Decision-making in TB vaccine development: the stage-gate process

GEORGES THIRY

TBVI – AERAS WORKING GROUP

GLOBAL FORUM TB VACCINES

NEW DELHI, 20 FEB. 2018

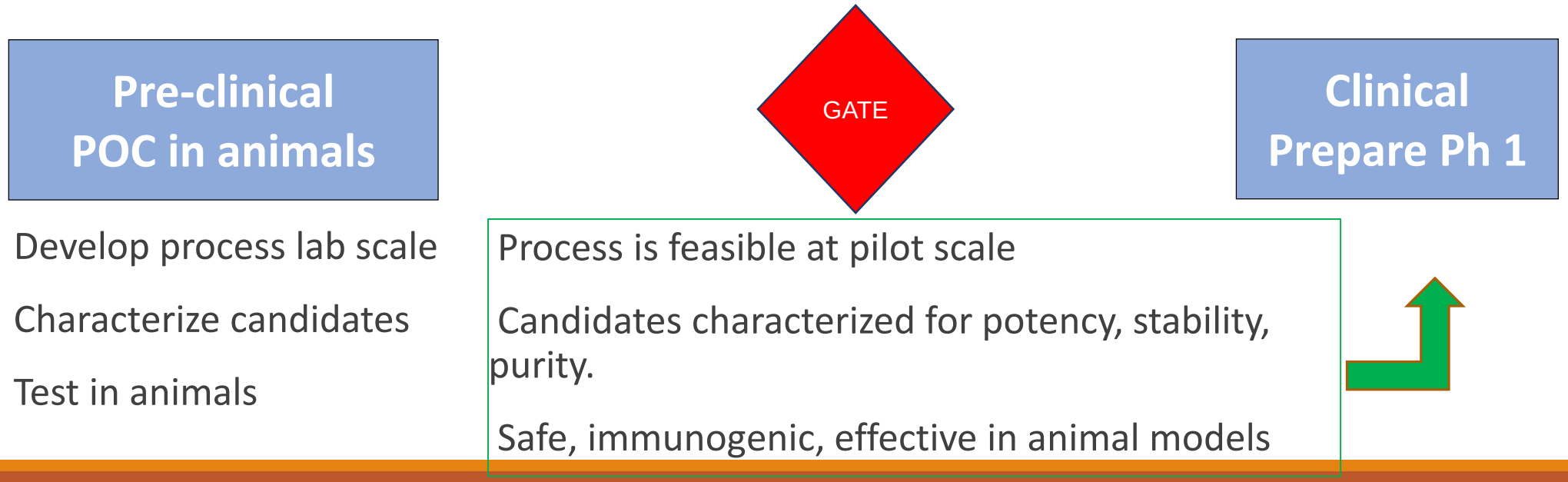
TBVI

AERAS

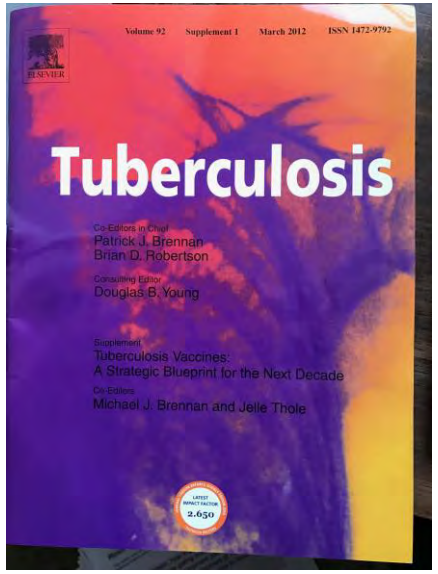
Definition of ‘Stage-Gate’ process

The SG Process is a Project Management tool that divides large projects into segments of activities running in parallel, the Stages, separated by check points, the Gates, where continuation of the project is decided based on Criteria.

An example:



Stage Gates for TB vaccines, 2012



Rational approach to selection and clinical development of TB vaccine candidates

Lew Barker[a,*], Luc Hessel[b], Barry Walker[c]

[a]*Aeras, 1405 Research Boulevard, Rockville, MD 20850, USA*
[b]*Consultant in Vaccinology, 1 Place Louis Chazette, 69001 Lyon, France*
[c]*Immunology and Cellular Immunity Section, Bacteriology Division, NIBSC, Blanche Lane, South Mimms, Potters Bar. EN6 3QG, UK*

ARTICLE INFO

Keywords:
Tuberculosis
Vaccines
Stage-gates

ABSTRACT

A rational process is clearly needed and can be extremely helpful for selection, assessing and advancing TB vaccine candidates from entry into preclinical and clinical development and for advancing candidates from early safety and immunogenicity clinical trials to proof-of-concept and pivotal efficacy trials. A joint effort between Aeras and the Tuberculosis Vaccine Initiative has focused on the development of objective criteria for a number of key general vaccine characteristics which can be assessed at critical stages of development. In order to maximize development efficiency, increase likelihood of success, and optimize use of scarce resources, this process includes establishment of *gates* for moving TB vaccine candidates through progressive development stages based on meeting the established criteria for specific vaccine candidates.

