**Templates: clinical trial protocol synopsis for TB vaccine development**

**Version 1.0**

**About EDCTP**

The [European & Developing Countries Clinical Trials Partnership (EDCTP)](https://www.edctp.org/) is a public– public partnership between 14 European and 16 African countries, supported by the European Union.

EDCTP’s vision is to reduce the individual, social and economic burden of poverty-related infectious diseases affecting sub-Saharan Africa.

EDCTP’s mission is to accelerate the development of new or improved medicinal products for the identification, treatment and prevention of infectious diseases, including emerging and re-emerging diseases, through pre- and post-registration clinical studies, with emphasis on phase II and III clinical trials. Our approach integrates conduct of research with development of African clinical research capacity and networking.

**About TBVI**

The [Tuberculosis Vaccine Initiative (TBVI)](https://www.tbvi.eu/) aims to support, integrate, translate, and prioritise R&D efforts to discover and develop new TB vaccines that are accessible and affordable for all. In an effort to optimise the discovery and development of new TB vaccines and biomarkers, TBVI facilitates and supports the generation of new knowledge and exchange among R&D partners. TBVI creates an enabling environment for consortium members to promote knowledge sharing through scientific meetings and workshops, publication in scientific and non-scientific journals, formal and informal networking.

This document was developed by TBVI, in collaboration with Beatrice De Vos, as one of the deliverables of the project ‘Development of tools and documents to support coordination of EDCTP TB-vaccine funded research’, which is part of the EDCTP programme support by the European Union. The document reflects the views of the authors. The European Union is not liable for any use that may be made of the information contained herein.

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For more information about this document, please contact the EDCTP Secretariat at [info@edctp.org](mailto:info@edctp.org).

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# Introduction

The clinical development plan (CDP) of a novel TB vaccine candidate should describe the entire clinical programme which includes the successive clinical trials (CT) (Phase 1, 2a, 2b, 3) needed to generate safety and efficacy data supporting the Target Product Profiles (TPP) of the investigational TB vaccine. Each clinical programme should be developed in line with the sponsor’s TPP(s) for the candidate vaccine, which may include one or more target age groups and indications.

The following three templates provide an outline for preparing CT synopses for each of the targets:

* Prevention of TB in neonates or infants
* Adolescent / adult TB vaccine prevention/protection study
* TB therapeutic vaccine study

Each field highlights a key element for consideration before completion. The template can be used for any clinical development phase and only serves as a guide and a tool to prepare a clinical protocol synopsis. It is a free tool for TB vaccine developers that are moving into clinical development with their vaccine candidate.

Information and recommendations for the use of BCG vaccine can be found in the [WHO Report on BCG vaccine use](http://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf).

Researchers, sponsors and investigators planning studies as the basis of a submission for a regulatory marketing approval, should address in the protocol all elements of the “Estimand framework” described in ICH E9(R1) and respective guidance documents from FDA and EMA. The objective of the estimand framework is “to align the clinical study objective with the study design, endpoint, and analysis to improve study planning and the interpretation of analysis.”

An estimand[[1]](#footnote-1) is a description of the treatment effect associated with a clinical trial objective. More specifically, it summarizes what the outcomes would be in “the same patients under different treatment conditions being compared.” The targets of estimation must be defined in advance, allowing design of a trial to estimate treatment effect.

The description of an estimand involves precise specifications of certain attributes, which should be developed based on clinical considerations and how intercurrent events (defined below) are reflected in the clinical question of interest. These attributes should be clearly defined prior to developing a protocol and included in both the protocol and statistical analysis plan.

The characteristics of an estimand include the following four attributes:

* Definition of the targeted study population
* Statement of the endpoint of interest
* Details of any intercurrent events
* Population level summary of the variable of interest.

# Template - Prevention of TB in neonates or infants

This template is to be used if the vaccine candidate is aiming at preventing TB in neonates or infants either as a BCG replacing vaccine or as a BCG boosting vaccine. The objective of the clinical development of the vaccine candidate is to demonstrate an improved efficacy and/ or an improved safety profile compared to an existing BCG vaccine.

When completing this template, please consider Section 7 of the document [WHO Preferred Product Characteristics for New Tuberculosis Vaccines describes the PPC for neonate/ infant TB vaccine](https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1).

For studies conducted with the intent to submit for a regulatory marketing approval the protocol should describe very clearly all elements of the Estimand framework described in ICH E9(R1) -2019 and respective guidance documents from FDA and EMA.

