TB,HIV and Lung Health Department Consultants Meeting

Policy Relevant Outcomes from Validating Evidence on ImpacT of Line Probe Assay (PROVE-IT LPA) and MTB/RIF on Presumptive Diagnosis of DR-TB in Brazil

REDE-TB: Afranio Kritski, Claudia Vater, Fatima Scarparo, Martha Oliveira, Jose Ueleres Braga, Ezio Tavora

The Union: Anne Detjen, Paula Fujiwara, I.D.Rusen

MRC UK: Patrick Phillips

LSTM: Bertie Squire, Ivor Langley, Kerry Millington

Lille, October, 31, 2011

Roterdam 2 Room

9h00-12h00

PROVE IT - LPA

Policy **R**elevant **O**utcomes from **V**alidating **E**vidence on **I**mpact of LPA

Policy Relevant Outcomes from Validating Evidence on Impact (of LPA/Genexpert, etc.)

Presentation

- Need for expanded impact assessment framework for new diagnostics
- Union/TREAT TB/LSTM Framework for Impact Assessment of New Diagnostics
- Prove-IT LPA
  - International Partnerships (**BRICS**)
  - **Brazil Sites**
  - Goal
  - Description
- Conclusion

USAID FROM THE AMERICAN PEOPLE

REDE-TB

treat TB
Technology, Research, Education, and Technical Assistance for Tuberculosis

Stop TB – WHO Strategy: 2006-2015

- Expand DOTS including

  case detection with quality assured bacteriology

- Address TB/HIV and TB-MDR
  - **Increase diagnosis of smear negative and drug resistant cases**
- Strengthening the Health System;
- Involvement of other public and private health providers (i.e.: university hospitals, prisons)
- Promote social mobilization of civil society
- Promote research to improve program implementation.
  - ***To incorporate new diagnostic tools***

http://www.who.int/tb/strategy/stop_tb_strategy/en/

Stop TB Partnership
2009 – Update (Cancun-Mexico)

Research has not been incorporated by National TB Programs as a key control tool

- **Implementation Services (IS) versus Operational Research (OR)**
- **Confuse Operational Research with monitoring and evaluation**
- **Few skilled personnel for OR**
- **Delays when use the Research ´s Approach (Ethic Committee)**
- **Coordinators tend to follow the WHO Recommendations**

How does STAG-TB/WHO Work?

Preparation of policy drafts and supporting documentation

1. Secretariat (WHO Stop TB Department)
2. **GRADE System**
3. Expert Group

Grading quality of evidence - 1979

FIRST ATTEMP - 1979 – The Canadian taks Force – Can Med Assoc 1979, 121: 1193-254

- **Tuberculosis –**
- Evidence quality – I, evidence obtained clinical trial

Hierarchy of evidence Bias

- 1, randomized control trials / **systematic review – meta-analysis**
- 2, cohort studies and case control /demonstration-feasibility studies
- 3, case reports and cases series
- 4, Opinions – Experts

Method simple, easy to use, too simple, many implicit judgments

What is wrong with explanatory RCT (level 1 of hierachy of evidence at GRADE)

Period 1976-2002: among 168,000 Randomized clinical trials
(167.905 were explanatory – respond to FDA-EMA)
(only 95 were pragmatic – under field conditions)

Comments - Trialists should :

1. give as much care and attention to issues of applicability as they already do to issues of internal validity and,

2. make every effort to make their trial widely applicable, which means that more trials **should be pragmatic in attitude.**

Shaun Treweek and Merrick Zwarenstein. **Making trials matter: pragmatic and explanatory trials and the problem of applicability.** *Trials 2009, **10:37 doi:10.1186/1745-6215-10-37***

Survey results performed in 16 high-burden TB countries' perspectives on retooling NTPs with seven new TB diagnostic tools and approaches.

Comments: WHO recommendations derived mainly from demonstration/feasibilty studies, not from pragmatic clinical trials and/or cost-effectiveness evaluation in different settings

Results:

1. More than 50% of countries adopted the new techniques [decisions relied on NTP managers]
2. The implementers stand more positive **towards adopting modern, technically demanding diagnostic techniques** than approaches to optimize smear microscopy,
3. **No impact evaluation on the health system has been carried out.**

van Kampen, Sanne C, et al. **Retooling national TB control programmes (NTPs) with new diagnostics: the NTP perspective. PLOS, 2010, i** Jul 19;5(7):e11649.

A blueprint for the development of TB diagnostics

By the New Diagnostics Working Group of the Stop TB Partnership

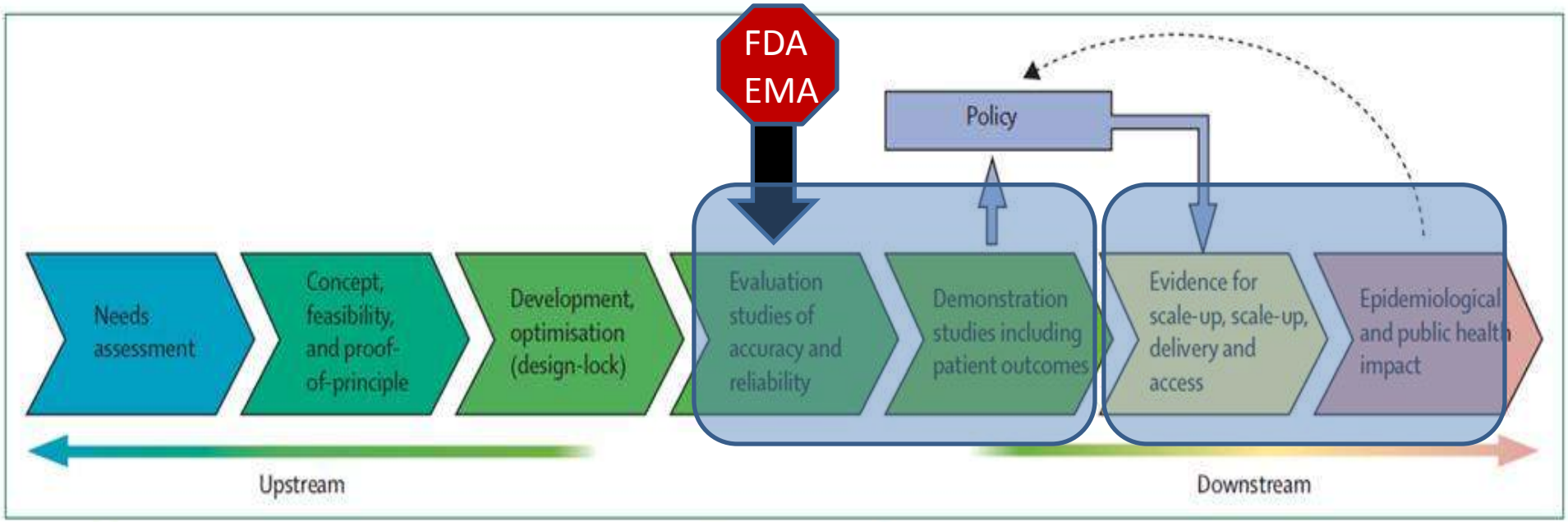


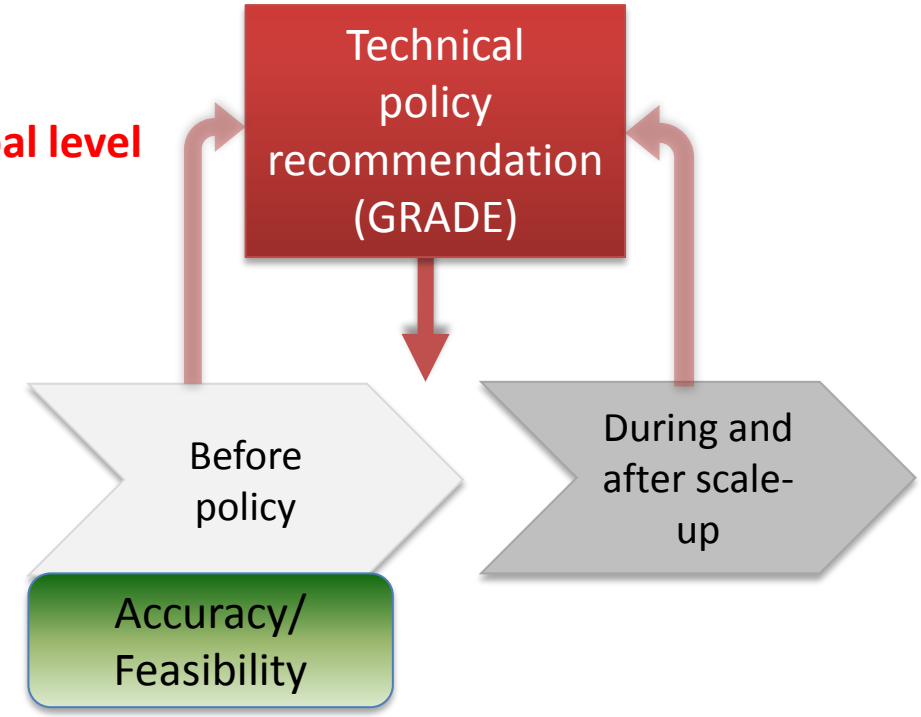
Figure 4: Schematic showing the pathway to tuberculosis diagnostics, from concept to delivery

Source: Stop TB Partnership's New Diagnostics Working Group. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics (2009),[180] and reproduced with permission from author and publisher.

http://www.stoptb.org/wg/new_diagnostics/assets/documents/BluePrintTB_annex_web.pdf

Lancet May 19 2010: DOI 1016/S0140-6736(10)60359-5

Global level



Type of Evidence

How are we currently collecting evidence on impact?

