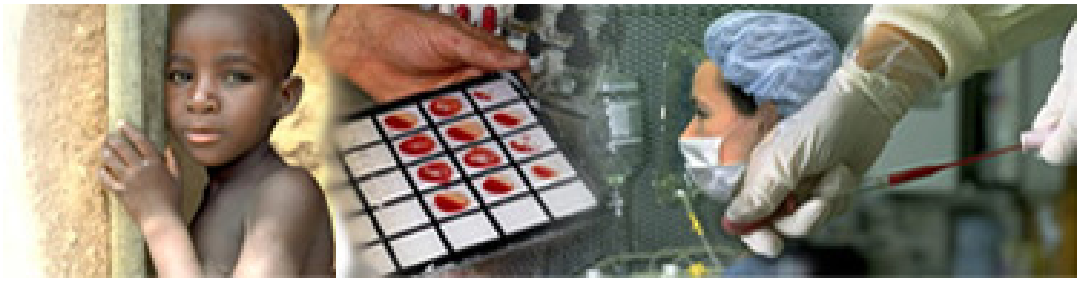
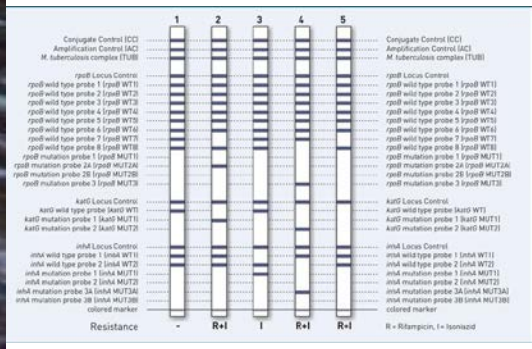


The architecture of demonstration studies

Advanced TB Diagnostic Research
July 5-8, 2011
Catharina Boehme

Leap of faith –
Rolling out diagnostics to resource-poor settings based on accuracy data?



Definition in FIND Clinical Trial SOP

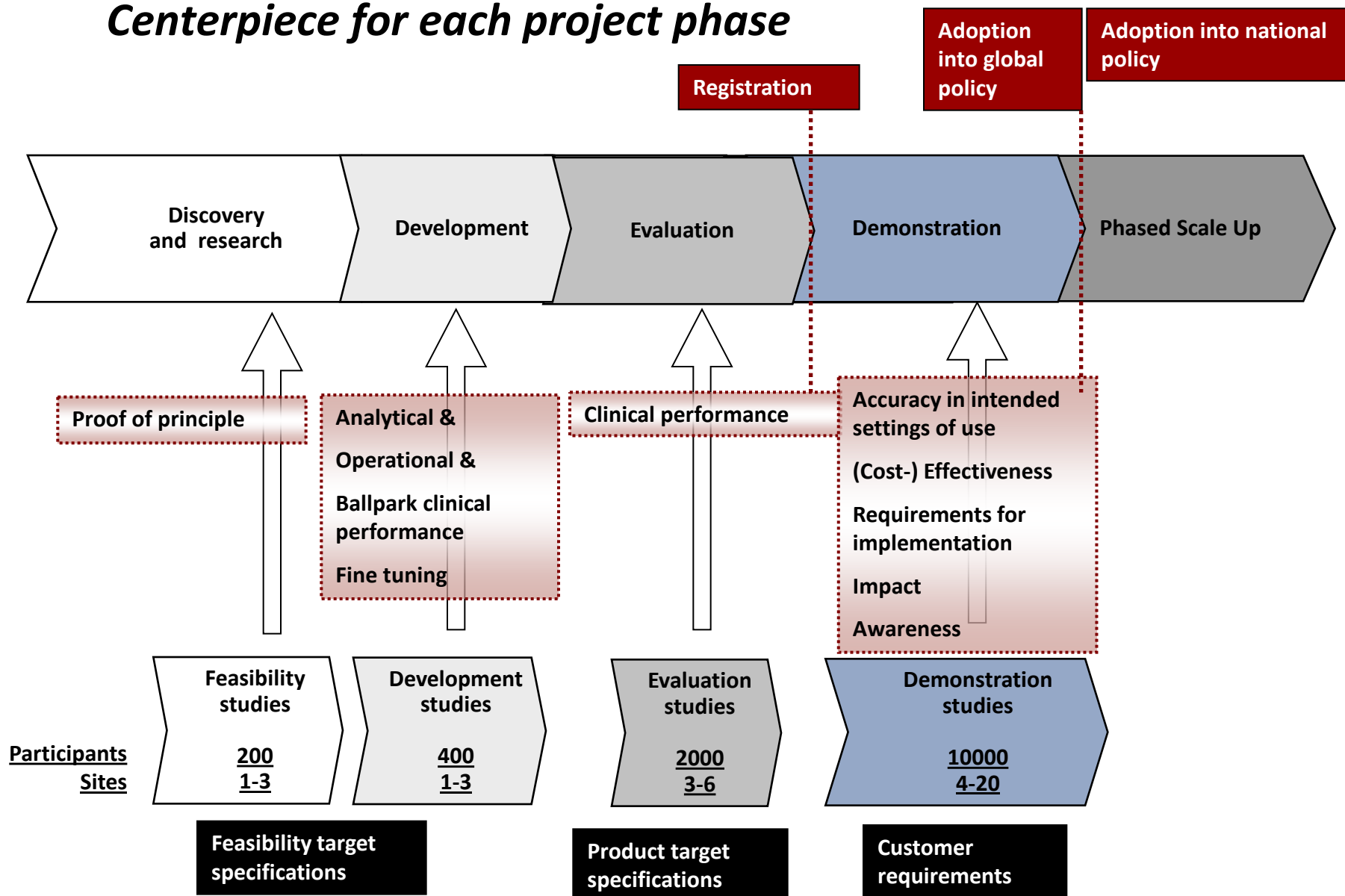
- Demonstration studies are large studies, in a geographically and otherwise representative number of settings, and are intended to provide the evidence that new tests that perform well in controlled settings can also do so in uncontrolled settings, and have an important medical and public health impact when implemented in programmatic settings.

