Mycobacteriology Laboratory Capacity Building for Tuberculosis Clinical Trials

Webinar, 25th March 2019

Gabriela Torrea, PhD
ITM, Belgium
• Overview of clinical trials

• Laboratory classifications

• Overview of guidelines and initial requirements to conduct clinical trials

• Challenges faced and lessons learned
  o Building capacity for lab procedures required for clinical trials
  o Laboratory infrastructure strengthening
  o Human resources strengthening
  o Quality and data management systems

• Conclusions
Introduction to Clinical Trials
2018 Global New TB Drug Pipeline

Preclinical Development

<table>
<thead>
<tr>
<th>Early Stage</th>
<th>GMP/GLP Tox.</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caprazene nucleoside</strong></td>
<td><strong>TBAJ-587</strong></td>
<td><strong>BTZ-043</strong></td>
<td><strong>OPC-167832</strong></td>
<td><strong>Bedaquiline</strong></td>
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<tr>
<td>CPZEN-45*</td>
<td>TBAJ-876</td>
<td>TBI-166</td>
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<tr>
<td><strong>Spectinamide 1810</strong></td>
<td><strong>GSK-286</strong></td>
<td><strong>Macozinone</strong></td>
<td><strong>Telacebec</strong></td>
<td><strong>Delamanid</strong></td>
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<tr>
<td><strong>Gyrase inhibitor</strong></td>
<td><strong>GSK-656</strong></td>
<td><strong>GSK-656</strong> (070)</td>
<td><strong>Delpazolid</strong></td>
<td><strong>Pretomanid</strong></td>
</tr>
<tr>
<td>SPR720*</td>
<td>TBI-223</td>
<td><strong>TBA-7371</strong></td>
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<tr>
<td><strong>Pyrazolopyridine carboxamide TB-47</strong></td>
<td><strong>Sanfetrinem</strong></td>
<td><strong>Contezolid</strong></td>
<td><strong>SQ-109</strong></td>
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<td><strong>S-004992</strong></td>
<td>(MRX-4/MRX-1)</td>
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Clinical Development

<table>
<thead>
<tr>
<th>Global Market</th>
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<tbody>
<tr>
<td>Bedaquiline*</td>
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<tr>
<td>Delamanid*</td>
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<tr>
<td>Pretomanid*</td>
</tr>
</tbody>
</table>

Underline = new to Phase since March 2018

New chemical class*: Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diaryquinoline, benzothiazidone, imidazopyridine amide, beta-lactam.

1 New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline/clinical](http://www.newtbdrugs.org/pipeline/clinical)

Ongoing projects without a lead compound series identified: [http://www.newtbdrugs.org/pipeline/discovery](http://www.newtbdrugs.org/pipeline/discovery)