|  |  |  |  |
| --- | --- | --- | --- |
| **Protocol title** | The title should reflect “infants”- “prevention of TB” -study phase (I-III) and objectives of this study.  “Prevention of TB” may reflect the indication for which the vaccine candidate is intended to be developed. | | |
| **Protocol number** | Number/code for this specific protocol that will be used in the future to refer to this protocol | | |
| **Name of sponsor** | Details of sponsor(s) to be added. If multiple sponsors; please add all | | |
| **Drug substance** | Describe generic name of new vaccine candidate | | |
| **Investigational drug product** | Could be a code or acronym of IP given by the sponsor | | |
| **Phase of development** | Phase I/II/III (please select) | Indication: | Prevention of TB disease and/or Prevention of TB infection |
| **Principal investigator** | Study Lead PI or Country lead PI | | |
| **Study centre(s)** | Concise description of participating clinical centres and countries | | |
| **Objectives** | Consider firstly if the vaccine candidate is a BCG replacement or a BCG boosting vaccine.  Describe the precise clinical research question to be answered in the primary and secondary objectives of this study in a detailed manner.  Depending on the stage of development and the available data set of earlier studies, the objectives will differ.  In **Phase 1a**, the objectives are safety and immunogenicity of the vaccine candidate in adults.  In **Phase 1b***,* the objectives are safety and immunogenicity of the vaccine candidate in **neonates in TB endemic areas**.  In **Phase I**, the reactogenicity (systemic adverse events and local: Injection site reaction, fever…) compared to BCG vaccine or placebo depending on strategy should be evaluated as principal objective.  In **Phase 2a***,* the objectives are to study the optimal dose (dose-ranging), formulation, route of administration, and schedule of immunization in terms of safety and immunogenicity. In phase II, the reactogenicity at escalating dose levels compared to BCG vaccine or placebo depending on strategy should be evaluated as principal or secondary objective.  In **Phase 2b** studies*,* a POC design (proof of concept) including efficacy objectives and endpoints is implemented to provide preliminary efficacy data that will help decision-making for further development in Phase 3. Safety objectives are still integrated as secondary objectives.  The **Phase 3** study evaluating the efficacy as primary objective should be conducted with at least one vaccine lot produced at the intended scale for marketing. Its design should consider a clinical assessment of vaccine efficacy and safety and consistency of 3 vaccine lots in terms of safety and immunogenicity (lot to lot consistency objective). Safety and protective efficacy should also be considered in sub populations such as pre-term neonates and neonates born to mothers living with HIV. Safety objectives are still integrated as secondary objectives.  **Phase 4** studies have the objective to assess vaccine’s effectiveness and safety in field conditions and in populations that have not yet been studied during Phase 3 studies.  The outcome measures to achieve these objectives will be worked out in the endpoint section (below) | | |
| **Study design** | Describe shortly the design of the study:   * Consider if the vaccine candidate is a BCG replacement or a BCG boosting vaccine. * Depending on the stage of development and the available data set of earlier studies, the design will target other objectives and influence the design. * Describe if study is using a Placebo group or an active commercial product as control group; open-label or double blind; dose-range; parallel or sequential groups; number of groups; decision points to move dose levels (increase or decrease); use of a Data Safety Monitoring Board.   In general, a **Phase 1** first in human (FIH) study design should be double-blind, randomised, controlled, and dose-escalating to evaluate safety comprising the reactogenicity and immunogenicity of the vaccine candidate in a limited number of healthy, BCG naïve, and, potentially, BCG vaccinated **adults** with no evidence of exposure to TB.  In **Phase 1b**, if neonates/ infants are the target population for the new vaccine candidate, the studies should be designed to evaluate the safety and immunogenicity of the vaccine candidate in **neonates in TB endemic areas**. The study design will be influenced by the vaccination strategy, i.e., BCG replacement or BCG boosting vaccine.  **Phase 2a** studies will then establish the conditions of optimal safety and immunogenicity in the target population(s) related to the dose, formulation, immunisation schedule and route of administration that are to be selected for subsequent efficacy trials.  Larger **Phase 2b** or **Phase 3** pivotal studies will aim at demonstrating the protective efficacy of the vaccine. Epidemiological data that have been collected at study sites should confirm the expected TB disease incidence related to the efficacy endpoint. Concomitant EPI vaccination is strongly advised in these trials.  Thereafter, **Phase 4** trials will study the vaccine effectiveness with an efficacy endpoint in line with the TPP of the product as well as safety in field conditions or in specific at-risk populations not or underrepresented in the pivotal phase III trials. These studies can also study the duration of protection and eventually the need for booster doses. | | |
| **Planned number of subjects** | Specify total N (including screen failure % and drop-out %) and specify minimal N of evaluable subjects | | |
| **Subject population** | Specify subject population: in this template it will be neonates or infants (definition of each age category is described in regulatory guidance documents).  Age criteria should comply with the WHO definition of your target population | | |
| **Diagnosis  and inclusion/ exclusion criteria** | Clearly describe the diagnosis of the disease that is requested to make the subjects eligible to participate in this study (if applicable).  Eligibility of subjects is described extensively in a list of inclusion and exclusion criteria.  In this template (infant prevention TB vaccine), the eligible subjects are healthy neonates / infants. Some specific populations can also be required such as HIV exposed infants. or mother not infected and no active TB case in the household.  *Please carefully consider the sections “HIV exposed and other immunocompromised populations as well as Vaccination of special populations, contraindications and precautions*” when considering the in- and exclusion criteria. | | |
| **Reference product** | Comparator product (if applicable) or a placebo  Definition of the control differs by vaccination strategy:   * if the vaccine candidate is a BCG replacement, BCG is administered at birth in the control group. * if the vaccine candidate is a BCG boosting vaccine, the control group receives a placebo, administered at a pre-defined time after birth BCG vaccination. * *Different BCG vaccine seed strains have evolved over time due to mutations and deletions during replication at different manufacturing sites. As a result, BCG products differ substantially in their genetic and phenotypic properties. Worldwide, the most commonly used vaccine strains are: Russian BCG-I/Bulgaria (approx. 100 countries), Danish 1331, and Tokyo 172-1[[2]](#footnote-2)*.   Choice of comparator BCG vaccine is guided by the country where the study is conducted (vaccine is licensed and used in a given country) and should match as close as possible the seed strain of the new vaccine candidate | | |
| **Route of Administration** | Describe the route of administration in the protocol and adhere to the summary of product characteristics (SmPC) of the comparator product if applicable.  *Commercial BCG vaccines should be administered strictly intradermally.* *BCG vaccination should be given in a healthy and clean area of skin, and the skin should not be cleaned with antiseptic prior to administration of the vaccine. The vaccine should preferably be given in the lateral aspect of the upper arm.*: *If antiseptics (such as alcohol) are applied to swab the skin, they should be allowed to evaporate completely before the injection is made.* | | |
| **Treatment regimens** | Describe in this section if different regimens are studied in a study; for ex 1 dose versus 2 doses; time interval between 2 doses, etc.  A single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter.  Ensure your protocol describes the recommended concomitant vaccines in the target age group.  As newborns are also recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours, co-administration of BCG with the hepatitis B birth dose is strongly recommended as it is safe to do so. BCG can be co-administered with any other infant routine childhood vaccines2. | | |
| **EPI vaccines** | Safety and immunogenicity data from study(ies) of concomitant administration with EPI vaccines should be available before conduct of Phase 3, or a rationale developed and agreed with National Regulatory Authorities justifying why this is not required.  Often a phase 2 study or a subset in phase 3 studies are chosen to study the interaction of the new vaccine candidate with existing EPI vaccines. | | |
| **Duration of treatment** | Describe duration of treatment in this protocol.  Duration of treatment is different from duration of study. Both are requested and are essential for a study protocol.  Duration of the study should take into consideration the WHO PPC for TB vaccines | | |
| **Safety monitoring** | Describe if a data safety monitoring board (DSMB) or independent data monitoring committee (IDMC) is considered during this study. An independent committee of experts is recommended in studies such as first in human studies or studies with vulnerable populations. | | |
| **Endpoints** | Describe the outcome measures or endpoints that translate the objectives of the study for the individual subject and the summary measure for the target population in accordance with ICHE9(R1) and regulatory guidance.  **safety endpoints**: If safetyis the objective of the study, recording of adverse events, treatment related adverse events, serious adverse events etc. will be the safety endpoints. The procedures for safety data collection (diary card, visits, etc.), timing (when) and duration (how long) of this collection of data will have to be determined.  Standardized definitions of adverse events following immunization and uniform data collection processes should be used across all clinical trials (from Phase 1 to Phase 3) to allow pooling of safety data. Due to the co-occurrence of Mtb infection and HIV infection in many TB-endemic regions and the severe outcome of Mtb infection in HIV-infected individuals, the safety of new TB vaccines will need to be assessed in both HIV-uninfected individuals and in persons living with HIV.  The active monitoring of adverse events may (must) be modified in case of occurrence of any unexpected event, especially if causally related to the vaccine candidate, during any phase of development.  Assessment of shedding in the case of a live attenuated vaccine can be considered as a safety endpoint or integrated in the efficacy endpoints.  **Immunogenicity endpoints**: If immunogenicity is the objective of the study, the aim is to define the immunogenicity of the vaccine candidate in humans. Its evaluation should be consistent with the hypothetical immunological mechanisms by which the vaccine is assumed to confer protection against TB infection and/ or disease.  Relevant immunological parameters should be defined, and suitable assays developed and validated, as the clinical plan progresses. Immunological assays should be validated prior to the Phase 2b study (as much as possible) but surely by the start of the pivotal Phase 3 study.  In addition, immunogenicity data of a vaccine candidate is an important opportunity for the identification of correlates of protection in TB, therefore biomarker studies should be designed as early as possible. Specifically, in studies with infants, the limited volume of blood that can be sampled is critical.  **Efficacy endpoints**: If efficacy is the objective of the study, it will be critical to define how this efficacy will be measured. Prevention of active TB disease in a general, healthy population remains the primary focus of vaccine development.  *Will the endpoint be prevention of TB infection (POI) or of TB disease (POD)?*  **Prevention of infection (POI)** would indicate biological activity of vaccine-induced immune response which could be a clinically relevant biological signal and potential indicator of vaccine efficacy, although *Mtb* infection may not be seen as a licensable clinical endpoint by a stringent regulatory authority.  However, the absence of a vaccine’s ability to prevent infection does not necessarily mean absence of efficacy in preventing disease as the immune mechanisms by which a vaccine might prevent infection and disease could be different. Also, demonstration of POI does not guarantee POD since approximately 90% of infected individuals never progress to active TB in the absence of effective vaccination. To know that a vaccine will protect people from active TB and avert cases and deaths, it must be demonstrated that a vaccine candidate shown to prevent infection does so in individuals who, without vaccination, would have developed active TB.  Another approach to obtaining proof of concept is to conduct a Phase 2b POD trial in a population with high risk of disease (to keep size and cost of the trial as low as possible).  **Protection against pulmonary TB Disease (POD):** The Phase 3 trial should confirm the protective efficacy against the primary “case definition” endpoint greater or equal to the minimum predefined efficacy as set in the TPP in the target population for licensure.  Case definitions for TB infection or TB disease employed in the protocol should be well described. The primary efficacy endpoint should be bacteriologically confirmed i.e., culture and/or GeneXpert cases of TB disease using standardized case definition (WHO definitions of TB 2014). Culture confirmation or WHO approved rapid diagnostic (WRD) such as Gene Xpert technology-based test is required rather than the less sensitive and less specific smear microscopy.  Preferably the case definitions should be widely accepted by the medical and scientific community for easy use in the clinic and subsequently in the analysis of the results of the study. Consider broad case definitions contemplating Quantiferon testing, radiographic examinations; clinical definitions, sputum collections (when symptoms only or at predefined timepoints).  Laboratory confirmation of TB should be an integral component of active surveillance for monitoring disease occurrence and vaccine efficacy (if applicable) during the study. The method for detection of TB should be clearly described and in line with current guidelines in case of use of central lab and standardized across all laboratories in case of multicentre participating in the study.  In relation to the immunogenicity or efficacy endpoints, collection and handling of specimens need to be described extensively in the protocol or in an appendix or in a separate manual. This will be instrumental to standardize the methodology across clinical sites. | | |
| **Statistical methods** | Statistical methods to study the safety and /or efficacy of the new vaccine candidate will have to be described. Basis for the sample size calculation, eventually interim analysis etc. will be outlined in the statistical section.  The pooled analysis of safety data should support an acceptable safety profile in the target population, as per TPP.  The approaches taken to the analysis of relevant post-randomization intercurrent events where applicable as per ICH E9(R1), should be described.  In infants, testing for superiority of efficacy over BCG will be conducted and the magnitude of superiority should reflect the expected improvement in public health outcomes. Non-inferiority efficacy testing could be considered for an investigational vaccine offering a substantial benefit compared to BCG (e.g. safety in HIV exposed infants). The margin of non-inferiority should infer non-inferior impact on public health outcomes.  Refer to [**WHO PPC for New TB Vaccines**](http://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1)**:** vaccine efficacy should be equal to or greater than 80% vaccine efficacy as compared to baseline incidence, or superior efficacy as compared to BCG, in preventing TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children.  A comprehensive document called “statistical analysis plan” (SAP) is prepared for each individual trial and must be in a final format before freezing and unlocking of the study database for analysis. | | |