- Carried out in the context of routine clinical services provision, either directly by the Ministry of Health (MOH), e.g., the National Disease Program or by other agencies working in collaboration with the MOH.

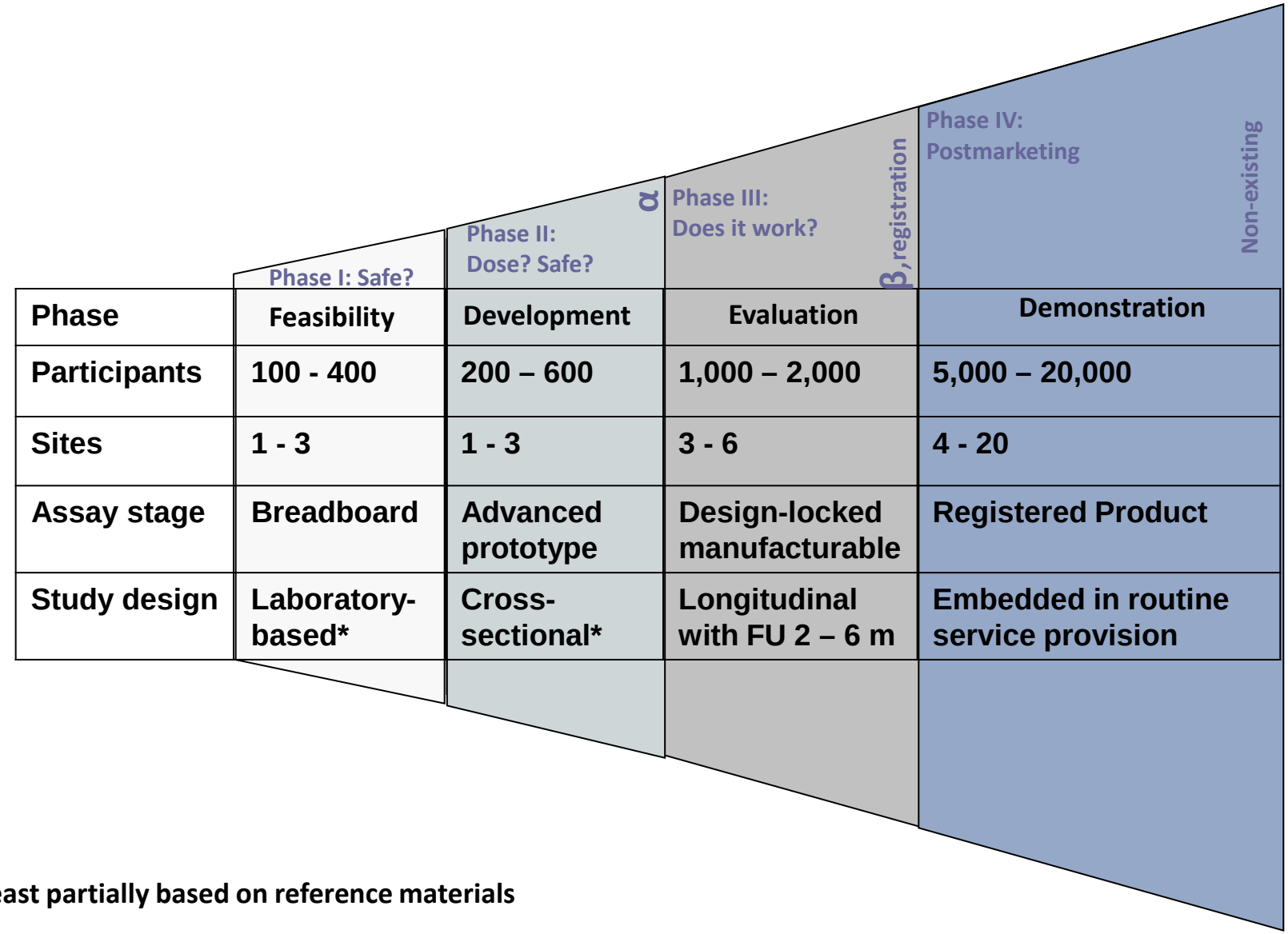
- The type of endpoints commonly studied include the feasibility of assay implementation, comparative costing between new and old technologies, and the impact on speed or accuracy of detection and subsequent patient management