Updated: October 2018
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Developer(s)</th>
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<tbody>
<tr>
<td>2HRZE + experimental drugs</td>
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<tr>
<td>2HRZE 2HR</td>
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<tr>
<td>Bedaquiline - Delamanid with MBT for MDR</td>
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<tr>
<td>Bedaquiline - Linezolid - Levofloxacin with OBR</td>
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<tr>
<td>Bedaquiline - Pretomanid - Linezolid</td>
<td>TB Alliance</td>
</tr>
<tr>
<td>Bedaquiline - Pretomanid - Linezolid - Moxifloxacin</td>
<td>Médecins Sans Frontières</td>
</tr>
<tr>
<td>Bedaquiline, Pretomanid, Moxifloxacin, Pyrazinamide</td>
<td>TB Alliance</td>
</tr>
<tr>
<td>Bedaquiline-Moxifloxacin-Linezolid-Pyrazinamide</td>
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</tr>
<tr>
<td>CC-11050, Auranofin, Everolimus, Vitamin D3 plus Rifabutin-modified TB Therapy</td>
<td></td>
</tr>
<tr>
<td>Delamanid with OBR</td>
<td>Otsuka Pharmaceutical Development &amp; Commercialization, Inc.</td>
</tr>
<tr>
<td>INH, RIF, PZA, MOX</td>
<td></td>
</tr>
<tr>
<td>Pretomanid - Moxifloxacin - Pyrazinamide Regimen</td>
<td>TB Alliance</td>
</tr>
<tr>
<td>Standard therapy</td>
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</tr>
</tbody>
</table>
## CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Pre-Clinical (GLP)</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
</table>
| **GSK-286**
GlaxoSmithKline, TB Drug Accelerator | **TBI-223**
TB Alliance, Institute of Materia Medica | **Rifampicin**
PanACEA, EDCTP, NIAID, NIH, DHHS, USAID | **TRUNCATE-TB**
University College, London, SPRINT TB (National University of Singapore) |
| **TBAJ-587, Diaryquinoline**
TB Alliance, University of Auckland | **BTZ-043**
University of Munich, Hans-Knöll Institute, Jena, German Center for Infection Research (DZIF) | **ReDEFInE High-Dose RIF for Meningitis**
| | **SPR720**
Spero Therapeutics, LLC | **Telacebec (Q203)**
Quient Co., Ltd, Quient Co. Ltd./LLC “Infectex”, a portfolio firm of Maxwell Biotech Venture Fund | **Bedaquiline**
Janssen Research & Development, LLC |
| **Spectinamide 1810**
Microbiotix, Inc. | **GSK 070, GSK 3036656**
GlaxoSmithKline | **High-Dose Rifampin**
| | **Contezolid (MRX-4/MRX-1)**
MicuRx Pharmaceuticals, Inc. | **Q203 Phase 1b Q203-TB-P1-US002**
| | **OPC-167832**
Otsuka Pharmaceutical Development & Commercialization, Inc. | **Phase 2 Telacebec (Q203) EBA**
| | **Macozinone (MCZ, PBTZ-169)**
IMTEF, Innovative Medicines for Tuberculosis and Tb-Era | **Macozinone (MCZ, PBTZ-169)**
Nearmedic Plus LLC | **Delamanid**
Otsuka Pharmaceutical Development & Commercialization, Inc. |
| | | **Phase 2a Study of PBTZ169**
| | | | **Delamanid with OBR for MDR TB** |
| | | | **Pediatric PK and Safety Trial Delamanid in MDR TB** |
| | | | **Rifapentine**
CDC TBCT, Sanofi |
| | | | **SQ109**
Sequlla, Inc. |
Site Mycobacteriology (TB) labs performing tests to enroll patients and monitoring of treatment
  o Hospital
  o National Tuberculosis Reference Lab (NRL)
  o Intermediate Reference Lab (IRL)
  o Private
  o Research Institutes

Central TB laboratory coordinating microbiological aspects
  o Supranational Reference Lab (SRL)
  o NRL
    • Initial assessment and training of site TB labs/manuals/protocols
    • Coordinate and monitor microbiological analyses in site laboratories
    • Perform specific tests for trial analyses
Guidelines

and

Initial lab requirements to conduct clinical trials
OVERVIEW OF GUIDELINES

• **ICH-Good Clinical Practice (GCP)**
  o Focus on ethics and scientific quality of trials
  o Designing, conducting, recording and reporting for trials
  o Origin in the Declaration of Helsinki (ICH GCP Guideline)

• **Good Laboratory Practice (GLP)**
  o Focus on quality and validity of test data
  o Planning, conducting, recording and reporting for lab studies

• **Good Clinical Laboratory Practice (GCLP)**
  o GLP principles relevant to the analysis of samples from clinical trials
  o Taking into account the principles of GCP
  o Reliability and integrity of data
INITIAL LABORATORY REQUIREMENTS TO CONDUCT CT

• Compliant with requirement ISO standards 15189
  ○ Mandatory for the central lab
  ○ BUT not always a reality in site labs

• Good Clinical Laboratory Practice Guidelines WHO/TDR

Elements of GCLP

- Organization and Personnel
- Safety
- Facilities and Equipment
- Verification of Performance Specifications
- Laboratory Information Systems (LIS)
- Testing Facilities Operation
- Test and Control Articles
- Records and Reports
- Specimen Management and Tracking
- Quality Management
LABORATORY ORGANIZATION

- Trial facility management responsibilities
- Well organized and trained staff
- Coordinator/Manager
- Trial staff – technician/technologist, quality officer
- Clear Organizational structure
  - To ensure clear communication during trial work
• In line with requirements from the trial (size, construction, location)
  
  o Proper designed areas
    • BSL2 – BSL3
    • Molecular lab

• Suitable facilities for the preparation of trial supplies

• Appropriate storage areas for samples and supplies
Equipment should be:

- In good working condition
- Periodically inspected, cleaned, maintained, and calibrated

Instructions for use must be available

Equipment users should be qualified and trained

Materials and consumables should be:

- Stored at appropriate environmental conditions
- Appropriately labelled
  - Identity
  - Concentration
  - Specific storage instructions
  - Stability (e.g. preparation date and expiration date)
TRIAL MATERIALS (TM)

Receipt

- Design procedures to prevent mix-ups and maintain their integrity
- Should be adequately identified
- Maintain records

Chain of Custody

- Maintain TM identification and traceability
- Retrospective evaluation of storage
- TM storage areas should be monitored
- Contingency plans with actions
STANDARD OPERATING PROCEDURES (SOPs)

- To ensure uniformity and quality of results
- KISS (Keep it Short and Simple)
- For procedures (pre-analytical, analytical, and post analytical phases)
- For handling test equipment
- For quality control procedures
- For staff training
- Approved by Trial Facility Management
- SOPs should be periodically reviewed
- A list of current SOPs with version numbers
- Published textbooks, articles and manuals may be used as supplements to the SOPs
Challenges and Lessons Learned

Lab Procedures

“The only mistake in life is the lesson not learned”

Albert Einstein
SITE LABORATORIES

Diagnostics for enrolment

• Smear microscopy
  o Microscope
  o Quality of stains and reagents
• FDA vital staining
  o Fluorescent microscope
  o Validation/implementation
• Xpert:
  o Maintenance/calibration
  o Errors not evaluated
• LPA
  o Lab design
  o Validation/implementation
  o Technical issues and interpretation

Treatment outcome

• Culture
  o Liquid culture - MGIT960
  o Solid culture – Simple culture method (Kudoh)
    • Media preparation – no inspissator?
      ✓ Provided by the central lab
      ✓ Impact of shipment on quality
• Fresh sputum samples required
• Validation/implementation

Validations to be done at least 3 months before trial initiation
United Nations Model Regulations

- *Mycobacterium tuberculosis* isolates: Category A (UN 2814)
  - Transport medium: dry, 0.5% CPC
  - Room temperature
  - UN 2814 boxes (Class 6.2 and accompanied by a Shipper’s declaration)

- Sputum specimen in MGIT not incubated: Category B (UN 3373)
  - MGIT tubes
  - Refrigerated
  - UN 3373 boxes (class 6.2)
PACKAGING AND DECLARATION FORM

SHIPPER: Air Waybill No

Page 1 of 1 Pages
Shipper’s Reference Number

CONSIGNEE: Two completed and signed copies of this Declaration must be handed to the operator.

WARNING
Failure to comply in all respects with the applicable Dangerous Goods Regulations may be in breach of the applicable law, subject to legal penalties. This Declaration must not, in any circumstances, be completed and/or signed by a consolidator, a forwarder or an IATA cargo agent.

TRANSPORT DETAILS
This shipment is within the limitations prescribed for Airport of Departure PASSENGER AND CARGO AIRCRAFT ONLY

Airport of Destination:
Shipment type: NON-RADIOACTIVE RADIOACTIVE

NATURE AND QUANTITY OF DANGEROUS GOODS

Dangerous Goods Identification

Proper Shipping Name

Class or Division (Subsidiary Risk)

Pack Group

Quantity and Type of packing

Packing List

Authentication

UN or ID No.

EMERGENCY CONTACT: +32 (0)3 247 65 03 L. CASIER

I hereby declare that the contents of this consignment are fully and accurately described above by the proper shipping name, and are classified, packaged, marked and labeled/placarded, and are in all respects in proper condition for transport according to applicable international and national governmental regulations. I declare that all of the applicable air transport requirements have been met.

Name/Title of Signatory
L. CASIER / EXPORT MANAGER

Place and Date
ANTWERPEN, 12.11.2008

Signature
(see warning above)
# SHIPMENT LIST

## STREAM Study Specimen Packing List

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Number of cryotubes</th>
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</thead>
<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Responsible for the shipment</th>
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<tbody>
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<table>
<thead>
<tr>
<th>Date of shipment</th>
<th>E-mail</th>
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<tr>
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</table>

<table>
<thead>
<tr>
<th>Name of the person who prepared the list</th>
<th>Date</th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of the person who prepared the package for the shipment</th>
<th>Date</th>
</tr>
</thead>
<tbody>
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</table>

<table>
<thead>
<tr>
<th>Name of the reviewer</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen type (Sputum, sediment, colonies, DNA extract)</th>
<th>Study number</th>
<th>Week visit</th>
<th>Local lab accession number</th>
<th>Transport medium (Ethanol, CPC, MGIT, None, Other : specify)</th>
<th>Spumum collection date</th>
<th>Smear results *</th>
<th>Culture results *</th>
<th>LPA results **</th>
<th>ITM ID</th>
</tr>
</thead>
</table>