Stage Gates Criteria II project

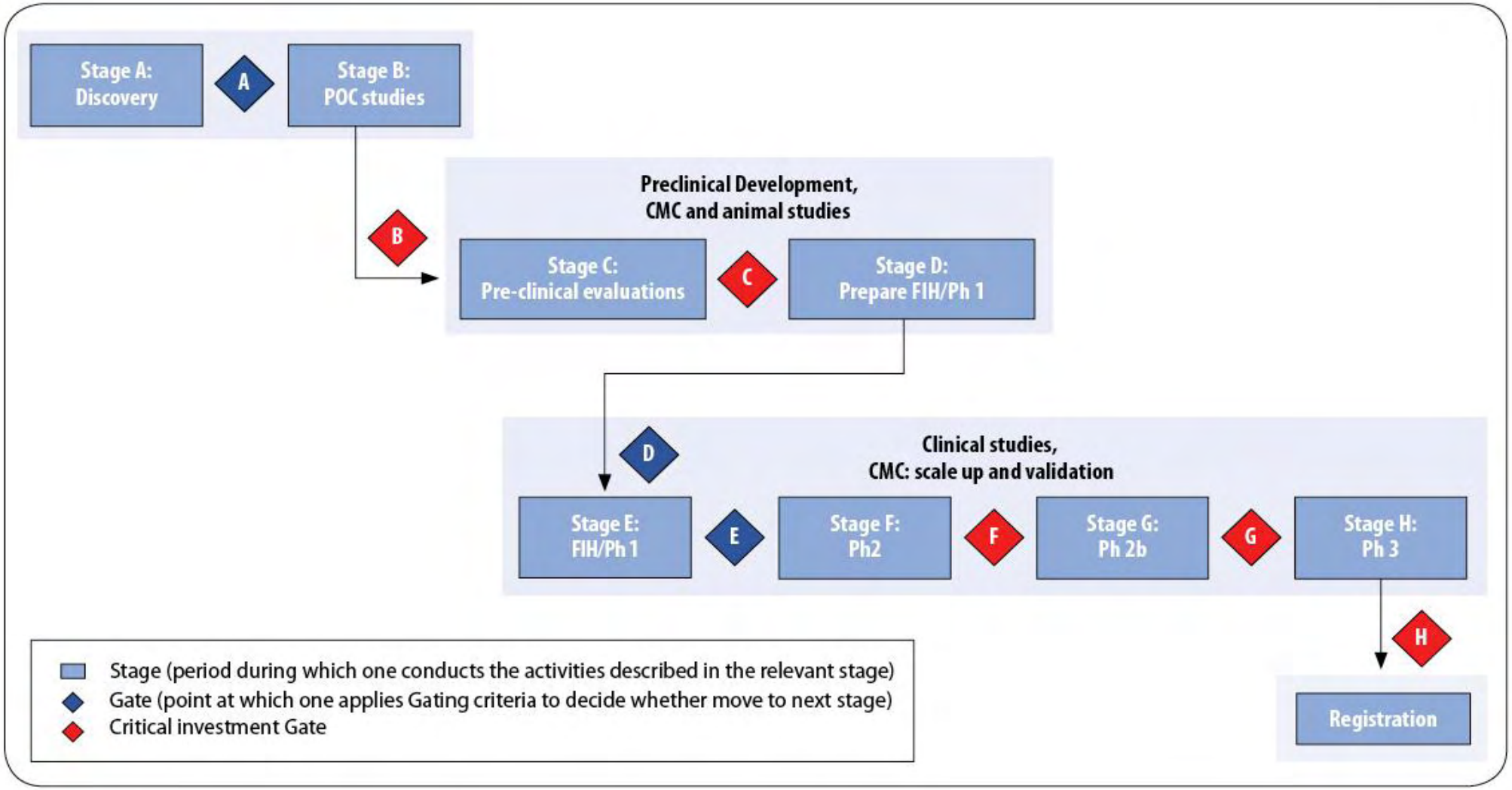
Objectives

1. Biennial revision of the SG criteria
2. Develop target specific SG for TB vaccines
3. Support to Portfolio
4. Validate and publish

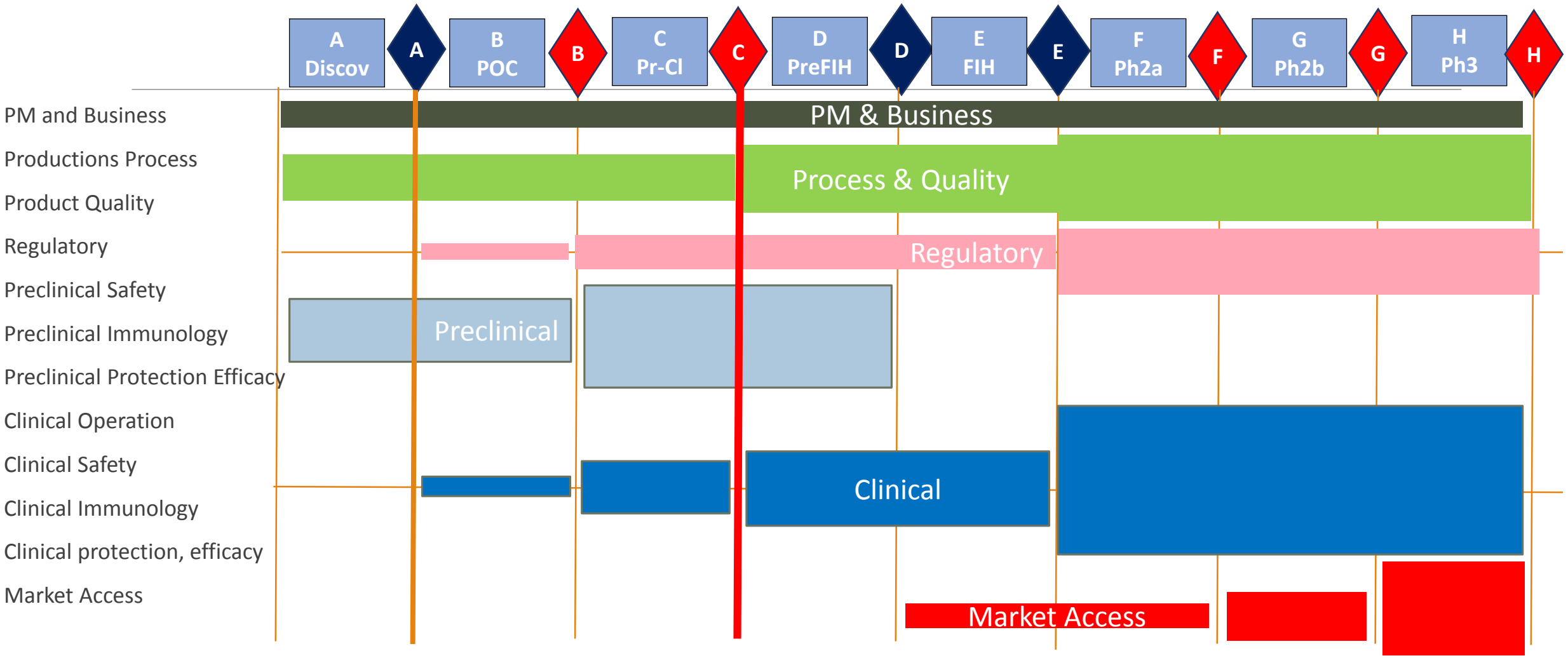
Endorsed by the GTBVP: Aeras, BMGF, EC, EDCTP, EIB, MESR (France), SA DST, SA MRC, TBVI and WHO