High quality studies

Centerpiece for each project phase



Is there an equivalent in IVD or Pharma industry?



Phase	Feasibility	Development	Evaluation	Demonstration
Participants	100 - 400	200 – 600	1,000 – 2,000	5,000 – 20,000
Sites	1 - 3	1 - 3	3 - 6	4 - 20
Assay stage	Breadboard	Advanced prototype	Design-locked manufacturable	Registered Product
Study design	Laboratory-based*	Cross-sectional*	Longitudinal with FU 2 – 6 m	Embedded in routine service provision

*At least partially based on reference materials

A changing landscape: WHO recommendations 2006 - 2010

More rigorous & systematic review process

2006	• Smear-positive case definition from 2 to 1 positive smears • Screening for TB with 2 instead of 3 smears • Conventional FM
2007	• Commercial liquid culture / DST • Rapid speciation (MPT64)
2008	• Line probe assay (Rif & INH)
2009	• LED-based FM • Non-commercial culture (MODS, CRI, NRA)
2010	• Cartridge-based Automated NAAT

Reviewed and not recommended / endorsed:

- Sputum processing methods to enhance microscopy sensitivity (bleach)
- IGRA
- 2nd line LPA
- Existing serological assays

Partner selection

Country criteria

- Contributes to overall representativeness of data (TB/MDR/HIV prevalence; strain types)
- Middle/Low income
- Political commitment (MOU NTP or MOH) / impact (prevalence of disease)
- Ease and speed of collecting data (local presence preferred)
- High expected medical need / benefit

Trial site criteria

- Representative sites for intended use and destined health care level (Infrastructure (space, volume), Logistics (supply chain, urban/rural), HR (workload, skills), Disease prevalence, other operational challenges (power supply, temperature)
- In reach of FIND certified supervisory site that meets quality standards
- Costs / Co-funding opportunities / opportunities to collaborate with implementing agencies

Endpoints (all sites)

Clinical performance

- Sensitivity/specificity/predictive values (stratified by site/smear/HIV)

Operational performance

- Assess robustness of reagents and equipment (temperature, dust, power irregularities, contamination rates) through indeterminate rates; intermittent testing of (blinded) controls; t/h log tags; customer support interventions
- Determine minimal training needs / performance dependence on skills/motivation/workload/user fatigue through proficiency testing tool & performance (stratification by user / over time)
- Assess user appraisal / requirements for implementation (such as waste management or storage) through user appraisal questionnaire and group discussions

Impact

- Time to detection of TB/DR compared to routine diagnostic algorithm

Endpoints (selected sites)