- Pilot Studies [Demonstration –Feasibility Studies]
  - Often take place in sites that are most likely to be successful

- Lessons not applicable to other settings (e.g. rural areas, different population groups)
- Data not always sufficient to ensure statistically significant findings
- Sometimes based on 'before and after' analysis – but what else is changing?

GeneXpert MTB RIF – Grade Evaluation

Study	Type of Study, Grade Evidence, Clinical Impact	Outcomes	Results (CI-95%)
Boehme *et al* Lancet. 2011 Apr 30;377(9776):1495-505., 2011	• Accuracy and effectiveness **[Demonstration study]** • **Grade level 2** • Mulcienter study (South Africa, Peru, Índia, Azerbaijão, Filipinas and Uganda) • HIV prevalence: 19% • Median age: 38 • PTB suspects, failure or close contact • **Intervention:** Xpert MTB/RIF • **Control:** cultura • **Outocme:** acurácia • **Measured: time from the laboratory order and the initial of anti-TB treatment.** • **Clinical impact was not evaluated** • **No cost-effectiveness analysis**	Sensitivity according culture (C+, B+/C+ e B-/C+) Specificity among those with culture negative and no clinical TB Positive predictive value Negative predicitve value Median time to start anti-TB treat. With MTB/RIF Median time to start anti_TB treat among AFB-/C+	• C+: 90,3% (88,4-92,0%) • B+/C+: 98,3% (97,0-99,0%) • B-/C+: 76,9% (72,4-80,8%) • 99,0% (98,5-99,3) • 96,8% • 96,8% • 5 days (2-8) • 56 days (39-81)

- **Conflict of interest – no declatrion was made, but some authors are working at FIND**

How should we evidence on impact?

- **We do need - Implementation by Research before the Implementation Services that have been carried out in low income countries**

  - **Strategy - Use of Pragmatic Randomised Control Trials (PRCTs)**

- S. B. Squire, A. R. C. Ramsay, S. van den Hof, K. A. Millington, I. Langley, G. Bello, A. Kritski, A. Detjen, R. Thomson, F. Cobelens, G. H. Mann. Making innovations accessible to the poor through implementation research. Int J Tuberc Lung Dis 2011;15(7):862-70.

What is a Pragmatic clinical trial?

Question	Effectiveness: does the intervention work **when used in normal practice?**
Setting	Normal clinical or public health practice
Participants	Little or no selection.
Intervention	Applied flexibly within the requirements of normal practice
Outcomes	Directly relevant to participants, funders, communities and healthcare practitioners
Relevance to practice	Direct: designed to meet the needs of those making decisions about intervention options in the setting in which the intervention will be implemented.

Advantages of PRCTs

- Does not prevent all implementation
- Provides locally or regionally or epidemiologically relevant data
- Select relevant outcome measures
- Use routine data collection tools, supplementing where necessary
- Calculate required sample size
- Take into account effects of ‘clustering’
- Ensure that relevant sites are included in the randomisation

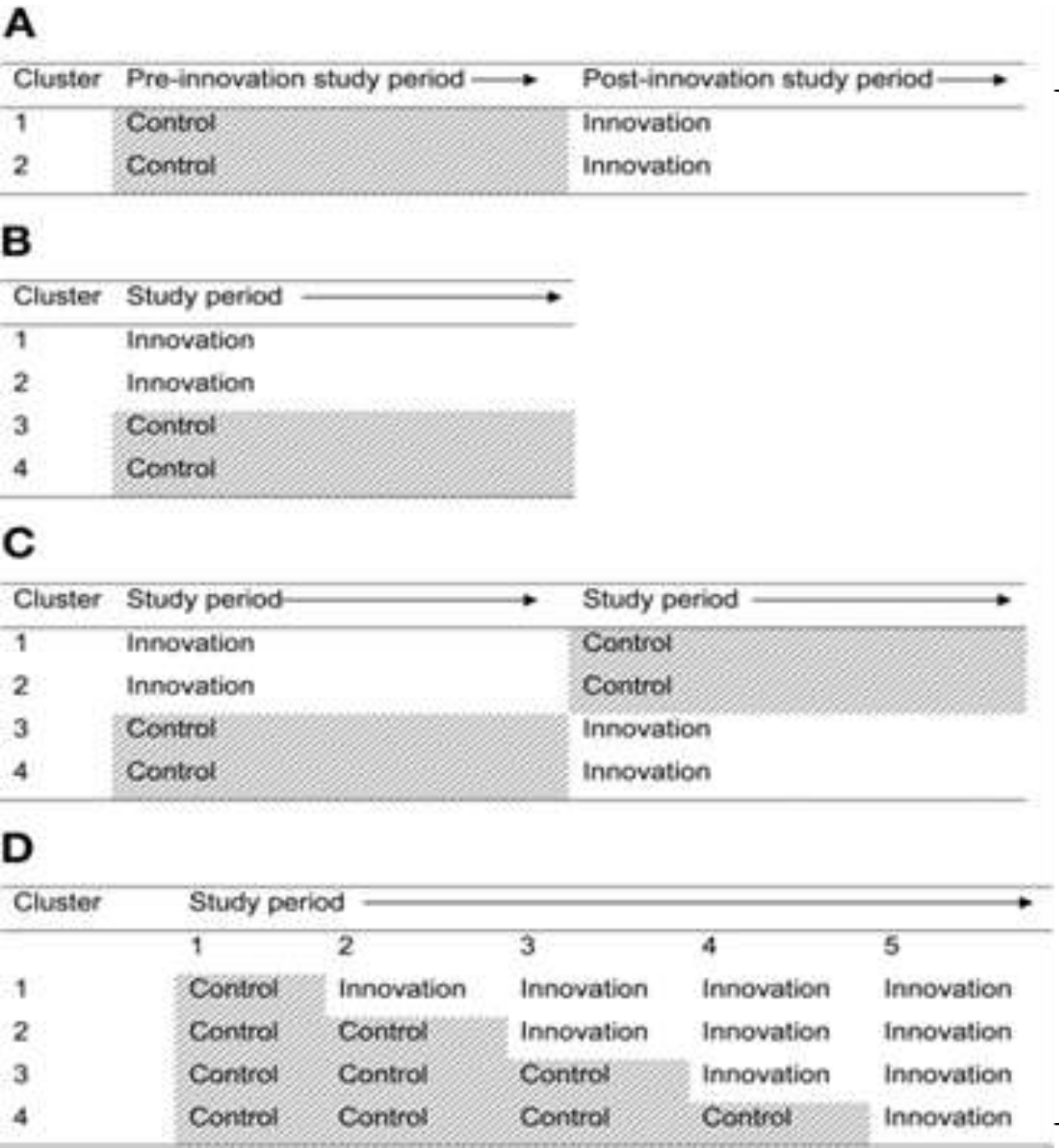


Illustration of different randomized trial designs, with concurrent innovation and comparator arms:

A) before and after;

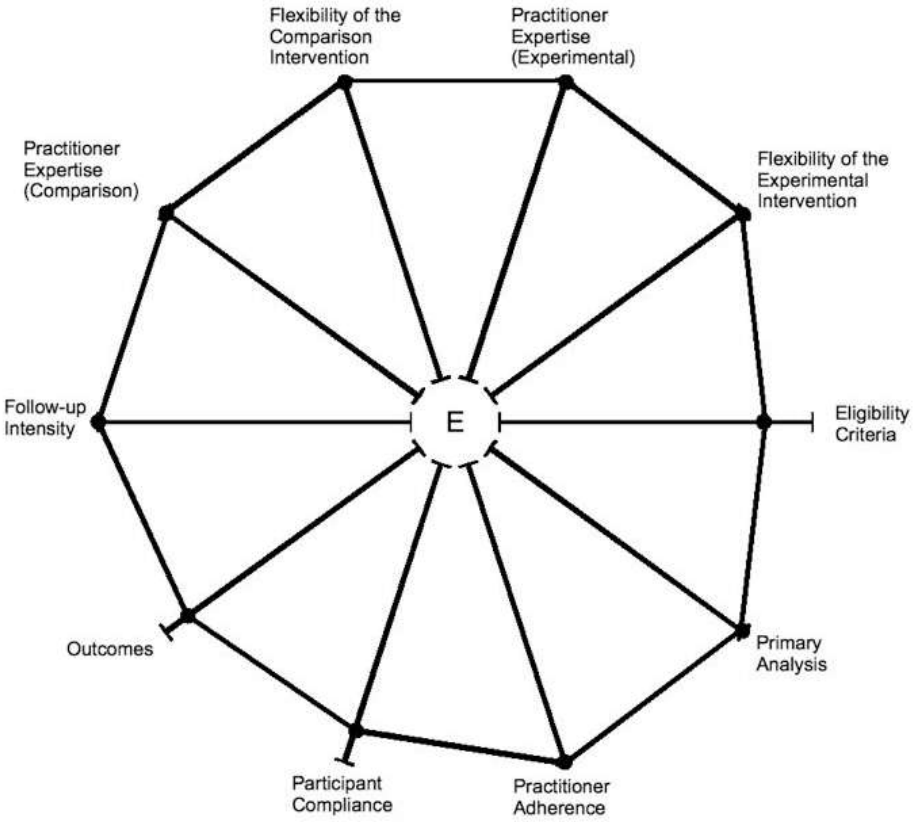
B) parallel groups;