Funding: BMGF (2017-2021)

Stages and gates for a TB vaccine



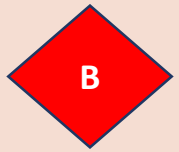
Stage Gate, functions and their dynamic

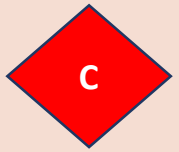


Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model
Gate A: Progress to proof of concept (POC) studies in animals

Function	Stage A: main activities	Gate A: criteria required
PM/ Business	• Draft the Target Product Profile (TPP) with indication, target population, etc.	• TPP with primary indication prepared
Production process	• Select expression system at lab scale for pre-clinical material • Select production process, at lab scale	• Suitable expression system and process that can produce target product quantity and quality selected • Specific strain(s) selected
Product Characterization & Quality	• Screen and select antigen(s), adjuvants, other excipients and delivery system. • Characterize vaccine candidate • In particular, demonstrate antigen expression and purity (e.g. proteins)	• Antigens, adjuvants, other excipients, delivery system selected • Characterization tests defined, including animal testing • Characteristics of the vaccine candidate documented
P-CL (Pre-Clinical) Safety	• Identify in vitro and animal models to test for safety • Test preclinical safety elements relevant to candidate	• Safety characteristic(s) of vaccine identified and demonstrated
P-CL Immunogenicity	• Evaluate immunogenicity • Compare to benchmark, if applicable	• Evidence of relevant immunogenicity to antigens in at least 1 animal species • Above baseline and/or benchmark (if applicable) responses to antigens preferred
P-CL Protection, efficacy	• Demonstrate protection in a small animal Mtb infection model • Compare to benchmark, as relevant	• Protection in a small animal Mtb infection model demonstrated • Protection statistically better than BCG or against a relevant benchmark preferred

Snapshot: Preclinical efficacy

Development Phase	Stage: main activities	Gate: criteria required
A: Discovery 	**Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model** • Demonstrate protection in a small animal Mtb infection model • Compare to benchmark, as relevant	**Gate A: Progress to proof of concept (POC) studies in animals** • Protection in a small animal Mtb infection model demonstrated • Protection statistically better than BCG or against a relevant benchmark preferred
B: POC studies 	**Stage B: Perform POC studies in animals** • Confirm robust protection in a small animal Mtb infection model • Prepare read-outs to evaluate protection in NHP (or other model) study	**Gate B: Progress to Pre-Clinical activites** • Protection in a small animal Mtb infection model confirmed • Protection statistically better than BCG or against a relevant benchmark reproduced independently in same species or in a second animal model confirmed • These data support proposed mode of protection, and support the NHP (or another advanced model) study design • Read-outs for NHP (or other model) ready

C: Pre-clinical evaluations 	**Stage C: Perform Pre-Clinical evaluations**
	• Confirm protection or PoC
	
	Note: the animal models for evaluation should be justified based on candidate's proposed mechanism of action
		Gate C: Progress to preparation for Ph 1, First-In-Human (FIH)
		• Protection vs Mtb challenge statistically better than BCG and/or relevant benchmark using primary endpoint in 2 animal models, as demonstrated by a read-out with high statistical power for the group size:
		  • Protection vs Mtb challenge in a small animal model confirmed
		  • Protection vs Mtb challenge in a NHP or justified, human-relevant, advanced animal model confirmed