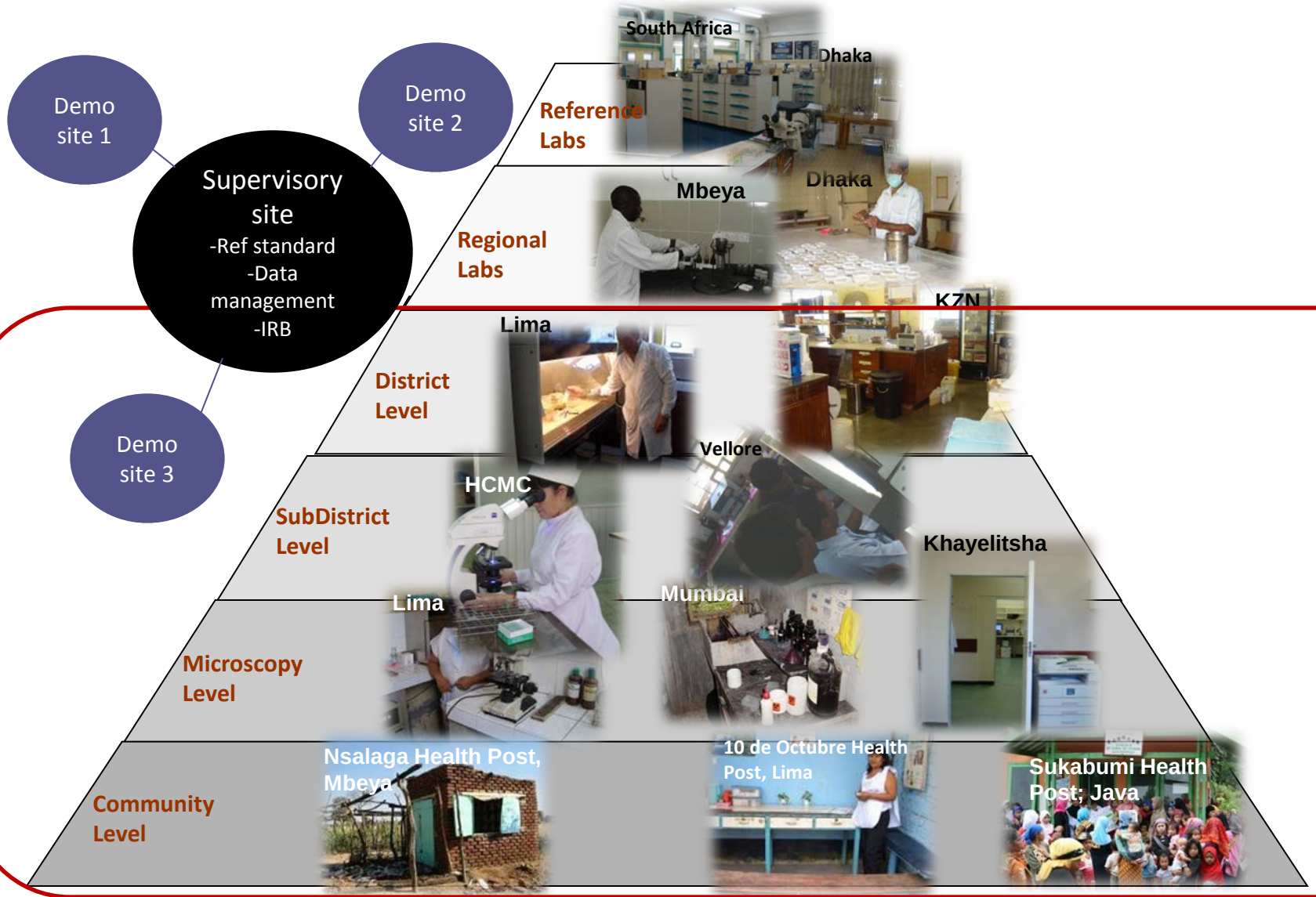
Impact

- Time to reporting compared to conventional results
- Time to initiation of appropriate treatment
- Patient dropout rate enrolment / prior to diagnosis
- Mortality for enrolled patients during follow up
- Hospitalization frequency and duration
- Time to return to work
- Determine most suitable algorithms of use
- Scalability / Batching