# Template - Adolescent/adult TB vaccine prevention/protection study

Adolescents and adults with TB disease represent the most common sources of Mtb spread and modelling predicts that vaccination of these two populations would have greater and more rapid impact on the TB epidemic than neonatal vaccines ([Harris et al., 2016](https://www.ncbi.nlm.nih.gov/pubmed/27448625)). Those populations are therefore WHO’s priority target for TB vaccine development. Demographic changes in some high endemicity countries justify inclusion of older adults in the target population.

Optimally, a TB vaccine candidate would provide protection against progression to TB disease (PoD) following primary infection, as well as following re-infection(s) and re-activation in subjects with latent infection. Given the absence of reliable correlates of immune protection, highly predictive animal challenge models or controlled human infection models (CHIMs) of mycobacterial infection, efficacy endpoints other than PoD are being explored which could provide clinically relevant evidence of biological activity. Prevention of recurrent TB (PoR) and preventing sustained Mtb infection (PoI) represent alternative efficacy endpoints being explored for early assessment of biological activity of TB vaccine candidates.

This template is to be used if the vaccine candidate is aiming at preventing active pulmonary TB disease in the adolescent/adult population as a BCG boosting vaccine. The objective of the clinical development of the vaccine candidate is providing 50% or more efficacy and/ or a favourable safety profile. Safety and reactogenicity profile should be similar to other current WHO-recommended routine vaccines for use in adolescents and adults.

The relevant WHO PPC for this population is described in section 6 of the document: [WHO Preferred Product Characteristics for New Tuberculosis Vaccines](http://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?ua=1).