Stage Gates Criteria II Project

Objectives

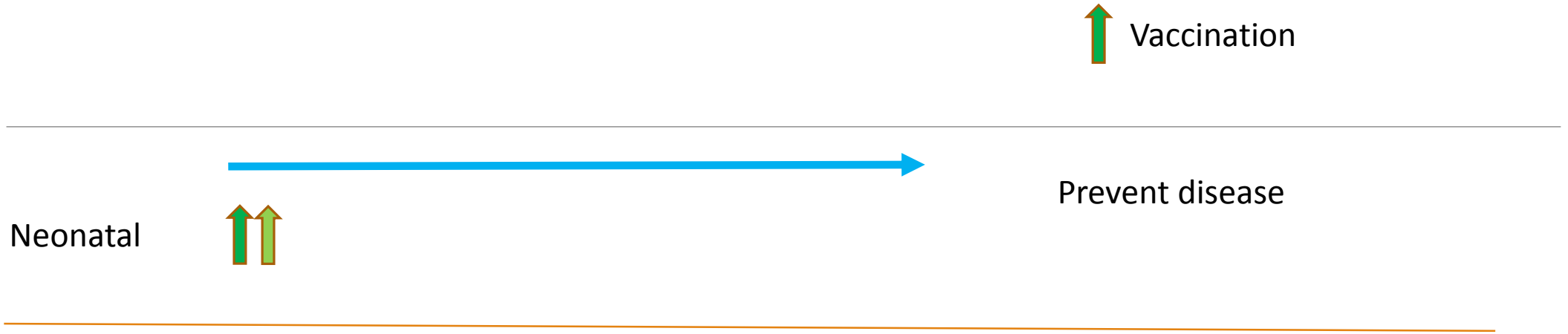
1. Biennial revision of the SG criteria

2. Develop target specific SG for TB vaccines

3. Support to Portfolio

4. Validate and publish

Populations & Indications



Populations & Indications

Populations & Indications

Specific Stage Gates Criteria

			Replace BCG	Prevent disease	Shorten therapeutic treatment, increase cure rate in DR-TB and/or DS-TB	Prevent recurrence
	Population		Neonates	Adolescents and adults	DR-TB and/or DS-TB	Adolescents, adults at completion of TB treatment for DS or DR TB.
STAGE	Indication		Prevent TB diseases: pulmonary TB, severe disseminated TB and TB meningitidis	Prevent pulmonary TB	Adjunct immunotherapy for treatment of disease.	Reduce recurrent pulmonary TB disease
A: Discovery		Generic SGC	Refer to generic SGC			
B: POC	P-CI	Protection statistically better than BCG or against a relevant benchmark reproduced independently in same species or in a second animal model confirmed)	Consider a plus to have evidence of protection and or immune response in neonatal model	Refer to generic SGC	Demonstrate treatment shortening and/or decreased relapse rate or bacterial load and immunogenicity in relevant animal species	Demonstrate decrease rate of relapse or bacterial load following drug treatment and immunogenicity, in relevant animal species