Costs

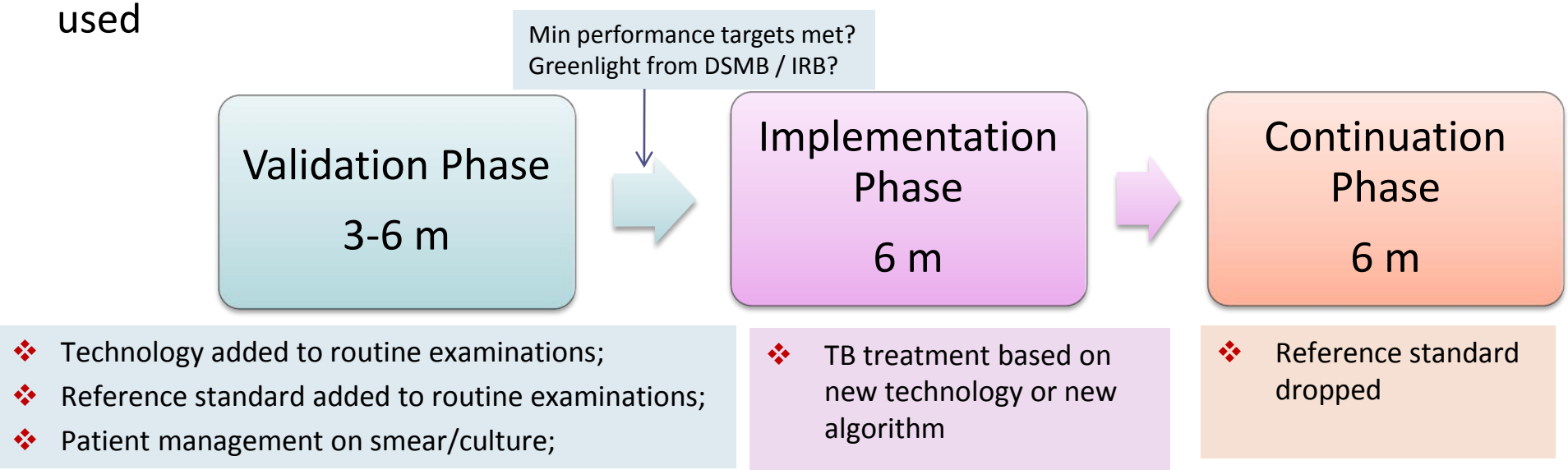
- Quantify “per test” and “per patient” costs for the health system compared to routine
- Assess cost-effectiveness compared to baseline (instead of and in addition to scenarios)

Assessing technologies for peripheral laboratories required design changes



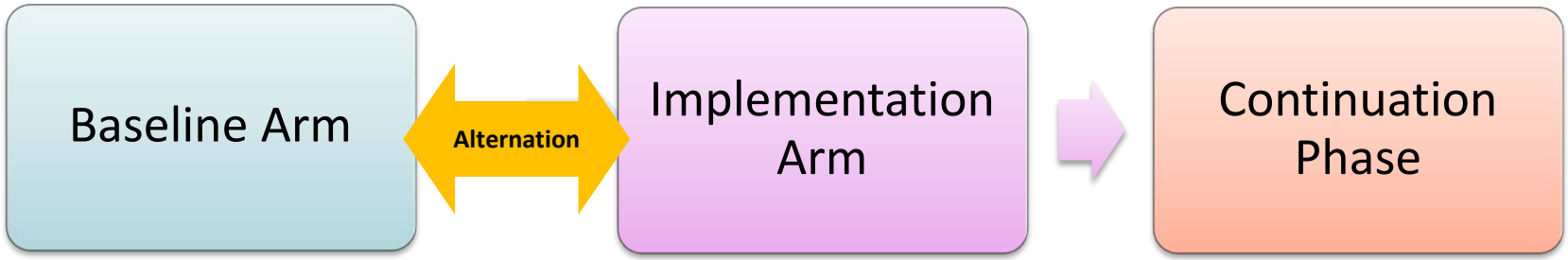
Designing a demonstration study

- Prospective, consecutive enrolment
- Inclusion criteria should not deviate from local guidelines (TB/MDR suspect);
- Analysis plan important (sample number; Tb tx; valid reference standard etc)
- Algorithm / Positioning reflect our thinking of how this new technology should be used



Design Variations (Cross-over; Baseline)

Xpert; LAMP (bleach treatment for smear did not allow to combine with new test; blinding)