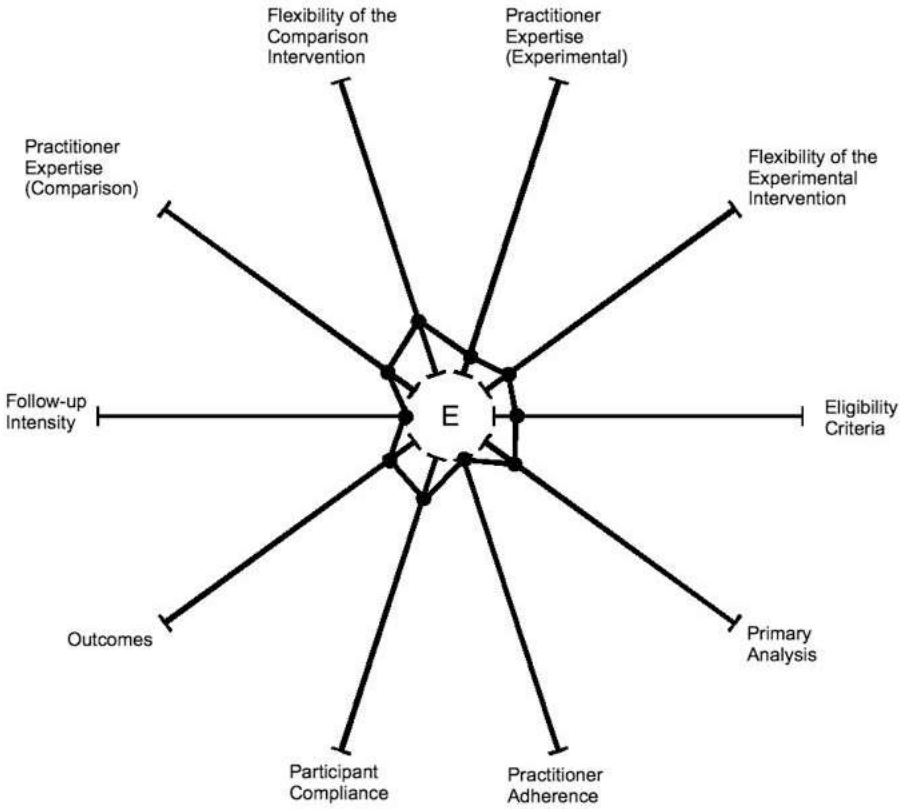
C) cross-over;

D) stepped-wedge.

(Source: Squire et al. 2011).

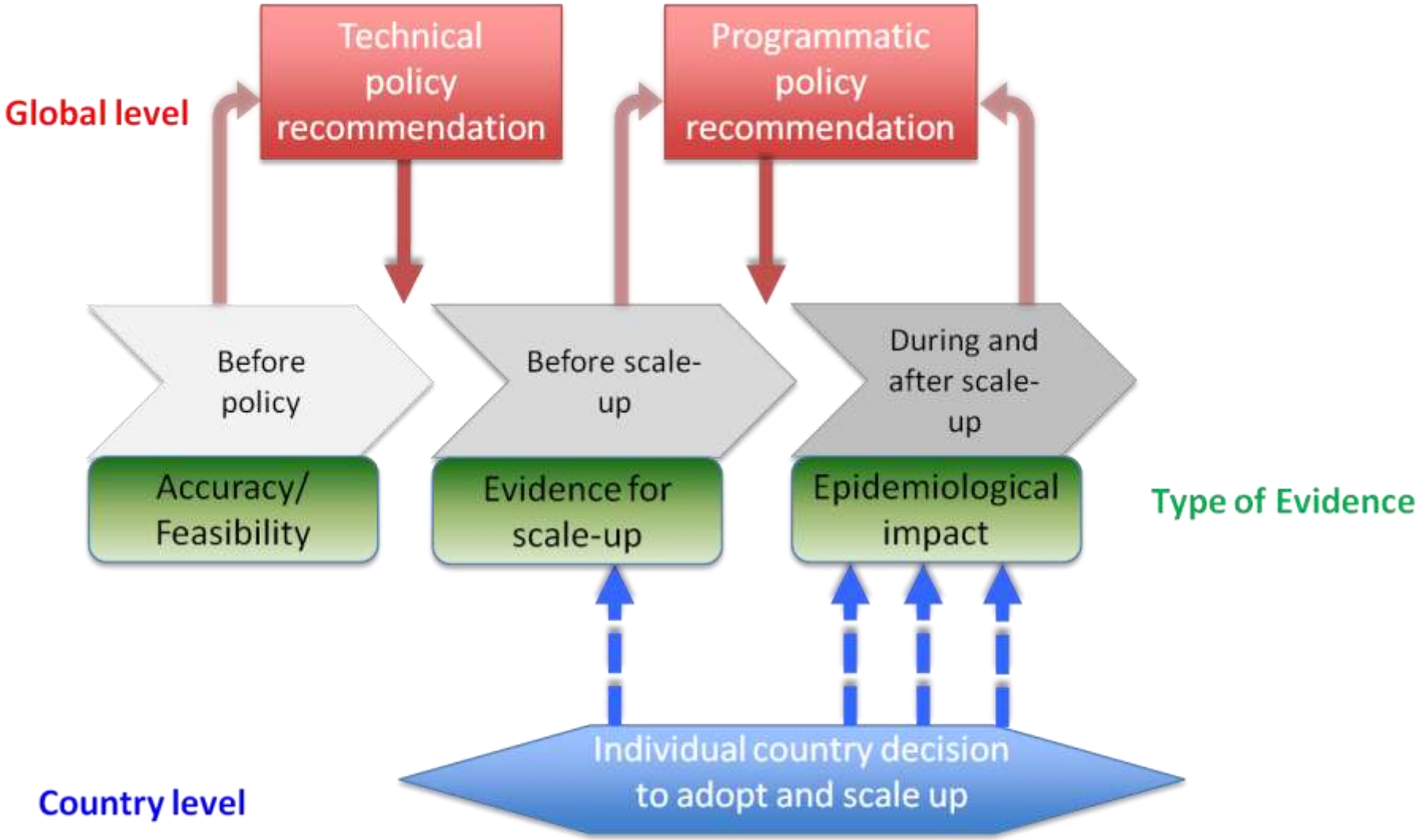
Just how pragmatic can a trial be?