Under preparation

Stage Gates Criteria II Project

Objectives

1. Biennial revision of the SG criteria

2. Develop target specific SG for TB vaccines

3. Support to Portfolio

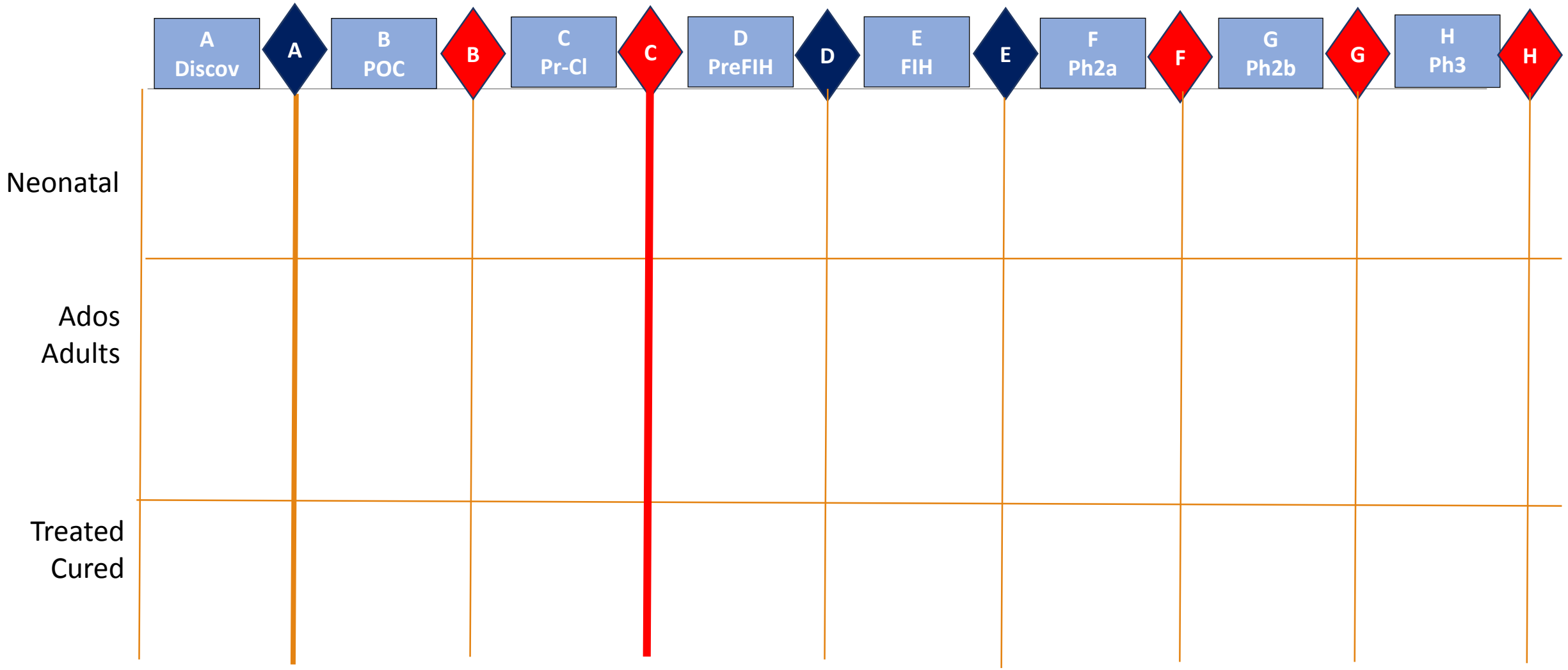
4. Validate and publish

Technological platforms

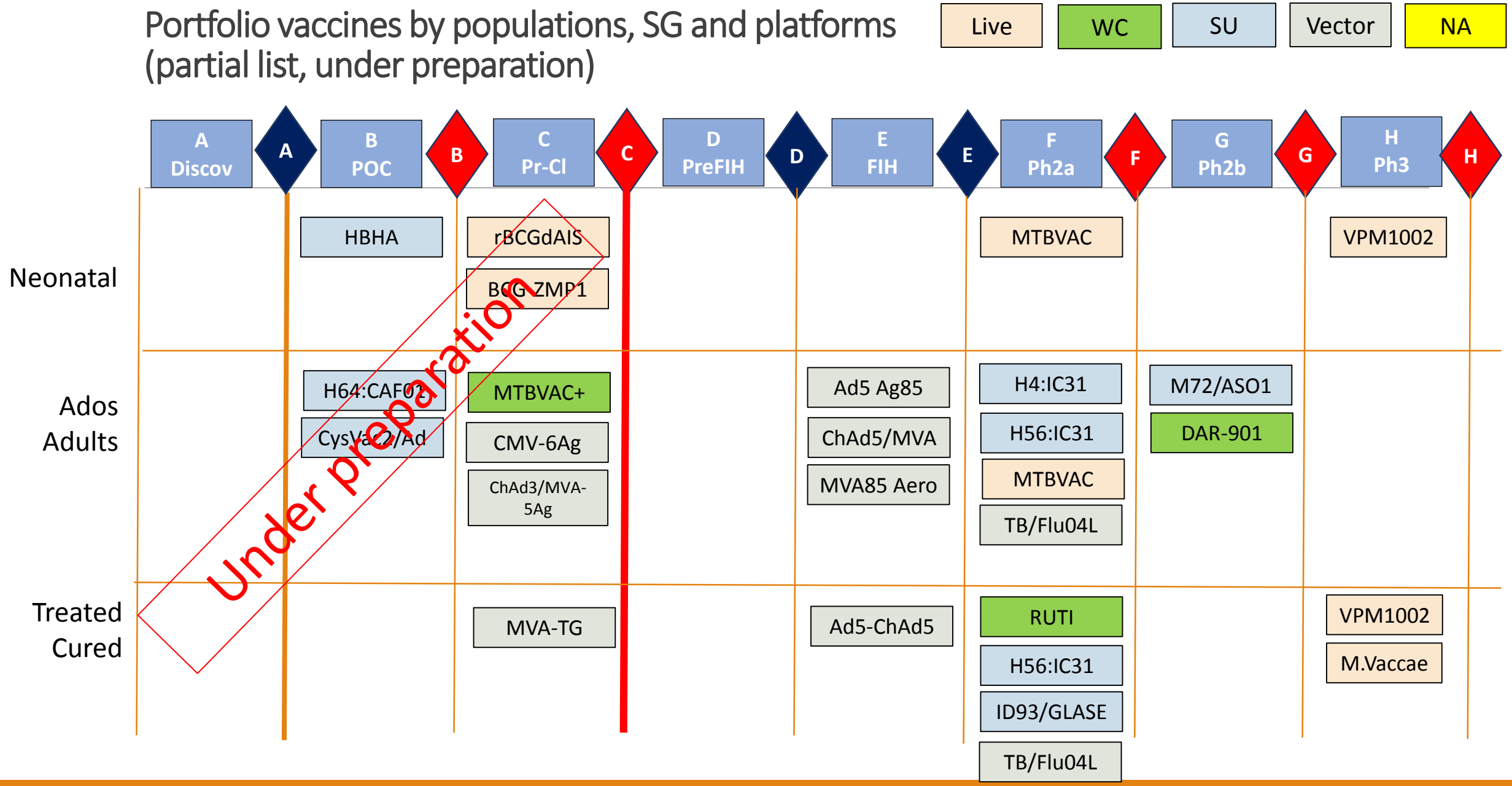
Live	Live mycobacteria, recombinant BCG
WC	Whole cell bacteria, extracts
SU	Sub unit, as proteins or lipids, adjuvanted
Vector	Vectored, viral vector
NA	Nucleic Acid, DNA, RNA

Portfolio vaccines by populations, SG and platforms

Live | WC | SU | Vector | NA



Portfolio vaccines by populations, SG and platforms (partial list, under preparation)