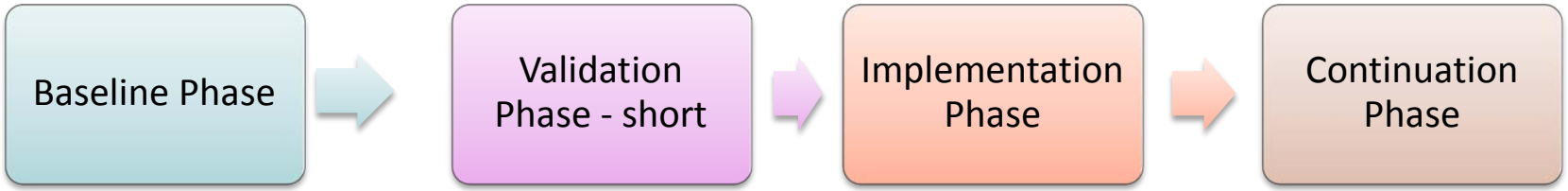


- Routine examination
- Culture / DST added as reference standard;
- Patient management on routine/reference;

- New test replacing routine

- Reference standard dropped

LED-FM; LPA (capacity of routine lab techs)



- Routine examination;
- Patient management on routine;
- Culture / DST added as reference standard;

Considered, but not used:

True baseline assessment (no reference standard at enrolment) Cluster randomization; Comparison of different algorithms (add on versus replacement)

Follow up

- Time to treatment, drop out rate or other impact endpoints: At least passive follow up through treatment registers for all gold standard positive patients

- Discrepant patients and random controls (deficient gold standard)

- Sensitivity / specificity of baseline algorithm (smear + clinical judgment (CXR, symptoms)) : At least passive follow up for all through patient records

Ethical Considerations

- Patients will be treated on the basis of the result of the new test.

→ Ethical approval will therefore be required for all participating sites/countries.

- If no foreseeable risk to patients (Registered product; strong accuracy data; sufficient benefits (culture/DST).

→ A waiver of informed consent can be requested from relevant IRBs.

- Data safety and monitoring board

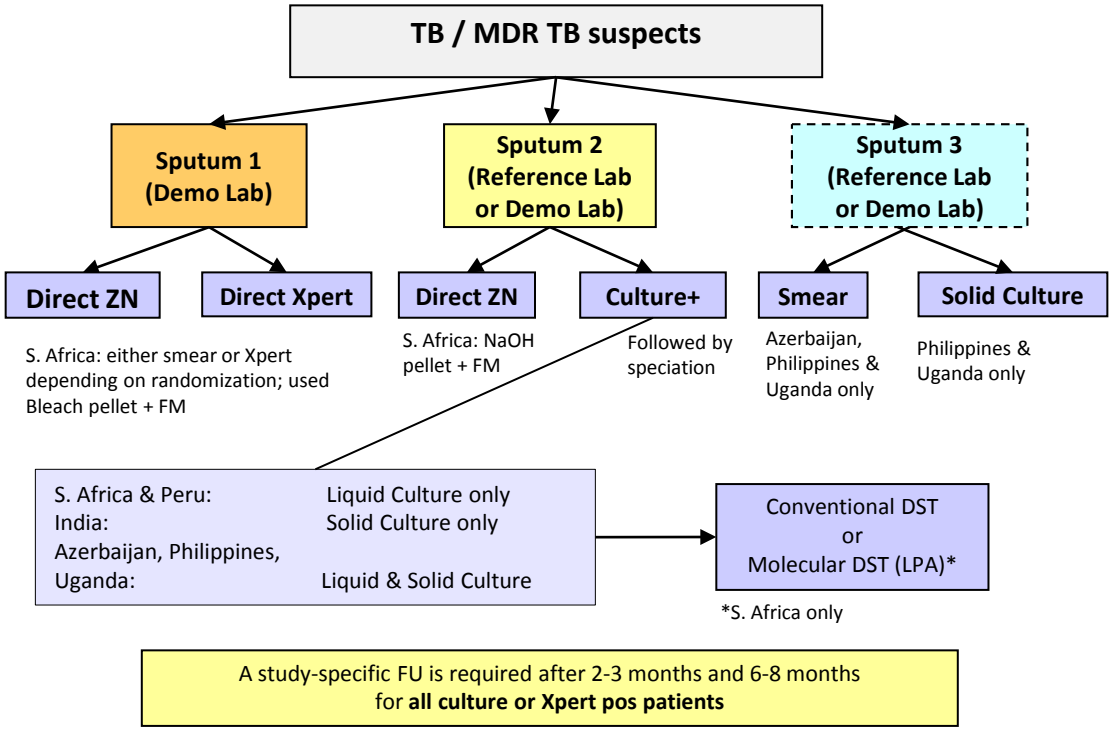
→ Adverse events, assay modifications

Standardization & data management

- Training plan / tool
- (Supervisory) site certification tool (standardization of reference standard and supplies (such as staining solutions))
- Proficiency testing & performance monitoring tool
- HR plan (!blinding)
- Questionnaire on lab technician appraisal
- Costing tool