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|---|---|---|---|---|---|---|---|---|---|
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| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
| 6 | | | | | | | | | |
| 7 | | | | | | | | | |

* Smear results
* Culture results
** LPA results

- *rpoB*
- *katG*
- *inhA*
- *gyrA*
- *gyrB*
- *rrs*
- *eis*
<table>
<thead>
<tr>
<th>Challenge</th>
<th>Resolution and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local issues with preparation of documents</td>
<td>To be solved by the site with the support of the ITM shipment department</td>
</tr>
<tr>
<td>Issue of biodiversity for sending isolates (isolated after Octobre 2014)/ Nagoya Protocol</td>
<td>To be solved by the site together with the Sponsor/ Please check: <a href="https://absch.cbd.int/countries/ET">https://absch.cbd.int/countries/ET</a></td>
</tr>
</tbody>
</table>
DST Methods:

- First line drugs: H, R, E, S, Z
  - Proportion Method (PM) on LJ or agar
  - Z: MGIT/Pzase assay/pncA seq.

- Second line drugs: FQL, SLI
  - PM on LJ/agar/MGIT
  - MIC on agar/MGIT
  - MIC by REMA

- New drugs: BDQ, DLM, CFZ
  - PM on MGIT/agar
  - MIC on MGIT/agar
  - MIC REMA

Validations:

- Pzase assay vs. MGIT/pncA seq.
- BDQ MIC in 7H11 agar
- MFX and LFX MIC in 7H10 agar
- CFZ MIC in 7H10 agar
- REMA for KAN, AM, S and LZD

Validations to be done at least 6–12 months before trial initiation
Central Laboratory Sample Flow-chart

**STREAM Stage I FLOW CHART**

- Arrive of specimens (Mtb isolates in 0.5% CPC) at purchasing department
  - Check labels and shipping list information versus “List of STREAM randomized patients”
    - Attach sticker on form
    - Registration

- Subculture on LJ

- DST: proportion method on LJ
  - INH – RMP – EMB – SM – and PNB

- DST proportion method on 7H11 agar
  - OFL – KAN – CAP - ETH

- If discrepant result between sites and ITM

- Failures/Relapses

- MIC determination on LJ for INH – RMP

- Sequencing of rpoB – katG – inhA

- Genetic species identification (16S PCR + sequencing)

- Deviations contact:
  - Site laboratory (TC) (+ PI in cc)
  - MRC in cc (CTM)

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**Key Terms:**

- **MtB:** Mycobacterium tuberculosis
- **DB:** Database
- **PI:** Principal Investigator
- **TC:** Trial Coordinator
- **CTM:** Clinical trial manager
- **LJ:** Löwenstein Jensen
- **INH:** isoniazid
- **RMP:** rifampicin
- **EMB:** ethambutol
- **SM:** streptomycin
- **OFL:** ofloxacin
- **KAN:** kanamycine
- **CAP:** capreomycine
- **ETH:** ethionamide

---

**Genotyping:**

- Spoligotyping
- MIRU-VNTR 15 locus

**Susception:**

- Arrivial of specimens (Mtb isolates in 0.5% CPC)
- At purchasing department
- Check labels and shipping list information versus “List of STREAM randomized patients”
- Attach sticker on form
- Registration
- Subculture on LJ
- DST proportion method on LJ
  - INH – RMP – EMB – SM – and PNB
- DST proportion method on 7H11 agar
  - OFL – KAN – CAP - ETH
- If discrepant result between sites and ITM
- Failures/Relapses
- MIC determination on LJ for INH – RMP
- Sequencing of rpoB – katG – inhA
- Genetic species identification (16S PCR + sequencing)

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**Institute of Tropical Medicine | Biomedical Sciences**
VALIDATION / IMPLEMENTATION

• Clinical Methods
  o Commercial methods
  o Approved methods or published methods (peer reviewed)
  o In-house developed methods
  o Approved methods or published methods (peer reviewed) with modifications

• Depending on nature of clinical method:
  o **Validation** – *Are we doing the correct test?*
  o **Verification** – *Are we doing the test correctly?*
• Validation dossier
  ○ Validation/verification plan: approved and signed off before starting validation and implementation
  ○ Validation/verification Report: ideally signed off before start of the trial activities
TIMING OF VALIDATIONS