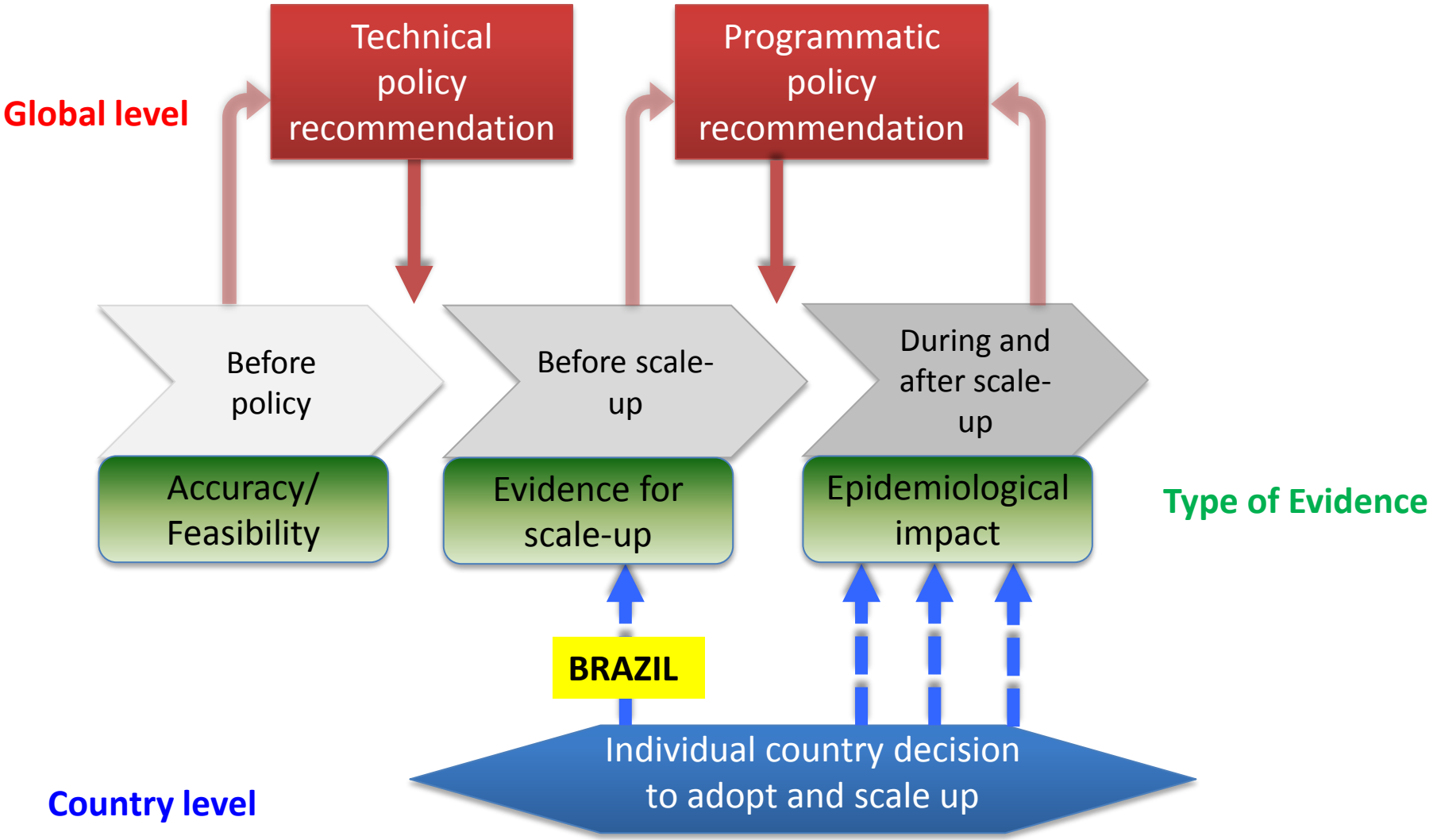




Source: Thorpe et al. CMAJ 2009 180:447-57

Is Evidence Enough?




Global level
Technical policy recommendation
Programmatic policy recommendation
Before policy
Before scale-up
During and after scale-up
Accuracy/ Feasibility
Evidence for scale-up
Epidemiological impact
Type of Evidence
BRAZIL
Individual country decision to adopt and scale up
Country level

Background - Brazil

1. In private sector: Xpert MTB/RIF (2009), MTBDR Plus-LPA (2008), and MGIT 960 (2007)– but not incorporated into the public health system (UNIVERSAL ACCESS since 1988)

2. 2008 - Commission on Technology Incorporation (CITEC) established in MoH ~ NICE /UK.
   - CITEC reviews studies on new technologies to decide if they should be incorporated into the public health system
   - For approval, studies must:

   a) Be carried out under field conditions in different regions
   b) Have used the most appropriate design
   c) Have included an assessment of the impact on the health system
   d) Have provided knowledge to assist decisions on scale up

• Projeto PROVE – IT – 1

Core UNION:

Brazilian Core

- Project Diretor,
- Clinical Coord
- Economy Coord
- Policy Transfer Coord)
- Comnunity Advisory Board (CAB) Coord
- Technology and Information Coord
- (Data Analysis Coord´
- Procurement Coord

• Local (5 Sites)

- Clinical Coord.
- Laboratory Coord
- Interviewer
- Lab Technician
- CAB Members

PROVE – IT - Brazil

Objectives

To compare, amongst DR/MDR TB suspects, the following between MTB/RIF, LPA, and MGIT960:

Two primary outcome measures :

1. Effectiveness
   a) Time from sputum submission to starting appropriate regimen for DR-TB
   b) culture conversion at 6 months

Several secondary outcome measures:

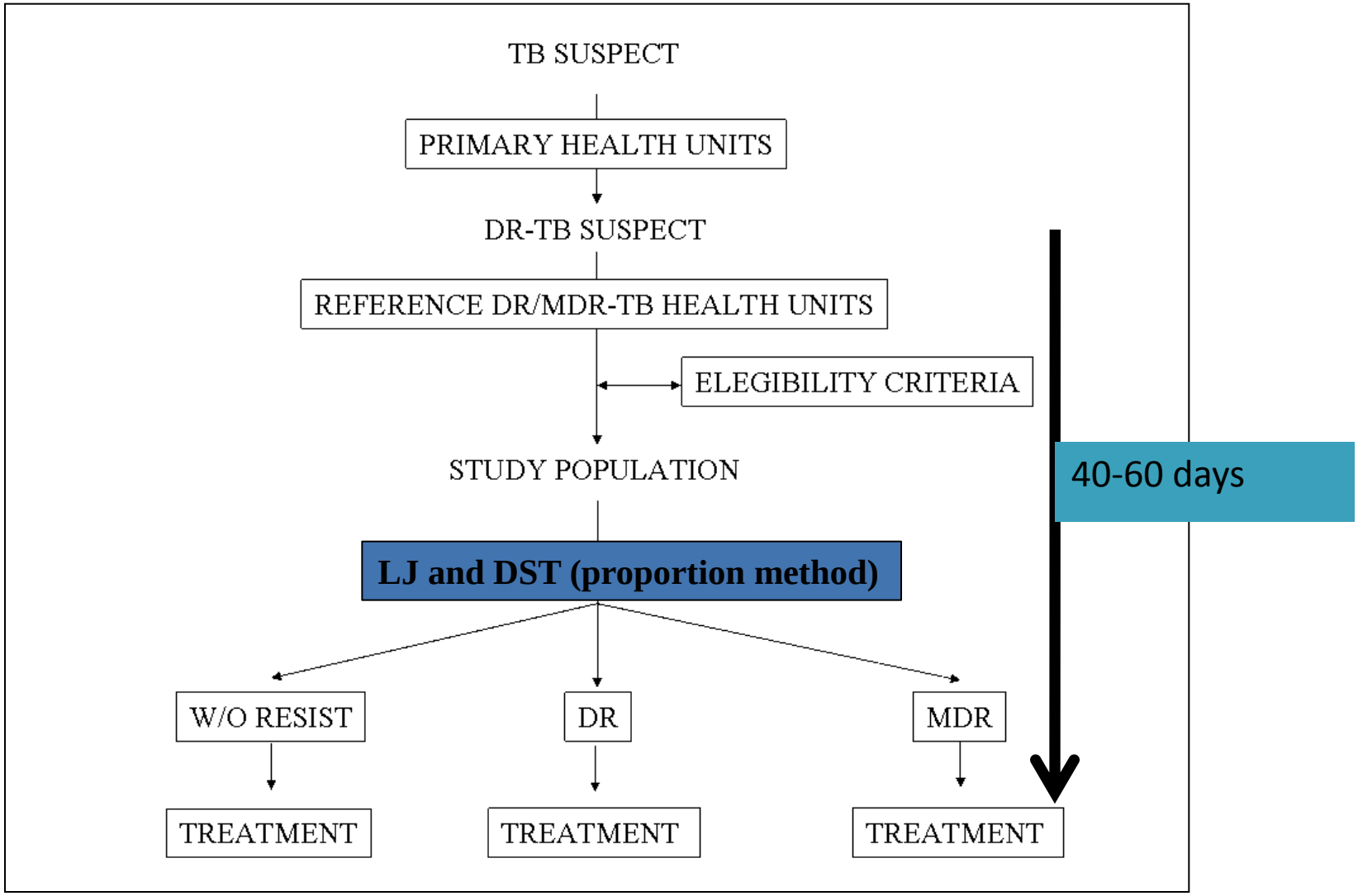
2. Equity:
   a) Median costs incurred by patients in reaching DR-TB diagnosis
   b) Costs in relation to income (derived from asset measure)

Objectives (cont)