Stage Gates Criteria II Project

Objectives

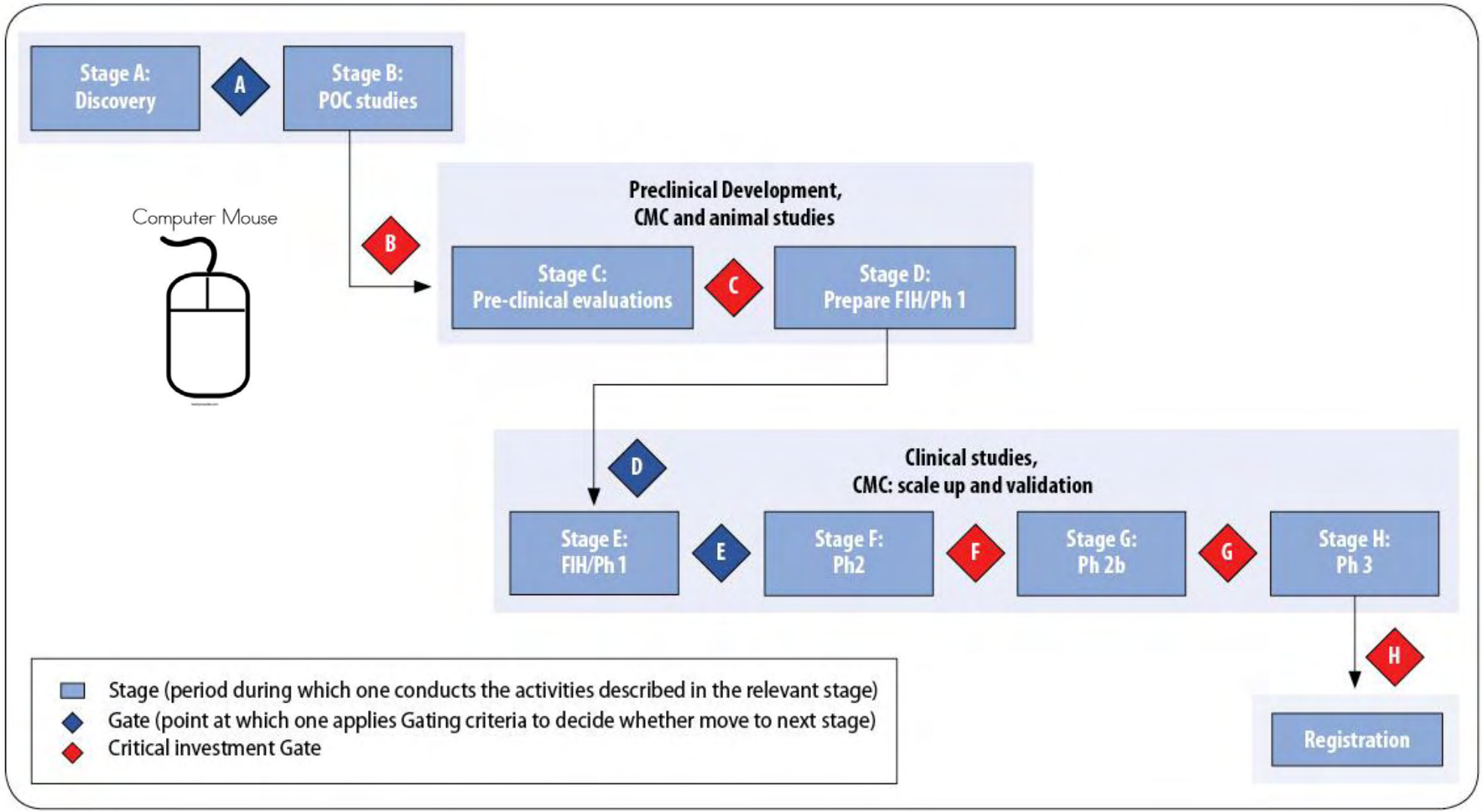
1. Biennial revision of the SG criteria

2. Develop target specific SG for TB vaccines

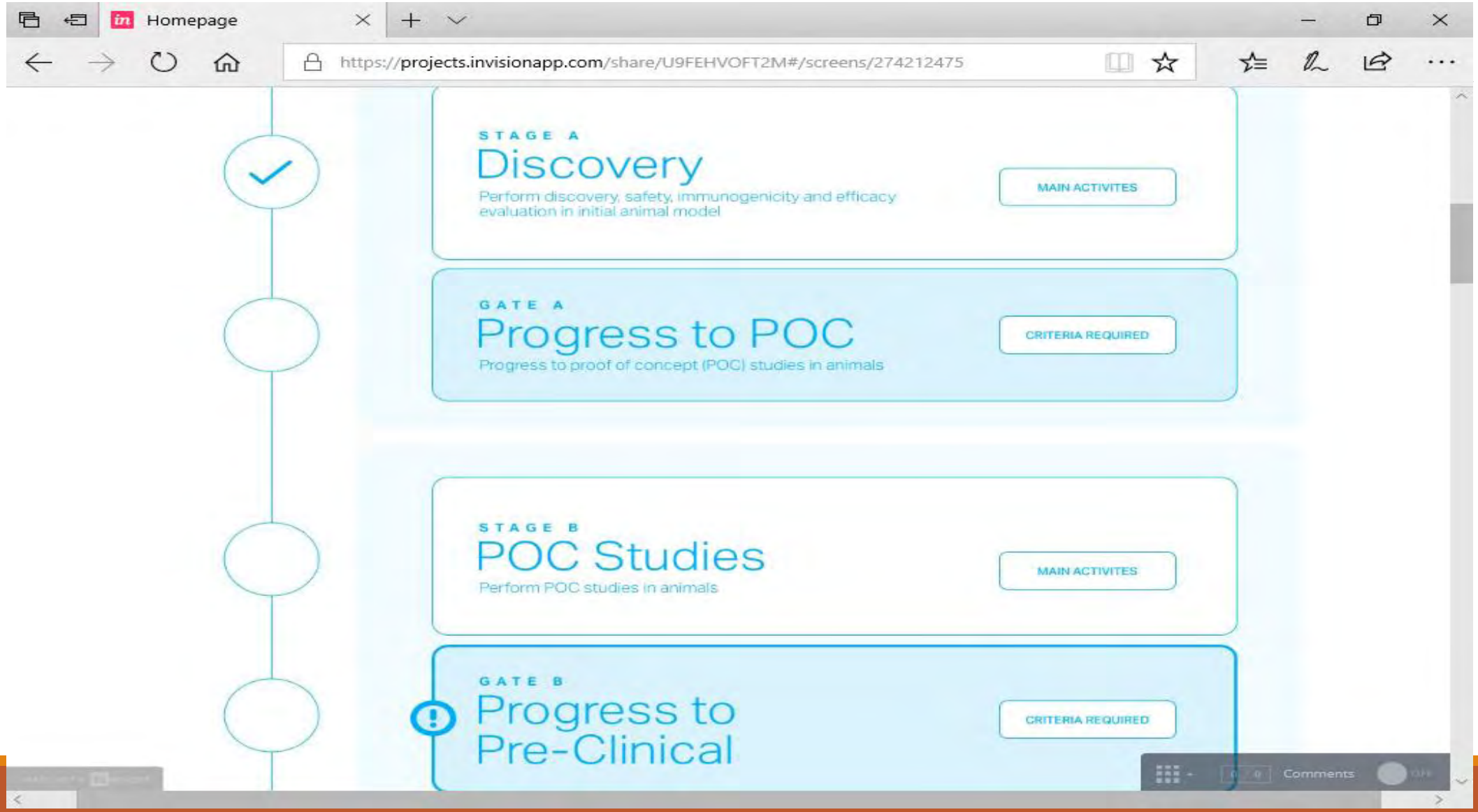
3. Support to Portfolio

4. Validate and publish

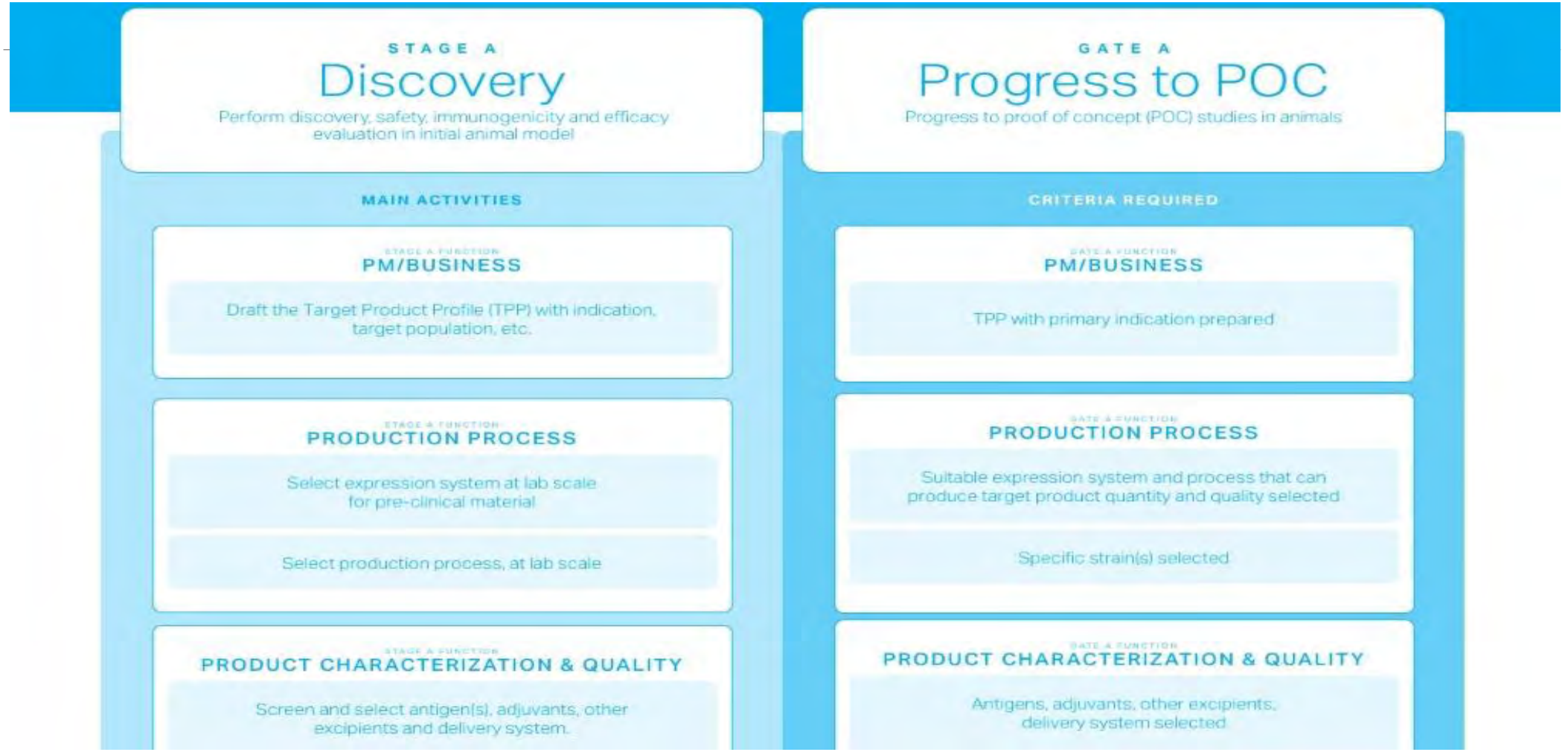
Stages and gates for a TB vaccine



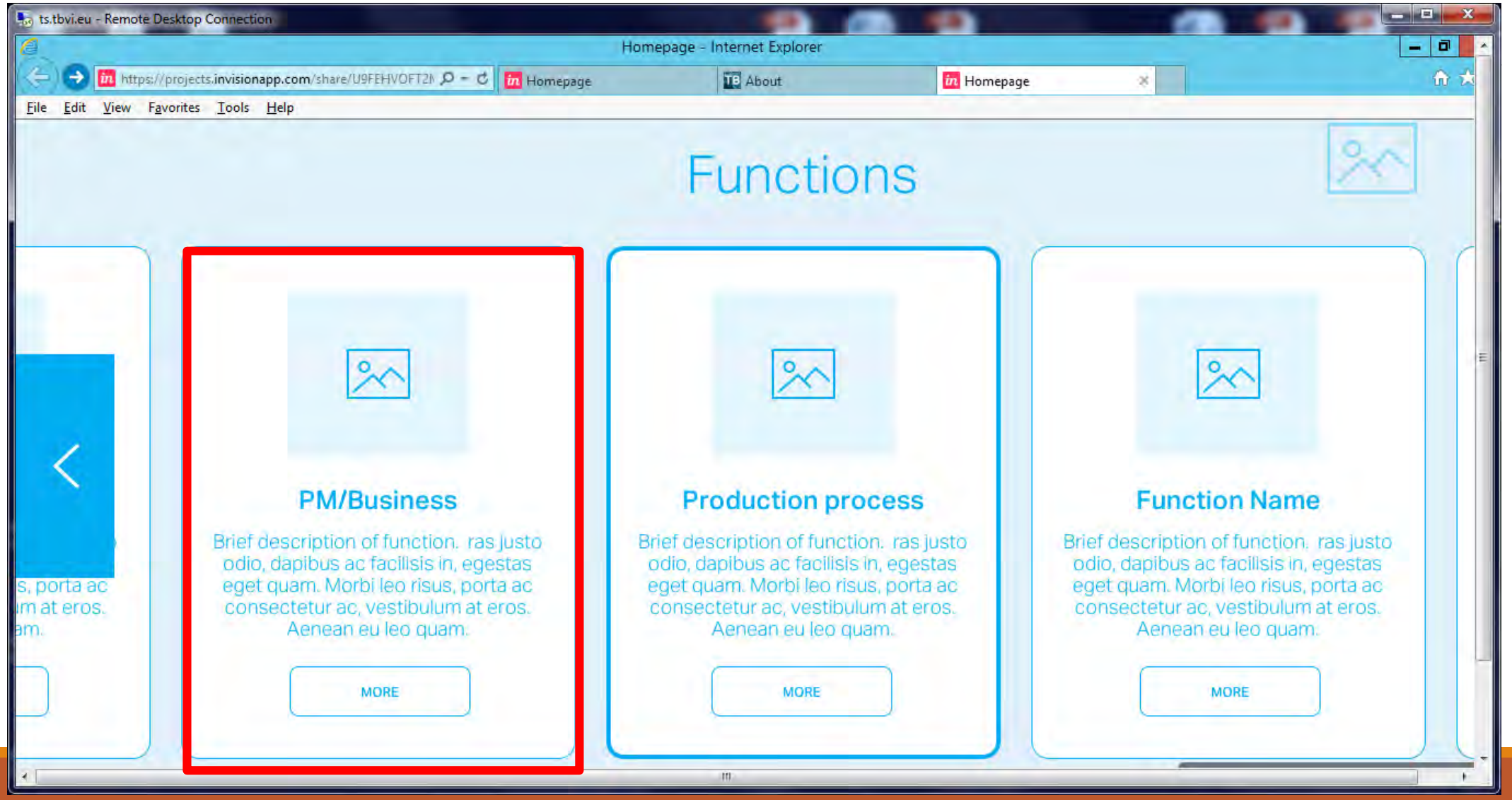
Webtool: navigate through Stages Gates



Navigate within Stages



Navigate through Functions



Example : PM & Business

FUNCTION

PM/ Business

Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model
Gate A: Progress to proof of concept (POC) studies in animals

MAIN ACTIVITIES	CRITERIA REQUIRED
• Draft the Target Product Profile (TPP) with indication, target population, etc.	• Draft the Target Product Profile (TPP) with indication, target population, etc.