For studies conducted with the intent to submit for a regulatory marketing approval the protocol should describe very clearly all elements of the Estimand framework described in ICH E9(R1) -2019 and respective guidance documents from FDA and EMA.

|  |  |  |  |
| --- | --- | --- | --- |
| **Protocol title** | The title should reflect “adolescents”- “prevention of TB” -study phase (I-III) and objectives of this study  In Phase I & IIa “Prevention of TB” may reflect the indication for which the vaccine candidate is intended to be developed. | | |
| **Protocol number** | Number/code for this specific protocol that will be used in the future to refer to this protocol | | |
| **Name of sponsor** | Details of sponsor(s) to be added. If multiple sponsors; please add all | | |
| **Drug substance** | Describe generic name of new vaccine candidate | | |
| **Investigational drug product** | Could be a code or acronym of IP given by the sponsor | | |
| **Phase of development** | Phase I/II/III (please select) | Indication: | Prevention of TB disease or Prevention of TB infection  In Phase I & IIa “Prevention of TB” may reflect the indication for which the vaccine candidate is intended to be developed. |
| **Principal investigator** | Study Lead PI or Country lead PI | | |
| **Study centre(s)** | Concise description of participating clinical centres and countries | | |
| **Objectives** | Describe the precise clinical research question to be answered in the primary and secondary objectives of this study in a detailed manner.  In **Phase 1**, the objectives are safety and immunogenicity of the vaccine candidate in BCG naïve and BCG vaccinated individuals, who have no evidence of latent TB infection, and subsequently in subjects from endemic areas who have evidence of latent TB infection. In phase I, the reactogenicity (systemic adverse events and local: Injection site reaction, fever…) compared to placebo should be evaluated as principal objective.  In **Phase 2a,** the objectives are to study the optimal dose (dose-ranging), formulation, route of administration and schedule of immunization of the vaccine candidate in terms of safety and immunogenicity. In phase II, the reactogenicity at escalating dose levels compared to placebo should be evaluated as principal or secondary objective.  In **Phase 2b** POC studies, the objective will be focusing on the preliminary efficacy in relation to the desired indication (PoD, PoR, PoI). Vaccination aims at preventing TB disease whether it results from reactivation or new infection. Reactogenicity and safety remain secondary objectives.  In **Phase 3** the objective is to confirm the superior efficacy of the vaccine candidate as compared to placebo as set in the TPP in the target population for licensure. In phase III, the reactogenicity and safety compared to placebo should be evaluated as secondary objectives.  **In Phase 4** studies the objective is to confirm long term vaccine effectiveness and safety in large populations under field conditions.  The outcome measures to achieve these objectives will be worked out in the endpoint section (below). | | |
| **Study design** | Describe shortly the design of the study:  For example, is the study using a Placebo group as control group; open-label or double blind; dose-range; parallel or sequential groups; number of groups; decision points to move dose levels (increase or decrease); use of a Data Safety Monitoring Board  **FIH studies (Phase Ia**) should evaluate the safety and immunogenicity of the investigational vaccine in BCG naïve and BCG vaccinated individuals, who have no evidence of latent TB infection, sequentially in the same study.  In addition, Phase 1b studies should evaluate the safety and immunogenicity of the investigational vaccine in subjects from endemic areas who have evidence of latent TB infection.  **Phase 2**  Beside investigating safety and immunogenicity of the vaccine candidate, the studies should assess the protection against pulmonary TB Disease (POD).  The study design of POD phase 2b will reflect the statistical hypothesis of superior efficacy over placebo as there is no current recommendation for BCG booster immunization. POD Phase 2b could be conducted among individuals considered at higher risk of disease to reduce sample size and study duration, e.g. latently infected (QFT+) individuals, health care workers, or household contacts.  Studies assessing prevention of recurrence (POR) could be interesting because POR studies are smaller than prevention of disease (POD) trials (due to higher incidence of recurrence in patients recently treated for TB compared to the incidence TB disease in the general population).  PoI (prevention of infection) studies aim to enrol adolescent and young adult participants who are not Mtb-infected (a determination usually based upon testing negative on a validated TB antigen-stimulated interferon gamma release assay (IGRA-negative) or on a PPD skin test), living in high TB endemicity areas and therefore at risk of acquiring Mtb infection, and assess the efficacy of a vaccine candidate in preventing the acquisition of Mtb infection (defined as conversion from IGRA-negative to IGRA-positive, conversion of a negative to positive PPD skin test) over a specified time period.  However, the absence of a vaccine’s ability to prevent infection does not necessarily mean absence of efficacy in preventing disease as the immune mechanisms by which a vaccine might prevent infection and disease could be different. Also, demonstration of POI does not guarantee POD since approximately 90% of infected individuals never progress to active TB in the absence of effective vaccination. To know that a vaccine will protect people from active TB and avert cases and deaths, it must be demonstrated that a vaccine candidate shown to prevent infection does so in individuals who, without vaccination, would have developed active TB.  According to WHO PPC, a definitive PoD trial would be needed to generate conclusive evidence of protection against TB. Such a **Phase 3** study would be expected to assess vaccine efficacy both in persons with latent TB infection at the time of vaccination, as well as in individuals uninfected with Mtb at the time of study enrolment (refer also to statistical methods). Furthermore, safety should be favourable in particular risk groups, such as individuals living with HIV/AIDS and other causes of immuno-deficiencies, the elderly, pregnant and lactating women.  **Phase 4** studies are designed to confirm vaccine effectiveness and safety in the target population under field conditions, in particular risk groups not yet studied in phase 3 trials and to evaluate the duration of protection and possible need for booster immunization. | | |
| **Planned number of subjects** | Specify total N (including screen failure % and drop-out %) and specify minimal N of evaluable subjects.  Available epidemiological data on the incidence of the relevant endpoint (e.g., Mtb infection and/or TB disease) in the targeted population should be reviewed, particularly in the specific populations where the trials are to be conducted, if available. If the epi data are not available, all efforts should be made to generate them. These data are used to set assumptions for determination of potential sample size requirements for appropriate power to demonstrate the clinical benefit of the investigational vaccine and ensure that these are within the limits of study feasibility. | | |
| **Subject population** | Specify subject population: in this template it will be adolescents (definition of each age category is described in regulatory guidance documents) and adults.  Age criteria should apply with the WHO definition of your target population.  New TB vaccines for adolescents and adults must cover those with and without evidence of latent Mtb infection and be safe for use in HIV-infected populations.  The study population age should be consistent with the predominant age range in TB disease burden in the region.  In **Phase I** studies, at first the subjects should be BCG naïve and BCG vaccinated individuals, who have no evidence of latent TB infection. Thereafter the subjects from endemic areas with evidence of latent TB infection should be studied.  In **Phase 2** proof of concept (PoC) studies, the study population will depend on the objectives of the study. In PoD studies, latently infected (QFT+) individuals, health care workers, or household contacts should be considered. In PoR studies, patients recently treated for Tb and cured should be considered. In PoI studies, subjects who are not Mtb-infected) and living in high TB endemicity areas should be considered.  As pre-vaccination screening for infection status cannot be routinely considered for programmatic reasons, it is critical that **Phase 3** study populations include both QTF- and QTF+ individuals.  Although study design and power should ideally be for protective efficacy against TB disease in both QTF- and QTF+ individuals, such a study would be extremely large and complex making it unlikely to be feasible.  If powered to show vaccine efficacy against primary endpoint in QTF + strata, the study should offer an acceptable assessment of safety and trend for efficacy in QTF- strata.  **Phase 4** studies should consider effectiveness and safety in relevant populations that have not yet been fully studied, e.g. QTF- population to confirm Phase 3 efficacy trend or specific populations such as elderly, HIV-infected adults. | | |
