



# Challenges for Clinical Trials in Developing Countries

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# Issues in clinical development of new TB vaccines

- **Need sites which have**

- **Clinical capacity**

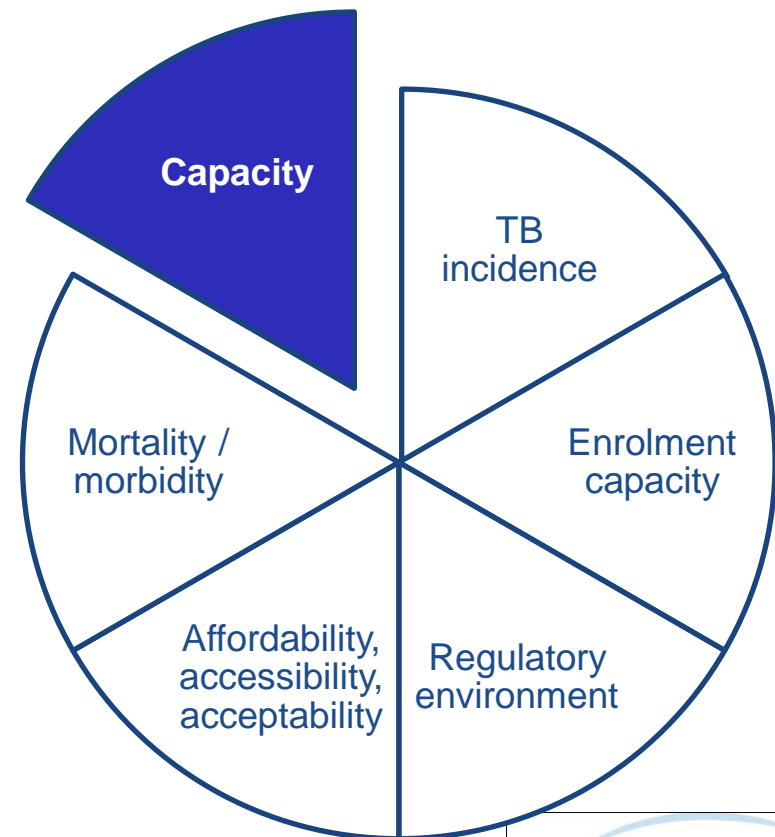
- Ability to reliably diagnose TB, including in infants and HIV+ adults.

- **Laboratory capacity**

- Tuberculosis laboratories
  - Performance of quality TB smears and cultures, speciation
- Immunology laboratories
  - Cell separation, shipping as minimum. Ability to perform minimal assays

- **Public health capacity**

- Funding to develop site capacity is becoming less available following the financial crisis of 2008/9/10.



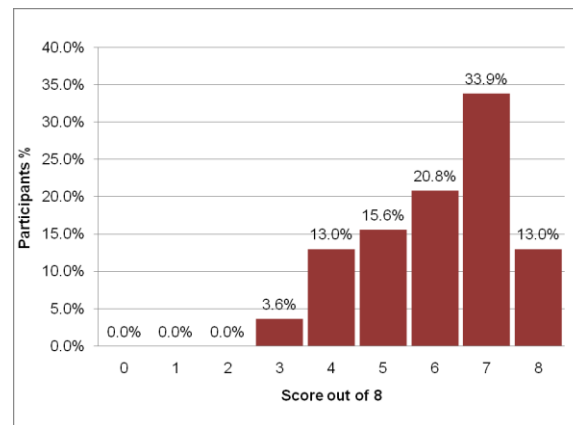
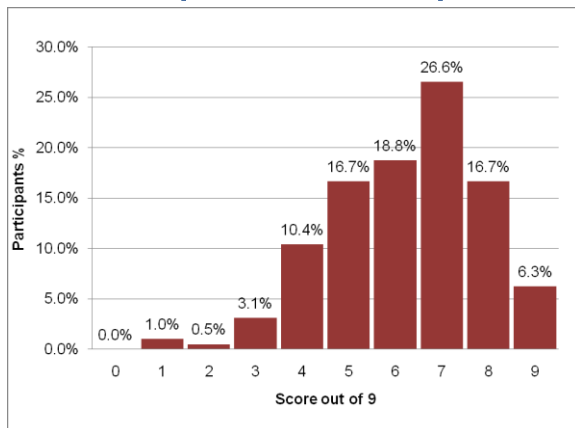
# Challenges in Clinical Trials