Stage B: Perform POC studies in animals
Gate B: Progress to Pre-Clinical

MAIN ACTIVITIES	CRITERIA REQUIRED
• Update TPP and draft Product Development Plan (PDP) • Describe Intellectual Property (IP) status • If necessary, identify potential partners to support development	• TPP revised; PDP drafted • No major IP obstacles or strategy for resolution in place • As necessary, viable partners identified, MTA and other agreements established

Stage C: Perform Pre-Clinical evaluations

Next steps

Activities	Dates
Review SG criteria	*November 2017*
Consult stakeholders and TB community	Ongoing
Document specific SG for 3 targets • Infants • Adults & Adolescents • Therapeutic	2q 2018
Publish in journal Write a Guidance Document and develop the Webtool	2-3q 2018

Conclusions

SG is a project management tool applied to TB vaccine development to assist developers, managers, funders and other decision-makers.

Engage stakeholders for validation, and community for use.

Combine with Portfolio Management.

TBVI - AERAS Working Group

TBVI	Aeras	Role
Georges Thiry	Maria Lempicki *	Lead
Leo van der Pol	Maria Lempicki	Production process, Product Characterization & Quality
Ann Rawkins	Dominick Laddy	Preclinical Safety, Immunogenicity, Protection and Efficacy
Bernard Fritzell	Ann Ginsberg Derek Tait	Clinical Safety, Immunogenicity, Protection and Efficacy
Emmanuelle Gerdil	Maria Lempicki	Regulatory
Anne Marie Graffin		Market access
Gerald Voss Jelle Thole		Business
Danielle Roordink Ilona van den Brink	Maria Lempicki	PM

* Barry Walker, 2012 - 2016
Danilo Casimiro, 2017

Thank you !