| **Diagnosis  and inclusion/ exclusion criteria** | Clearly describe the diagnosis of the disease that is requested to make the subjects eligible to participate in this study (if applicable).  Eligibility of subjects is described extensively in a list of inclusion and exclusion criteria.  Adolescents and adults with and without evidence of latent Mtb infection should be studied.  Elderly should be studied if the epidemiological data indicate a need in elderly e.g. China (optimal timing to study the subpopulations need to be considered when writing the synopsis)  HIV-infected adults should be studied. (optimal timing to study the subpopulations need to be considered when writing the synopsis) | | |
| **Route of Administration** | Describe the route of administration in the protocol and adhere to the SmPC of the comparator product.  BCG vaccines should be administered strictly intradermally. BCG vaccination should be given in a healthy and clean area of skin, and the skin should not be cleaned with antiseptic prior to administration of the vaccine. The vaccine should preferably be given in the lateral aspect of the upper arm. If antiseptics (such as alcohol) are applied to swab the skin, they should be allowed to evaporate completely before the injection is made. | | |
| **Reference product** | Comparator product is a **placebo**  There is no current recommendation for BCG booster immunization. | | |
| **Treatment regimens** | Describe the proposed regimen for the given trial; evaluate if different regimens are to be studied in a study; for example, 1 dose versus 2 doses; time interval between 2 doses, etc. | | |
| **Duration of treatment** | Describe duration of treatment in this protocol.  Duration of treatment is different from duration of study. Both are requested and are essential for a study protocol and should be customized to the vaccine candidate.  Duration of the study should take into consideration the WHO PPC for TB vaccines. | | |
| **Safety monitoring** | Describe if a data safety monitoring board (DSMB) or independent data monitoring committee (IDMC) is considered during this study. An independent committee of experts is recommended in studies such as first in human studies or studies with vulnerable populations. | | |
| **Endpoints** | Describe the outcome measures or endpoints for the individual subject and the summary measure for the target population in accordance with ICH E9(R1) and regulatory guidance that translate the objectives of the study.  **Safety endpoints**: If safety is the objective of the study, recording of adverse events, treatment related adverse events, serious adverse events etc. will be the safety endpoints. The timing (when) and duration (how long) of this collection of data will have to be determined.  Standardized definitions of adverse events following immunization and uniform data collection processes should be used across all clinical trials (from Phase 1 to Phase 3) to allow pooling of safety data. Due to the co-occurrence of Mtb infection and HIV infection in many TB-endemic regions and the severe outcome of Mtb infection in HIV-infected individuals, the safety of new TB vaccines will need to be assessed in both, HIV-uninfected and HIV-infected, individuals. In case of a live attenuated vaccine, assessing vaccine shedding should be integrated in the endpoints.  Safety data in both QTF- and QTF+ adults are required.  The active monitoring of adverse events may (must) be modified in case of occurrence of any unexpected event, especially if causally related to the vaccine candidate, during any phase of development.  **Immunogenicity endpoints**: If immunogenicity is the objective of the study, the aim is to define the immunogenicity of the vaccine candidate in humans. Its evaluation should be consistent with the hypothetical immunological mechanisms by which the vaccine is assumed to confer protection against TB infection and/ or disease. Relevant immunological parameters should be defined appropriately, and suitable assays developed and validated as the clinical plan progresses. Immunological assays should be validated prior to the Phase 2b study (as much as possible) but surely by the start of the pivotal Phase 3 study.  In addition, immunogenicity data of a vaccine candidate is an important opportunity for the identification of correlates of protection in TB, therefore biomarker studies should be designed as early as possible or working out a plan to identify biomarkers.  **Efficacy endpoints**: If efficacy is the objective of the study, it will be critical to define how this efficacy will be measured. Different efficacy endpoints are under consideration.  **Prevention of infection (POI):** endpoint to assess efficacy of the vaccine candidate in preventing acquisition of Mtb infection measured by conversion from IGRA-negative to IGRA-positive or conversion of a negative to positive PPD skin test) over a specified time period.  **Prevention of recurrence (POR):** endpoint to assess efficacy of the vaccine candidate in preventing recurrence of disease in patients recently treated for TB and cured.  **Protection against pulmonary TB Disease (POD):** endpoint to assess efficacy of the vaccine candidate in protection against pulmonary TB disease. To reduce sample size and study duration this endpoint could be studied among individuals considered at higher risk of disease, e.g. latently infected (QFT+) individuals, health care workers, or household contacts.  The Phase 3 trial should confirm the protective efficacy against the primary “case definition” endpoint greater or equal to the minimum predefined efficacy as set in the TPP in the target population for licensure.  In POD, the primary efficacy endpoint should be bacteriologically confirmed i.e., culture and/or GeneXpert **cases of TB disease** using standardized case definition (WHO definitions of TB 2014). Culture confirmation or WHO approved rapid diagnostic (WRD) such as Gene Xpert technology-based test is required rather than the less sensitive and less specific smear microscopy.  Case definitions for TB infection or TB disease employed in the protocol should be well described. Preferably the case definitions should be widely accepted by the medical and scientific community for easy use in the clinic and subsequently in the analysis of the results of the study. Consider broad case definitions contemplating Quantiferon testing, radiographic examinations; clinical definitions, sputum collections (when symptoms only or at predefined timepoints) ….  Laboratory confirmation of TB should be an integral component of active surveillance for monitoring disease occurrence and vaccine efficacy (if applicable) during the study. The method for detection of TB should be clearly described and in line with current guidelines in case of use of central lab and standardized across all laboratories in case of multicentre participating in the study.  In relation to the immunogenicity or efficacy endpoints, collection and handling of specimens need to be described extensively in the protocol or in an appendix or in a separate manual. This will be instrumental to standardize the methodology across clinical sites.  Standards for reading Chest X-rays should be described in the protocol or in an appendix or in a separate manual. and shared across clinical centres. | | |
| **Statistical methods** | Statistical methods to study the safety and /or efficacy of the new vaccine candidate will have to be described. Basis for the sample size calculation, eventually interim analysis etc. will be outlined in the statistical section.  The approaches taken to the analysis of relevant post-randomization intercurrent events where applicable as per ICH E9(R1), should be described.  The study design for Phase 2b will reflect the statistical hypothesis of superior efficacy over placebo as there is no current recommendation for BCG booster immunisation.  For Phase 3, the target efficacy of the vaccine candidate is 50% or greater in preventing confirmed pulmonary TB in line with WHO PPC.  Analysis of the data from the Phase 3 trial should confirm protective efficacy against the primary case definition endpoint greater or equal to the minimum predefined efficacy as set in the TPP in the target population for licensure.  A comprehensive document called “statistical analysis plan” (SAP) is prepared for each individual trial and must be in a final format before freezing and unlocking of the study database for analysis. | | |