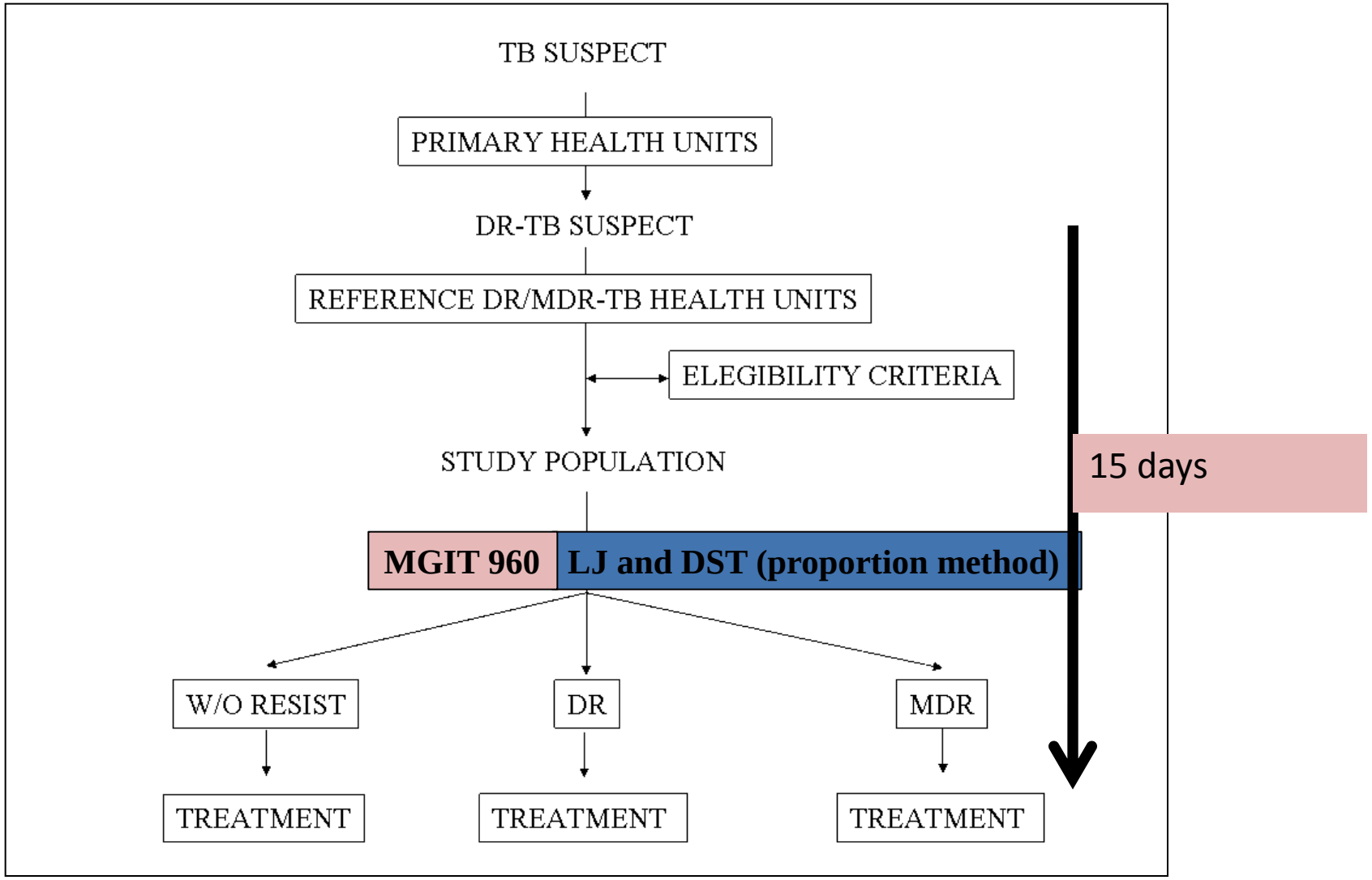
3. Health System impact :
   a) Health system costs (median cost per patient starting DR therapy)
   b) Health system requirements: disaggregated into component costs
      - Often discussed: e.g. laboratory human resources, training,
      - Less discussed: quality assurance, generators, disposal, human resources outside of laboratory – risk assessment, treatment decisions etc.

4. Scale up potential :
   a) Cost effectiveness in terms of: (e.g.) cost per case starting DR treatment, cost per case cured, cost per DR case averted
   b) Modelling of operational requirements (e.g. HR requirements across the whole algorithm, not just in the laboratory)