- Paper-based recording of results at demo sites & central labs (clinic/lab CRFs)
- Electronic double data entry by supervisory sites or FIND India (FIND central database)
- Data analysis by contracted statisticians
- Joint study report for WHO expert review has priority over publication of data

Example


TB / MDR TB suspects
Sputum 1 (Demo Lab)
Sputum 2 (Reference Lab or Demo Lab)
Sputum 3 (Reference Lab or Demo Lab)
Direct ZN
Direct Xpert
Direct ZN
Culture+
Smear
Solid Culture
S. Africa: either smear or Xpert depending on randomization; used Bleach pellet + FM
S. Africa: NaOH pellet + FM
Followed by speciation
Azerbaijan, Philippines & Uganda only
Philippines & Uganda only
S. Africa & Peru: Liquid Culture only
India: Solid Culture only
Azerbaijan, Philippines, Uganda: Liquid & Solid Culture
Conventional DST or Molecular DST (LPA)*
*S. Africa only
A study-specific FU is required after 2-3 months and 6-8 months for all culture or Xpert pos patients

A fine balance

1. Quality standards vs representativeness

More monitoring and supervision,

More endpoints (CRF length, follow up)

Higher clinical trial standard (study nurses, data managers)

=

Results less representative of average routine setting

Greater bias

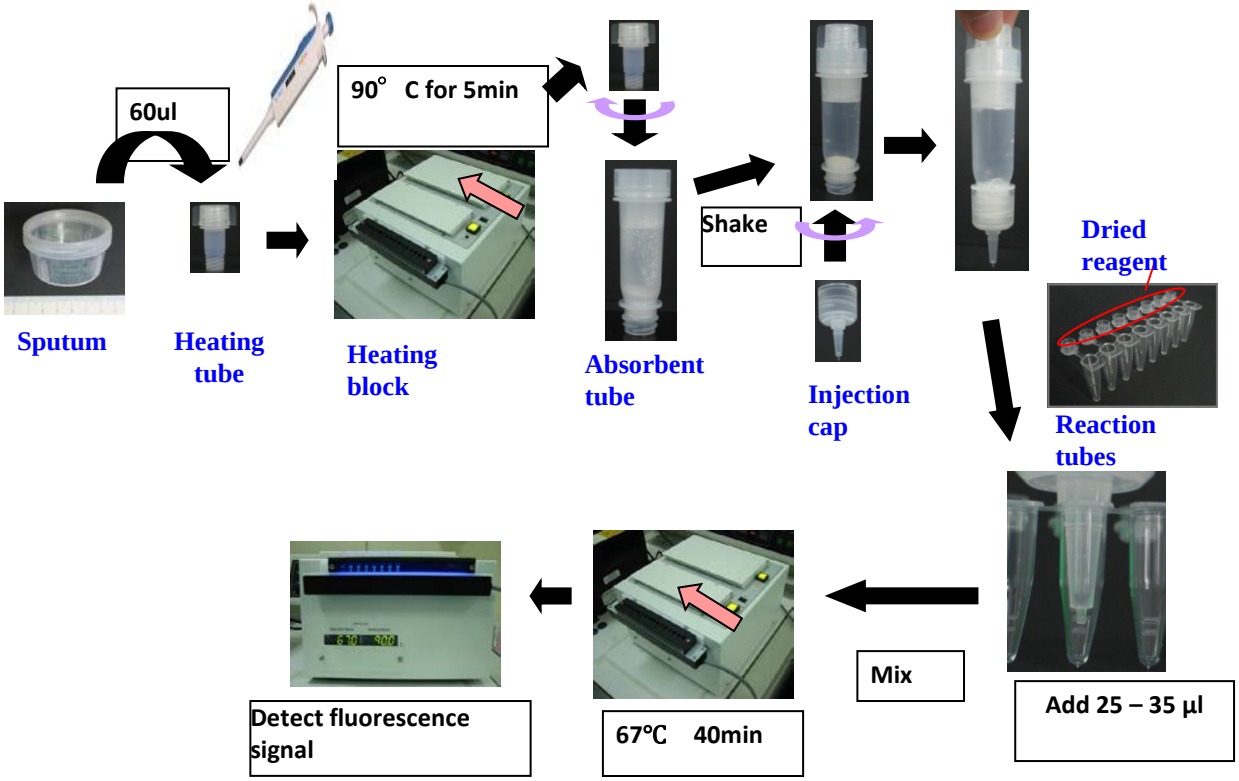
Less real-world scenario

2. Solidity of data vs urgency for change

Risk that findings do not translate to other settings / aspects overlooked