Template - Clinical trial protocol synopsis for a ’TB therapeutic vaccine study’

The clinical development plan (CDP) of a novel therapeutic TB vaccine candidate should describe the entire clinical programme which includes the successive clinical trials (Phase 1, 2a, 2b, 3) needed to generate safety and efficacy data supporting the Target Product Profiles (TPP) of the investigational TB vaccine.

Treating tuberculosis (TB) requires a multidrug course of treatment lasting 6 months for drug-sensitive TB (DS), or longer for drug-resistant TB (DR), multidrug-resistant TB (MDR), and extensively drug-resistant TB (XDR) respectively. This treatment is difficult to finish and often not well tolerated. Treatment failure and recurrence after end-of-treatment can have devastating consequences, including progressive debilitation, death, the transmission of *Mycobacterium tuberculosis* — the infectious agent responsible for causing TB — to others, and may be associated with the development of DR TB.

Therapeutic vaccines are primarily intended to be used as an adjunct to TB drugs and suitable for any age group. The aim of therapeutic vaccination is to improve treatment efficacy in individuals who suffer from TB disease actively or post TB drugs treatment. Consequently, the design of the vaccine candidate and the development pathway for therapeutic TB vaccines is substantially different from prophylactic indications, in particular the design of clinical studies. The target outcomes of therapeutic vaccines are to improve success of treatment, particularly for MDR TB, or to decrease or prevent relapse. Shortening the duration of TB drug treatment and/or reducing the number of TB drugs necessary to cure TB disease should also be considered. A connected TB vaccine indication relates to the prevention of progression to TB disease in individuals with latent TB infection (LTB), sometimes referred to as a **post-exposure vaccine strategy.**

Because of these multiple possible outcomes, there will be a number of aspects of the development pathway which differ compared to prophylactic vaccines. Notably, clinical trial designs will need to evaluate safety, define optimal timings, and dosage in relation to drug treatment, and ensure that standard chemotherapy is not adversely affected by vaccination. Furthermore, other indications including prevention of TB in the general population or in recently exposed individuals should be considered in the late phase of the development plan.

Adolescents and adults are the primary sources of Mtb transmission. Ultimately, the target population for therapeutic TB vaccines is all persons, regardless of age, during or towards the end of treatment for active TB disease, due to drug-sensitive or drug-resistant strains. The medical need for a therapeutic vaccine against TB is global. TB patients otherwise healthy as well as patients with co-morbidities or other risk factors should be allowed to benefit from an intervention proven effective.

This template is to be used if the vaccine candidate is aiming at treating or curing TB in TB infected population (LTB, DR TB, MDR TB, XDR TB) either as an adjunct to chemotherapy during or after the TB drugs or as a treatment to prevent relapse. The objectives of therapeutic vaccines are to improve success of treatment, particularly MDR and XDR TB, or to decrease or prevent relapse. Shortening the duration of TB drugs and/or reducing the number of drugs necessary to cure TB disease should also be considered.

More information can be found in the document [Preferred product characteristics for therapeutic vaccines to improve tuberculosis treatment outcomes: Key considerations from World Health Organization consultations](https://doi.org/10.1016/j.vaccine.2019.10.072) and in the [WHO PPC for Therapeutic Vaccines to improve TB treatment](https://apps.who.int/iris/bitstream/handle/10665/330448/WHO-IVB-19.05-eng.pdf?ua=1).

For studies conducted with the intent to submit for a regulatory marketing approval the protocol should describe very clearly all elements of the Estimand framework described in ICH E9(R1) -2019 and respective guidance documents from FDA and EMA.