(an Asia perspective)

- Cultural
- Regulatory
- Logistical
- Ethical
- Unexpected

# Cultural

- Lack of sponsor awareness of needs to involve local health care providers in early stages of protocol development
- Lack of sponsor awareness on the use of local medical practices, especially traditional medicine
- Lack of translations for certain words, phrases, or concepts
- Continual use of clinical trial language that may be foreign
- Ethics Committee make-up, regulation, and implementation of informed consent
- How biopsies, sample collection, and blood draws are locally viewed



# Regulatory

- Focus is on US and EMEA health authorities
- Slow and variable timelines for review lead to complications, especially on protocol amendments
- Need to use local licensed controls which may vary across countries
- Disagreement on use of placebo subjects required by some health authorities but not allowed by ethics committees
- Lack of CMC expertise by many country HA, despite excellent preclinical and clinical staff
- Lack of industry and academia to better address ethnic (and environmental factors) in vaccine immunogenicity and efficacy
- GCP and QA concepts are foreign to many sites
- Trial “insurance” can be a point of contention



# Logistical

- Power grid and failure of cold storage of vaccine or samples
- Intermittent service for electronic data capture using local internet services
- Staff turnover
- Lack of appropriate expertise in staff back-up
- Import/export licenses and expiration date policies
- Sample movement (e.g., genetic samples)
- Standardization of laboratories and reference ranges, and laboratory QC
- Standardization of monitoring practices



- Delivery of results to participants

- Lack of sophisticated imaging (PET, MRI, CT), bronchoscopy and laboratory devices and expertise

Davis SL PLoS One 2009. e6297

# Unexpected

- Worldwide travel problems (SARS, volcanoes)
- “Late” involvement of politics in scientific and trial implementation discussions
- Instability in governments
- Financial viability of sponsor organizations
- Differing levels of government support
- Theft of investigational or control product
- Unforeseen competition from local industry
- Rare event safety signals

# Value of the Local Organizations

- Knowledge of local customs and norms
- Scientific expertise combined with knowledge of local research environment
- Establishment in the community (enhances ability to gain trust and support of community for trials)
- Familiarity with regulatory environment
- Retain local talent and expertise (contributes to creation of a profession)

# Tuberculosis trial specific

Issue	Potential solutions
Size of trials required by lack of biomarkers	Invest in research to solve this issue; no large trial without a large biomarker component
Lack of standardization of immunological assays	Facilitate the working group and standardized protocols
Reliability of diagnosis of TB	Being addressed by FIND, and working group
Disagreement on key populations to be studied	Agree that any finding is of significance so encourage scientific diversity
Lack of assured funding of late stage trials	Continue dialogue with funders about criteria
Susceptibility of different populations (Age, Ethnic, Environmental, Co-infections)	Data mining, sharing, and genomic/genetic approaches

# Recombinant BCG (rBCG) - A Better BCG

## Goals

- Safer in HIV infected infants or others with immune-suppression
- BCG or rBCG boosted with another TB vaccine is much better than either vaccine alone
- Rationally constructed to prevent initial infection, latency and reactivation



# AERAS-422 rBCG

- Expression of perfringolysin – better antigen presentation, priming for boosting, & increased safety (animal models)
- Over expression of antigens in the absence of antibiotic resistance marker
  - Classic secreted: Ag85A, Ag85B
  - Reactivation: Rv3407
- Phase I clinical testing expected to begin in US in Q4 2010