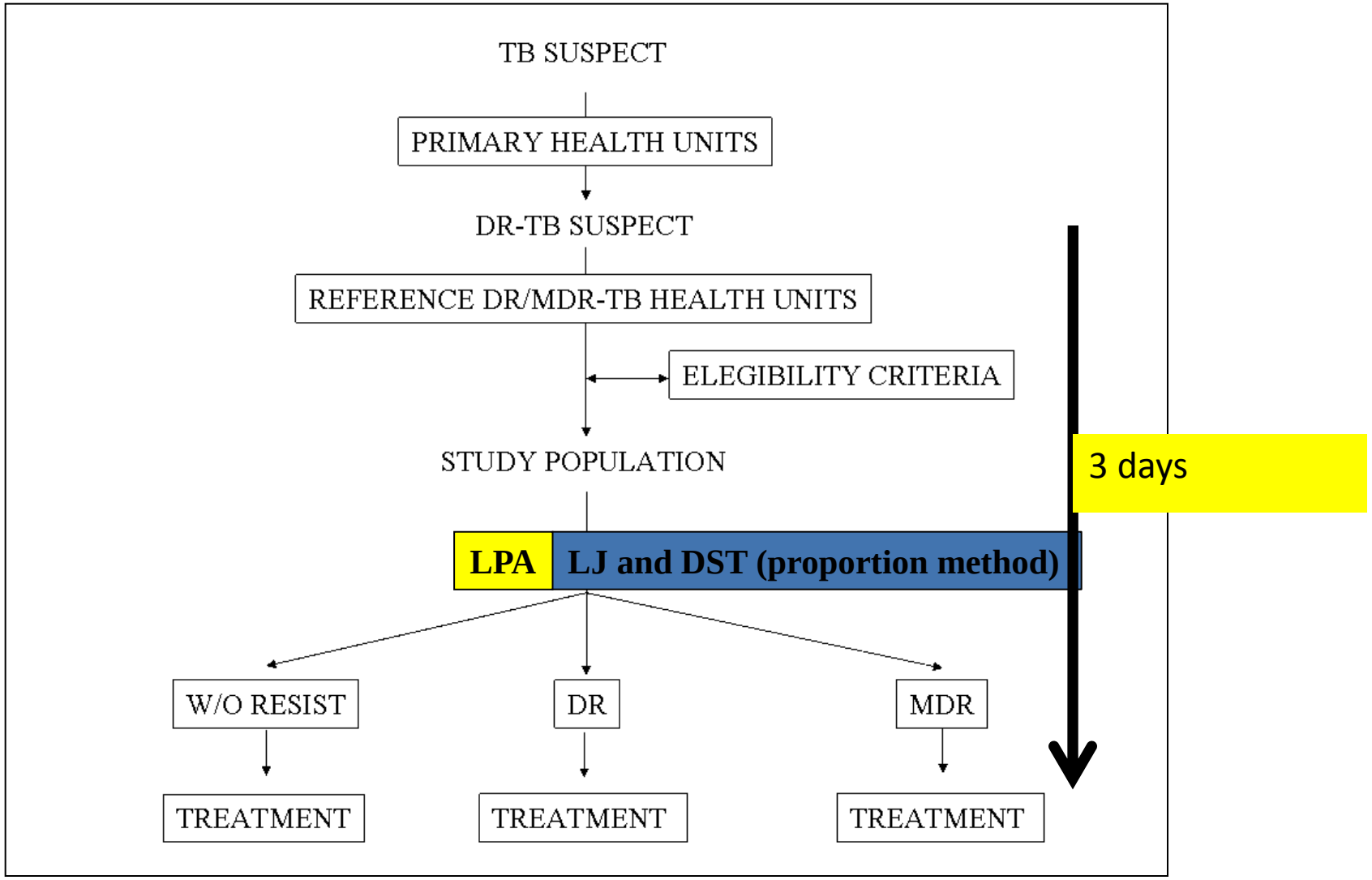
Sample size assumptions 1



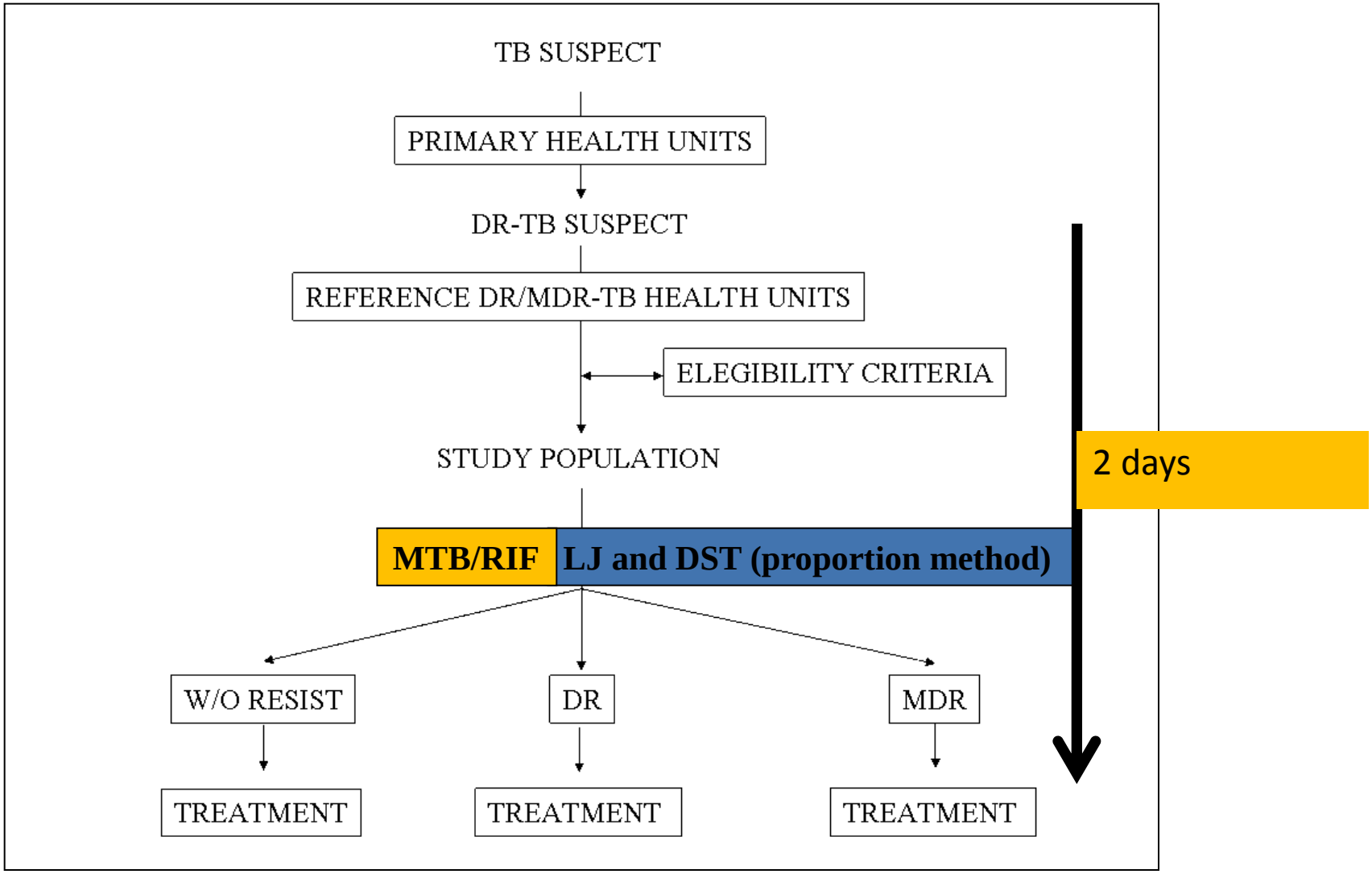
Sample size assumptions 2



Sample size assumptions 3

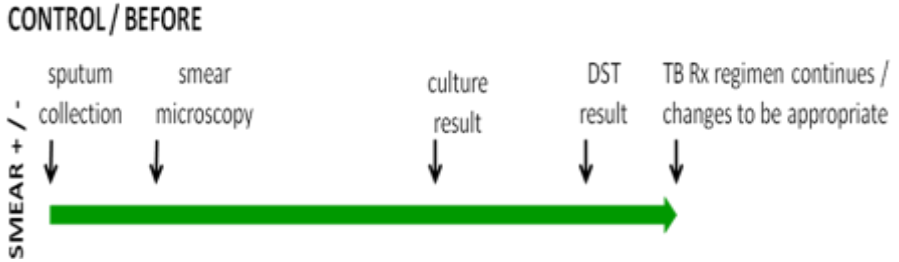


Sample size assumptions 4

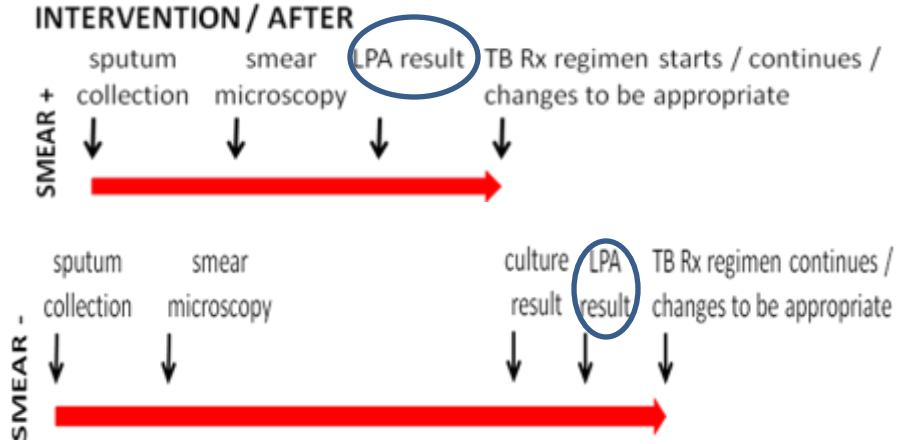


Study Interventions 1

Phase 1 (***Baseline)***: Detailed data collection for the existing algorithm (control) for DST. Will permit optimisation of procedures and data collection for all sites. Will take 5 -6 months in all sites before implementation of new diagnostic tests allocated in each site.

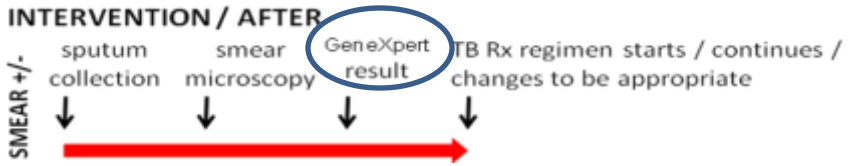


Phase 2 *(Initial Implementation)*: Training of relevant staff and implementation of intervention algorithms. For those Health Units that will use **Line Probe Assay**:



Study Interventions 2

For health units using **GeneXpert**



For health units using **MGIT 960**

Phase 3: *(Follow-up):* For 6 months after the intervention in each site, patients will be followed-up in order to evaluate respectively the smear conversion and culture conversion at 2nd and 6th months, after the first attendance

Sample size projections

1. Two comparisons
   a) MTB/RIF vs MGIT in 2 arms
   b) LPA vs MGIT in 2 arms

2. Two main end-points
   a) Time to initiation of DR therapy
   b) Outcome at 6 months in DR patients

3. Power
   a) Only one patient per arm required to detect difference with 80% power
   b) Assuming 40% culture negative at 6 months in MGIT arm, 242 patients per arm required to detect increase to 56%in culture negativity at 6 months, assuming 10% LTF, need 270 per comparison

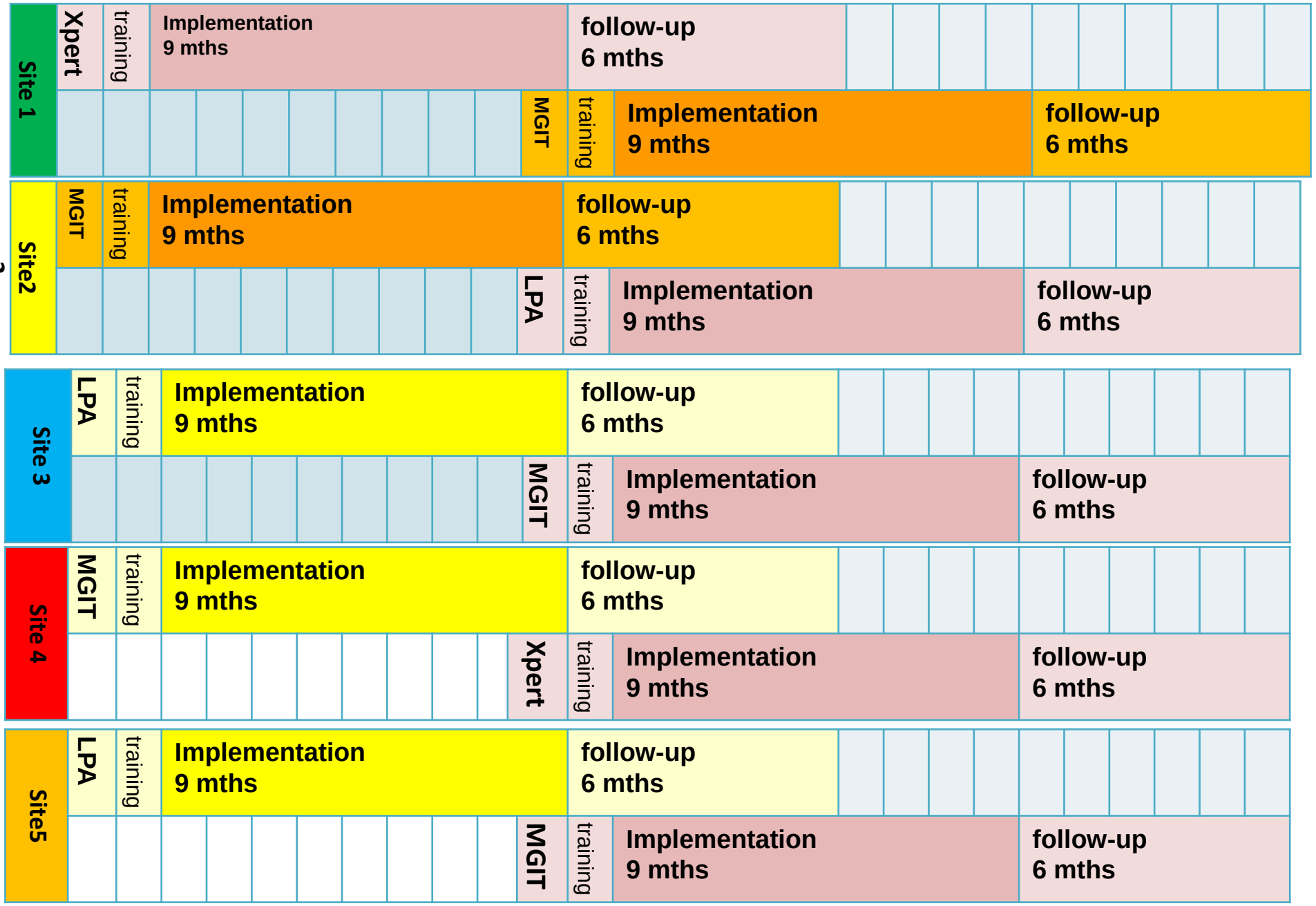
Final randomization (Sept 2011)

site	First New test	Second New Test
1-Instituto Clemente Ferreira	GeneXpert	MGIT
2- Inst Ary Parreiras	MGIT	LPA
3 - Centro de referência Helio Fraga/ Hosp Curicica	LPA	MGIT
4 - Hospital Messejana	MGIT	GeneXpert
5 - Hospital Parthenon	LPA	MGIT