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| --- | --- | --- | --- |
| **Protocol title** | The title should reflect “age group”- “treatment of TB or therapeutic TB vaccine candidate” - study phase (I-III) – disease condition of target population (LTB, DS TB, DR TB, MDR TB, XDR TB)\* – adjunct to or post TB drug treatment- and objectives of this study (safety, immunogenicity, efficacy).  \*please select whatever is applicable | | |
| **Protocol number** | Number/code for this specific protocol that will be used in the future to refer to this protocol | | |
| **Clinical Trial Number** | Please add Clinical Trial Number | | |
| **Trial Acronym or code** | Please add Trial Acronym or code if applicable | | |
| **Name of sponsor** | Details of sponsor(s) to be added. If multiple sponsors; please add all | | |
| **Drug substance** | Several vaccine candidates are presently considered for use as therapeutic TB vaccines, including attenuated and inactivated-whole organisms, fragmented mycobacteria and adjuvanted protein subunit molecules.  Describe the generic name of new vaccine candidate and its type | | |
| **Investigational drug product** | Could be a code or acronym of IP given by the sponsor | | |
| **Phase of development** | Phase I/II/III (please select) | Indication: | Therapeutic vaccine Treatment of active TB disease/ drug-resistant TB disease/ multidrug-resistant TB disease |
| **Principal investigator** | Study Lead PI or Country lead PI | | |
| **Study centre(s)** | Concise description of participating clinical centres and countries | | |
| **Objectives** | Describe the precise clinical research question to be answered in the primary and secondary objectives of this study in a detailed manner (see also design of study).  The outcome measures to achieve these objectives will be worked out in the endpoint section (below). | | |
| **Study design** | A therapeutic vaccine for TB patients, administered towards completion of a prescribed course of drug therapy or at certain time(s) during treatment, could improve outcomes through immune-mediated control and even clearance of bacteria, potentially prevent re-infection or relapse, and provide an opportunity to shorten and simplify drug treatment regimens. Please also refer to the section of endpoints.  **Phase 1a** studies in healthy volunteers might not be required for a therapeutic vaccine. This could be discussed with the regulator.  **Phase 1b** studies might not be required if safety and immunogenicity data are available from BCG vaccinated Mtb infected individuals. Proceed to Phase 2a (dose and regimen selection). Alternatively, individuals with LTB could be envisaged for a FIH study.  **Phase 2a** Safety and immunogenicity studies are designed to define the optimal dose level and timing of therapeutic vaccination relative to antibiotic treatment. Phase 2 safety data support the dose and timing of vaccine administration related to the antibiotic treatment.  **Phase 2b** Proof of-concept efficacy testing may be best done in adults with TB and without co-morbidities known either to reduce the likelihood of curing their TB disease or diminish the potential effectiveness of a new vaccine. Furthermore, proof-of concept testing should be established in individuals with drug-sensitive TB, before moving into DR TB.  Alternatively, proof of concept efficacy testing could be studied in MDR TB as the vaccine effect may be more easily observed. This needs to be balanced against the fact that MDR TB is a much more heterogenic population. Although subjects with drug-resistant TB represent a very important potential target for therapeutic vaccines, the large variation between individuals in disease course and types of resistance is likely to influence treatment outcome, increasing background variability and potentially affecting estimation of the vaccine effect. Additionally, enrolling a cohort of persons with drug-resistant TB into large-scale clinical efficacy trials is likely to prove difficult, requiring multiple sites and high costs.  For initial proof-of-concept testing, the administration of vaccines at the end of TB treatment in individuals enrolled only after end of standard of care treatment delivered in a routine setting, may be appropriate. The standard of care TB treatment may differ from country to country and should therefore be compatible with national requirements where the specific study is conducted.  The **Phase 3** study should be designed and powered to evaluate a primary endpoint such as prevention of recurrence/relapse (POR) or shortening the duration of TB drug treatment or reducing the number of TB drugs (less toxicity with equal or improved efficacy) or reduction of mortality or preventing progression to TB disease in LTB.  The single or multiple co-primary efficacy endpoints are directly linked to the primary objectives of the study with a given target population and related standard of care TB drugs.  Separate analysis by relapse and reinfection could also be considered. The increase in the cure rate of TB drugs regimens is likely to be a very difficult endpoint to reach under clinical trial conditions.  **Phase 4** effectiveness studies will be designed to confirm the increase in cure rate of TB drugs, to evaluate potential additional benefits of therapeutic vaccination such as TB drug treatment shortening, and / or reduction in toxicity of TB drug treatment (shortening or reducing number of drugs).  Describe shortly the design of the study for this synopsis:   * For example, use of a Placebo or active product as control group; open-label or double blind; dose-range; parallel or sequential groups; number of groups; decision points to move dose levels (increase or decrease); use of a Data Safety Monitoring Board * Use of TB drugs (use of one or multiple drugs) and duration of treatment (should be according to approved use of the drug(s) according to summary of product characteristics (SmPC) * Time relationship of vaccination to TB drug treatment * Single or multiple vaccinations with the vaccine candidate | | |
| **Planned number of subjects** | Specify total N (including screen failure % and drop-out %) and specify minimal N of evaluable subjects | | |
| **Subject population** | Therapeutic vaccines are administered to persons who have already manifested signs and symptoms of infection by the targeted organism and are therefore most likely adolescents and adults. If paediatric population is considered, a specific paediatric investigational plan (PIP) should be worked out and presented to the NRA/EMA/FDA.  Specify the target population: Latent TB (LTB), drug-resistant TB (DR TB), multi drug resistant TB (MDR TB), extensively drug-resistant TB (XDR)  in this template it will be subjects with a specific TB condition depending on the stage of clinical development of the vaccine candidate and the composition of the vaccine candidate.  Age criteria should comply with the WHO definition of the target population.  New therapeutic TB vaccines must also be safe for use in HIV-infected populations. | | |
| **Diagnosis  and inclusion/ exclusion criteria** | Describe clearly the diagnosis of the disease that is requested to make the subjects eligible to participate in this study (if applicable).  Eligibility of subjects is described extensively in a list of inclusion and exclusion criteria. | | |
| **Reference product** | In therapeutic vaccine development most likely, a placebo will be acceptable as BCG has not been approved as a therapeutic vaccine. | | |
| **Route of Administration** | Test vaccines (active and placebo) should be administered strictly intradermally. The vaccination should be given in a healthy and clean area of skin, and the skin should not be cleaned with antiseptic prior to administration of the vaccine. The vaccine should preferably be given in the lateral aspect of the upper arm. If antiseptics (such as alcohol) are applied to swab the skin, they should be allowed to evaporate completely before the injection is made. | | |
| **Treatment regimens**  **Chemotherapy: TB drugs** | Globally, an estimated 85% of cases of DS TB, and only 55% of cases of DR TB and 30% in XDR-TB, are successfully cured at the end of the initiated treatment.  Reports of recurrence rates vary, often between 2 and 15%, with higher rates seen in countries demonstrating high TB incidence and poor TB control. Most recurrence occur between 6 months and 2 years of completing treatment.  Standard TB drug treatment recommendations for DS TB or DR TB should be followed. Clearly describe the TB drugs and adhere to the SmPC of the drug products. | | |
| **Timing of immunization** | * A therapeutic vaccine could be administered around the time of completion of TB drug treatment (focus on reducing the rate of TB recurrence). * A therapeutic vaccine administration could be administered around the conclusion of the initial, intensive phase of drug treatment (potential to increase cure rates in addition to reduce rates of recurrence). * A therapeutic vaccine could be administered around the time of TB diagnosis or initiation of treatment. | | |
| **Duration of treatment** | Describe duration of treatment in this protocol. In case chemotherapy is part of the active treatment phase, the duration of the chemotherapy should be clearly described as well as the acceptable therapeutic windows.  Duration of treatment is different from duration of study. Both are requested and are essential for a study protocol.  Based on current WHO TPP, a reduction of recurrence rates over one year or more following a drug mediated cure is the objective. | | |
