 2C trials where combination and duration selection typically occur adds an additional layer of complexity, entailing complex adaptive design stopping decisions dependent on regimen, durations, *and* risk strata. Furthermore, power would be greatly reduced in risk-strata subgroups.

Areas of research

There are outstanding questions on where in the clinical development pathway to best conduct dosefinding and duration-response studies. **Dose-finding** is often done in monotherapy studies to provide efficacy and safety data for regulatory approval. Innovative and creative approaches for monotherapy and early combination studies such as adaptive trial designs and platform trials may become more feasible as real-time biomarkers become viable and preclinical-clinical translational platforms evolve. Nonetheless, dose-finding should also be included in Phase 2B studies and developers might consider capturing and measuring dose-response relationships in regimen rather than as a monotherapy, done throughout early and intermediate stages of development to support dosing rationale (15).

More investigation is needed on whether **duration-randomization designs** to estimate durationresponse relationship are more applicable to a Phase 2 setting than a Phase 3 setting, or if they are needed in both sets of trials (16, 17). Because estimating the shape of the duration-response relationship is critical to inform clinical trial designs as early as the middle development phase, the role of preclinical studies and translational platforms to provide suitable information on these relationships should be considered, particularly since observed duration-response relationships may be different between regimens. As an alternative to modelling and estimating **the duration-response relationship** curve, the order-restricted, multi-arm multi-stage design may provide a viable approach to rank durations without making assumptions on the relationship a priori (16, 17). Overall, there are two possibilities: i) determine a range of suitable durations in Phase 2C to take forward to Phase 3, or ii) determine a single duration in Phase 2C to take forward to Phase 3, combined with other methods such as prediction-based or meta-regression to inform possibly (risk-stratified) multi-duration Phase 3 trials.

New Phase 3 trial designs and how they will facilitate ultimate regimen development.

The understanding of the definition of a Phase 3 trial might differ from the perspective of different stakeholders. Generally, a Phase 3 trial is considered a pivotal confirmatory trial that provides the *main* basis for regulatory authority approval by demonstrating robust safety and efficacy of a single drug or drug regimen. Importantly, Phase 3 trials also produce evidence to establish, revise or change treatment guidelines and inform programmatic aspects. It may, however, take more than one Phase 3 trial to achieve these ends, and therefore Phase 3 can encompass more than just those trials designed to immediately inform regulatory approval. Guideline development groups are often faced with operational and programmatic questions that the Phase 3 trial cannot fully address. Critically important to established guideline development processes is the careful consideration of patient preferences, the impact of the interventions on health equity, the impact for programmatic implementation, all elements of which should be considered in designing and implementing Phase 3 TB clinical trials. To assess such pragmatic issues for new regimens, additional Phase 3 or Phase 4 trials may be needed and investments in addressing these domains would be well-justified.

The landscape of TB treatment has evolved considerably over the last 10 years, necessitating careful consideration of various trial aspects and characteristics to ensure that Phase 3 trials deliver high-quality evidence on safety and efficacy of drugs and regimens. This field is evolving, with new and promising approaches to accelerate and de-risk Phase 3 trials currently being developed. These aspects are addressed in greater detail, below.

Areas of research

Platform trials appear suitable for TB drug development as they allow for evaluation of several interventions compared against a common control, resulting in improved efficiencies in recruitment, staffing, regulatory and ethics approvals. Platform trials provide an opportunity to compare multiple regimens, multiple arms, and possibly multiple durations to a common control and use adaptive designs to drop or add new arms as the trial progresses. These trials require clear definitions and standardization of endpoints as well as clear definitions and pre-specification of stopping rules in the protocol. Real-time biomarkers that could accurately predict long-term outcomes of interest would be of considerable benefit to these trials in informing interim analyses for lack of benefit (futility) and

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