Implementation Phase started in Oct 26, 2011

Design:

Pragmatic, cluster-randomised, cross-over



Prove it LPA Brazil

- Training Courses: GCP, GLP and Quality

  [integrate regular staff and those from the study project]

  – Ary Parreiras site – March 2011

  – Helio Fraga Reference Center – August 2011

  – Core Group – September 2011

  – Next training courses

    - Messejana Hospital – Fortaleza – Dec 2011
    - Clemente Ferreira Institute – Sao Paulo – Dec 2011
    - Parthenon Hospital – Porto Alegre – Feb 2012

Feasibility

1. In the implementation phase it is expected to include from October 2011:

   a) >270 DR cases in 15 months for 2 arms comparing MGIT and MTB/RIF

   b) >270 DR cases in 15 months for 2 arms comparing MGIT and LPA

2. Twenty four months total (including analysis and write-up) – results available October 2013

Baseline Results

- Clinical and Laboratory Areas
  - DR-TB suspects enrolled [Feb-Oct, 2011]
    - Total – 309

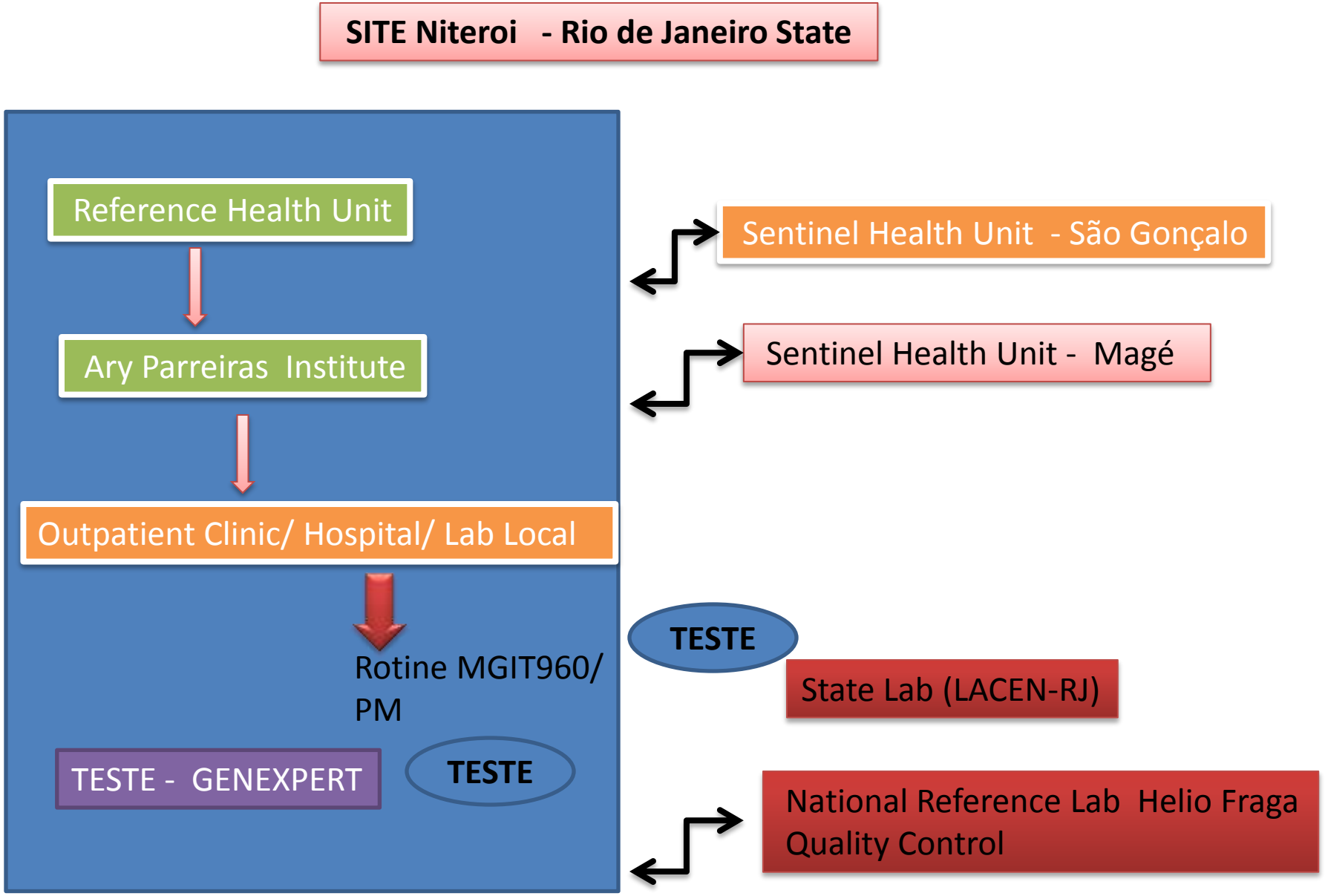
      - **TB-MDR treated cases: 84 (27%)**

      - Failure: 145 (47.0%)
      - Retreatment: 111 (35.9%)
      - HIV 22 (7.2%)
      - Homeless/IVDU 19 (6.0%)
      - Close contact of MDR 12 (3.9%)

Baseline Evaluation

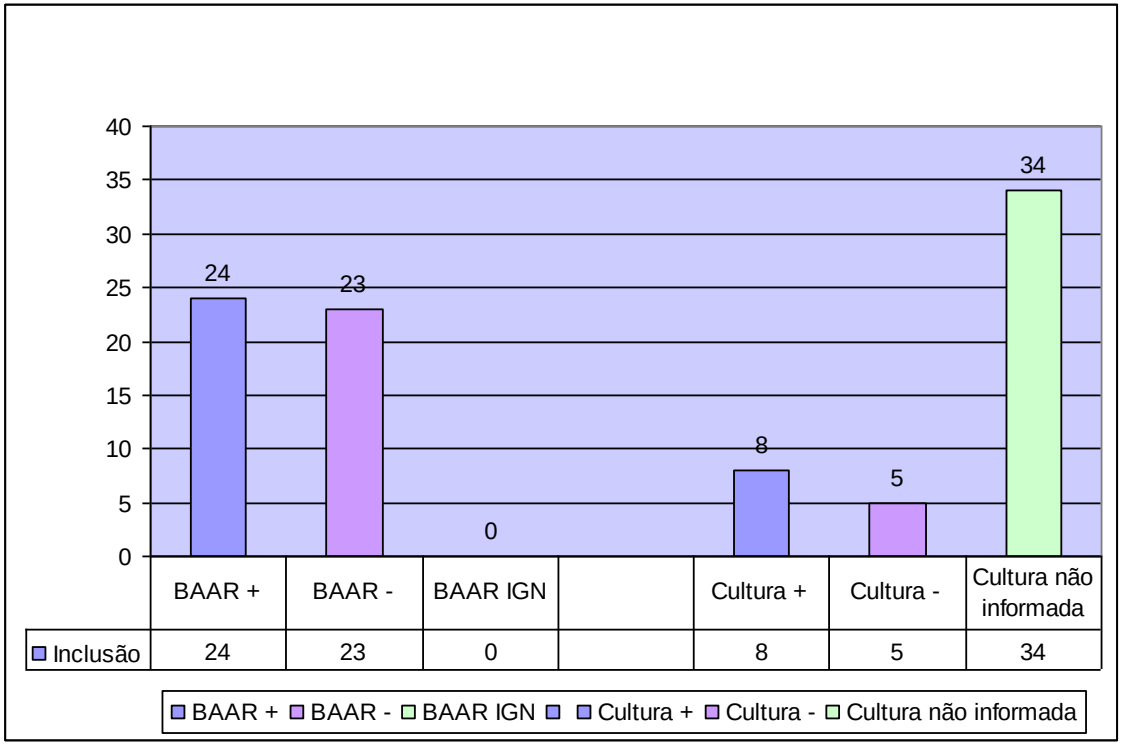
- **Case description**
  - **One of 5 sites**

  (Ary Parreiras Institute Rio de Janeiro)


SITE Niteroi - Rio de Janeiro State
Reference Health Unit
Ary Parreiras Institute
Outpatient Clinic/ Hospital/ Lab Local
Rotine MGIT960/ PM
TESTE - GENEXPERT
TESTE
Sentinel Health Unit - São Gonçalo
Sentinel Health Unit - Magé
TESTE
State Lab (LACEN-RJ)
National Reference Lab Helio Fraga
Quality Control