Holding up market introduction in view of large unmet diagnostic need

Status TB LAMP



July 2011

WHO submission 2012

August 2005

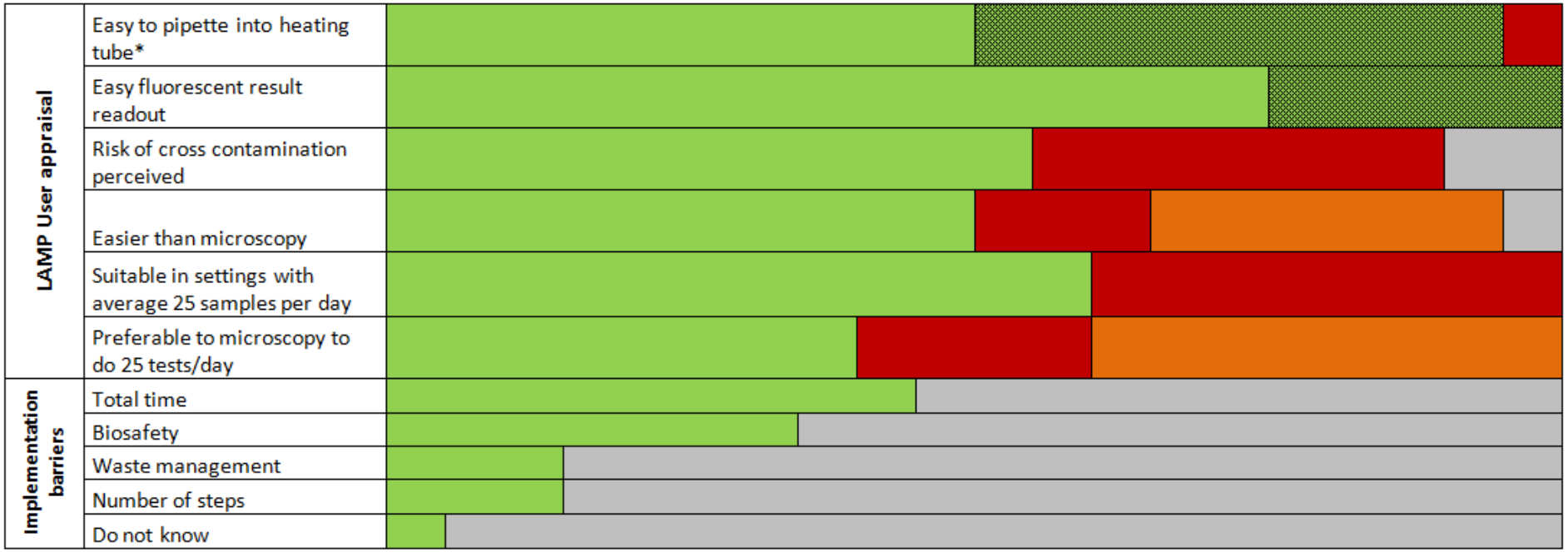
Development → Evaluation → Demonstration → Evidence for scale up

LAMP Demonstration study status

- Phase 1 started in India, Uganda, Peru in March 2011
- 11 microscopy centers / 3 supervisory sites
- Registration (CE; Japanese GMP) June 11
- Ease of use / Specificity critical endpoints
- Challenging settings in terms of infrastructure (power, temperature, space) and staffing
- Sample flow easier than for Xpert. But blinding; follow up; monitoring are more intense
- So far, 2000 TB-suspected patients have been enrolled
- Enrolment phase I expected to close in July / Joint review meeting

Ease of use

- 16 / 20 users passed proficiency testing after 5 days training
- 2/4 after 10 days training and 2/4 after 15 days training
- Average hands on time 45 min



Design changes for POC test demonstration study?

Diagnosis and Treatment: Hand in hand?

Community health worker applying a RDT and treating Malaria on the spot

What would we do with a TB POC test? – Diagnose & Treat or Screen & Refer?

- Patient values / preferences more important?
- Ease of use assessment and assessment of operational feasibility even more important (seen now for LAMP; currently under-stated in GRADE)
- Larger number of CHW to reach sample size and representativeness