| **Safety monitoring** | Describe if a data safety monitoring board (DSMB) or independent data monitoring committee (IDMC) is considered during this study.  An independent committee of experts is recommended in first in human studies or studies with vulnerable populations or novel indications. It could also be useful to consider such committee during large phase 3 trials when interim analyses are planned. | | |
| **Endpoints** | Describe the outcome measures or endpoints for the individual patient and the summary measure for the target population in accordance with ICH E9(R1) and regulatory guidance that translate the objectives of the study.  **Safety endpoints:** The aim is to monitor and evaluate the safety of the product through clinical studies as described in the clinical development plan. Standardised definitions of adverse events following immunisation and data collection should be used across all clinical trials (from Phase 1 to Phase 3) to allow pooled analysis of safety data.  When safety is the objective of the study (primary or secondary), recording of adverse events, treatment related adverse events, serious adverse events etc will be safety endpoints. The timing (when) and duration (for how long) of this collection of data will be determined. Collection of local adverse reactions (injection side reactions, swelling, redness etc) or systemic adverse reactions (fever, malaise, pain etc) immediately after vaccination (up to 7 or 14 days) are the so-called reactogenicity profile of the new vaccine candidate. All adverse events with severity grading are collected throughout the entire study duration (in early phase studies). In later stages of the development when the safety profile is already well documented, only serious adverse events may be collected.  Due to the co-occurrence of Mtb infection and HIV infection in many TB-endemic regions and the severe outcome of Mtb infection in HIV-infected individuals, the safety of new TB vaccines will need to be assessed in both HIV-uninfected and HIV-infected individuals.  In case of therapeutic vaccine development, the safety data of the vaccine administration may be closely related to the TB drug treatment. It is therefore important to carefully distinguish the side effects of the drug treatment from the vaccine. The published safety package (SmPc) of the TB drug treatment needs to be extensively described in the protocol so that the investigator can evaluate the relationship to drug treatment versus vaccine candidate.  When therapeutic vaccines are administered to sick patients, special attention should be paid to the occurrence of a delayed-type (Type IV) hypersensitivity reaction, resulting in necrosis at the site of injection as well as the possibility of developing pulmonary and systemic inflammatory reactions, and the breakdown of granuloma structure potentially resulting in Mtb dissemination These safety endpoints should be pro-actively monitored.  **Immunogenicity endpoints**: If immunogenicity is the objective of the study, the aim is to define the immunogenicity of the vaccine candidate in humans. Its evaluation should be consistent with the hypothetical immunological mechanisms by which the vaccine is assumed to confer protection against TB infection and/ or disease.  Relevant immunological parameters should be defined appropriately, and suitable assays developed and validated as the clinical plan progresses. Immunological assays should be validated prior to the Phase 2b study (as much as possible) but surely by the start of the pivotal Phase 3 study.  In addition, immunogenicity data of a vaccine candidate is an important opportunity for the identification of correlates of protection in TB, therefore biomarker studies should be designed as early as possible, or a plan worked out to identify biomarkers.  **Efficacy endpoints**: If efficacy is the objective of the study, it will be critical to define how this efficacy will be measured. Different efficacy endpoints are under consideration. Refer to WHO Preferred Product Characteristics (PPC) for Therapeutic TB Vaccines.  **Prevention of recurrence (POR):** endpoint to assess efficacy of the vaccine candidate in preventing recurrence of disease by endogenous relapse or exogenous reinfection in patients recently treated for TB and cured.  **Prevention of progression to TB disease in individuals with LTB** (referred to as a post-exposure vaccine strategy): endpoint to assess efficacy of the vaccine candidate in preventing progression to TB disease in LTB patients.  **Increasing the proportion of patients surviving to cure (reduction of mortality):** consider this endpoint particularly in cases of DR TB given the poor rates of survival and cure when treating MDRTB and, particularly, XDR-TB. Prevention of long-term pulmonary disability is also an important patient-centred goal. Both endpoints could be considered as secondary efficacy endpoints of the therapeutic vaccine candidate.  **Shortening the duration of TB drug treatment**  For a therapeutic vaccine, WHO recommends initial demonstration of efficacy by protection against TB recurrence following initial cure or an increase the proportion of cured patients at end of drug treatment. Initial proof-of-concept for prevention of recurrence when added to standard therapy could be demonstrated on the basis of one year of follow-up. Subsequent confirmatory comparative randomised studies of vaccines added to standard therapy versus a desired experimental regimen would then be required. WHO PPC target as 50% or greater efficacy in reducing the rate of recurrent TB after a standard course of drug treatment, and/or 50% or greater reduction in treatment failure at the end of drug treatment.  **Reducing the number of TB drugs necessary to affect cure.**  As above.  In the absence of reliable animal or early clinical models for therapeutic vaccines, proof of-principle for therapeutic vaccine efficacy should first be established in study participants receiving standard of care drug regimens, before attempts are made to shorten or simplify new drug regimens in combination with vaccination.  Define the criteria to confirm the diagnosis of an active pulmonary TB disease by bacteriology using culture and/or GeneXpert in line with standardised case definitions (WHO definitions of TB 2014). Culture confirmation or WHO approved rapid diagnostic (WRD) such as Gene Xpert technology-based test is required rather than the less sensitive and less specific smear microscopy.  Laboratory confirmation of TB should be an integral component of active surveillance for monitoring disease occurrence and vaccine efficacy (if applicable) during the study. The method for detection of TB should be clearly described and in line with current guidelines in case of central lab and standardized across all laboratories in case of multicentre participating in the study.  Case definitions employed in the protocol should be well described. Preferably the case definitions should be widely accepted by the medical and scientific community for easy use in the clinic and subsequently in the analysis of the results of the study. Consider broad case definitions contemplating several aspects such as radiographic examinations, clinical definitions, blood and sputum collections (when symptoms only or at predefined timepoints) etc  Obtain and bank mycobacterial specimens prior to the onset of initial drug treatment to support strain characterization will be important. This will contribute to differentiating relapse from re-infection during the post-treatment phase and identifying de novo emergence of drug-resistant strains.  Collection and handling of specimens need to be described extensively in the protocol or in an appendix or in a separate manual. This will be instrumental to standardize the methodology across clinical sites.  Standards for reading Chest X-rays should be described in the protocol or in an appendix or in a separate manual and shared across clinical centres. | | |
| **Statistical methods** | Statistical methods to study the safety and /or efficacy of the new vaccine candidate will have to be described. Basis for the sample size calculation, eventually interim analysis etc will be outlined in the statistical section.  The approaches taken to the analysis of relevant post-randomization intercurrent events where applicable as per ICH E9(R1) should be described.  For each study, a statistical analysis plan (SAP) is prepared that describes in extenso the statistical methods, cohorts (safety, per protocol for immunogenicity or for efficacy), output of data presented in tables, figures, and listings). This document should be final before freezing and unlocking the database for analysis.  Available epidemiological data on the incidence of the relevant endpoint (e.g., LTBI and/or TB disease) in the targeted population should be reviewed, particularly in the specific populations where the trials are to be conducted. These data are used to set assumptions for determination of potential sample size requirements for appropriate power to demonstrate the clinical benefit of the investigational vaccine and ensure that these are within the limits of study feasibility. | | |

1. References on estimands:

   <https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf>

   <https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf>

   <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical> [↑](#footnote-ref-1)
2. [Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections](https://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf) [↑](#footnote-ref-2)