Ary Parreiras Site - Baseline Phase

Feb 16, 2011 – Oct 12, 2011:
DR-TB patients: 47 patients included, 6.7 patients/month



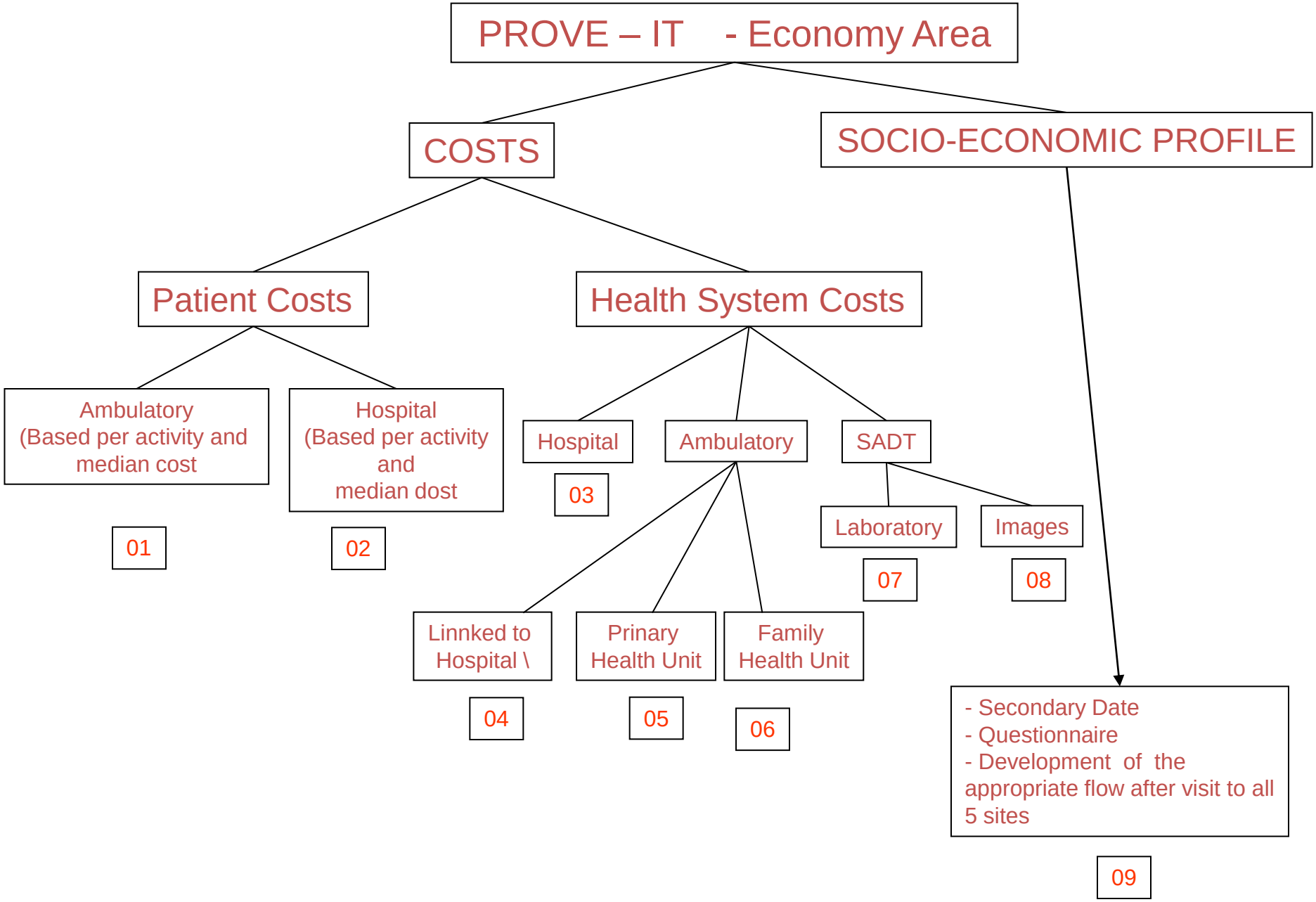
- **AFB Pos: 24; AFB Neg: 23; -**

-**Culture Pos: 8; - Culture Neg: 5; - Culture: pending : 34 [Private sector)**
-**[LJ medium]**

-**DST results: resistant: 2; - susceptible: 4; - contaminated: 2 pending: 34?**
-**[MGI960 ???]**

TOPICS

- **Economy Area**


PROVE – IT - Economy Area
COSTS
SOCIO-ECONOMIC PROFILE
Patient Costs
Health System Costs
Ambulatory (Based per activity and median cost
Hospital (Based per activity and median dost
Hospital
Ambulatory
SADT
01
02
03
Laboratory
Images
07
08
Linnked to Hospital \
Prinary Health Unit
Family Health Unit
04
05
06
- Secondary Date
- Questionnaire
- Development of the appropriate flow after visit to all 5 sites
09

Economy Area – Sept 2011

				Current status					
					CHECK-LIST				
site	State	Municipality	Health Unit	visit	Ambulatory	Laboratory	Hospital	Report	Patient cost
1	CE	FORTALEZA	HOSPITAL DE MESSEJANA DR CARLOS ALBERTO STUDART GOMES - SES-CE	X	X	X	-	X	X
2	RJ	Niterói	SESDEC INSTITUTO ESTADUAL DE DOENCAS DO TORAX ARY PARREIRAS- SES-RJ	X	X	X	X	X	X
3	RJ	Rio de Janeiro	CENTRO DE REFERENCIA PROFESSOR HELIO FRAGA ENSP -FIOCRUZ	X	X	X	-	X	X
4	RS	PORTO ALEGRE	HOSPITAL SANATORIO PARTENON	X	X	X	-	X	
5	SP	São Paulo	INSTITUTO CLEMENTE FERREIRA SAO PAULO	X	X	X	-	X	X

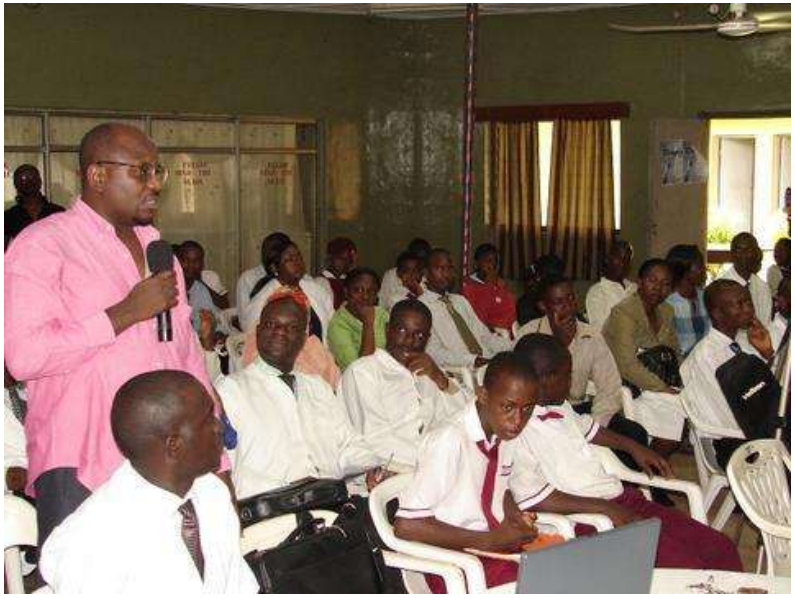
- **Policy Transfer Area**

Policy Transfer Area

- Focuses on how and why people adopt tools, or take up or reject policy.
- Analyses how policy is influenced, decided, shared, processed or shifted over time
- Collects and represents the perspectives of multiple actors.
- Analyses different ways of working, learning, communicating.

- Looks at where policy has got stuck or what helps it get accepted and adapted.
- Looks at marketing and branding

  of strategies, policies, products.
- Looks at who is involved and what role they play in decision-making process.
- Is interested in social and political interests and processes, lobbying, advocacy at all levels in a country.



- **Community Advisory Board Area**

- **Management Science for Health**

  - **Procurement –**
    - **Importation –**

      vs

    - **use the available supplies at country level**

Challenges

- **Increase the DR-TB suspects enrolled in the study during the implementation phase**
- **Improvement of focal points for proper enrollment and process monitoring**
  - **Interaction between clinical and laboratory personnel**
- **Standardization and quality data collection**
- **Improvement in planning outreach and follow-up activities between Community CAB Members and Local Sites Coordinators**

Conclusions

1. More prospective, comparative implementation studies are needed to inform rational policy uptake in different settings.

2. Several cluster-randomised designs are possible – only one example has been shown here

3. If prospective, comparative studies are not possible, it is still important to conduct operational research in association with before-and-after implementation work

4. The Impact Assessment Framework provides a way of thinking about the kind of studies that could be “bolted on” to implementation

Thanks for your attention

kritskia@gmail.com

REDE-TB

www.redetb.org