- **Prospective validation/verification**: before implementation of the method in the lab
  - Ideal but difficult to achieve
  - At least 3 to 12 months before

- **Concurrent validation/verification**: exceptionally, validation/verification can be performed during the first month(s) after implementation of the method in the lab

- **Retrospective validation**: method that is already implemented in the lab for a long time and for which historical data can be used to support the performance characteristics of the test
## Action Plan

### Action Plan STREAM stage 2 validations

<table>
<thead>
<tr>
<th>Validation</th>
<th>Responsible</th>
<th>2014</th>
<th>2015</th>
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</thead>
<tbody>
<tr>
<td>Modified Ogawa medium Stability at 2-8°C</td>
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<tr>
<td>Validation plan</td>
<td>GT</td>
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<tr>
<td>Experimental work</td>
<td>CD</td>
<td></td>
<td></td>
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<tr>
<td>Final Report</td>
<td>GT</td>
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<tr>
<td>REMA DST for Amikacin and Streptomycin</td>
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<tr>
<td>Addendum</td>
<td>GT</td>
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<tr>
<td>Experimental work</td>
<td>CD</td>
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<td>Intermediate Report</td>
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<tr>
<td>Final Report</td>
<td>GT</td>
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<tr>
<td>MIC determination of MFX on 7H10</td>
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<td>Addendum</td>
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<td>Experimental work</td>
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<td>Intermediate report</td>
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<tr>
<td>Final Report</td>
<td>GT</td>
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<tr>
<td>PZase assay</td>
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<tr>
<td>Validation plan</td>
<td>GT</td>
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<tr>
<td>Experimental work</td>
<td>MD</td>
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<tr>
<td>Final Report</td>
<td>GT</td>
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</table>

The table above outlines the action plan for STREAM stage 2 validations including Modified Ogawa medium Stability at 2-8°C, REMA DST for Amikacin and Streptomycin, MIC determination of MFX on 7H10, and PZase assay. Each validation is assigned to a responsible party and marked with corresponding dates for 2014 and 2015.
Challenges and Lessons Learned

- Infrastructures and Equipment
- Human Resources
- QMS & DMS

“The only mistake in life is the lesson not learned”

Albert Einstein
INFRASTRUCTURE AND EQUIPMENT

Mycobacteriology lab

• Space and ventilation: BSL2, BSL3?

• Safety cabinets
  o Class 1 or 2
  o Certification

• Centrifuges
  o Speed (rcf) Not well set up
  o Temperature

• Incubators
  o Space
  o Temperature monitoring

• Autoclave
  o Replacement

• Inspissator
  o Solid media provided by central lab

• Microscope
  o Replacement

• Freezers
  o Not sufficient number
Molecular lab:
- 4 separate work areas
  - Not properly designed
- Equipment and consumables allocated to each area not interchangeable
  - Pipettes shared in all areas
- Different set of PPE with different colours
  - Not implemented
- Thermal cycler calibration
- Twincubator
  - better than GTBlot 48?
  - Calibration
- Mini spin
  - Not used
- Water bath
  - Not existing

INFRASTRUCTURE AND EQUIPMENT
• List of supplies with specifications before the start of the trial

• Maintenance and Service of equipment
HUMAN RESOURCES

Staff development

• Training plan    Not always
• Refresher training   Rarely done
• GCLP training   Not followed by all staff
• IATA certification   Non valid certificates

• Workload

<table>
<thead>
<tr>
<th></th>
<th>Number staff per lab</th>
<th>No. of smears / year / staff</th>
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<tbody>
<tr>
<td>Smear microscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td>No. of cultures / staff/day</td>
</tr>
<tr>
<td>Phenotypic DST</td>
<td></td>
<td>No. of DST / year / staff</td>
</tr>
<tr>
<td>Genotypic DST</td>
<td></td>
<td>No. of DST / year / staff</td>
</tr>
</tbody>
</table>

Staff experience

• Number of years
• Full time/part time
• Motivation

• The current lab staff
  o Technician overwhelmed
  o Quality officer not existing
  o Coordinator (communication)

• Recruitment of new staff
  o Ideally with TB experience
  o Trained and proficiency assessed
QUALITY MANAGEMENT SYSTEM

• NTP guidelines for QA
  o Microscopy:
    • IQC  Not properly done
    • EQA
      ✓ PT  Widely used
      ✓ Rechecking  Not always in place
  • Culture
    o IQC  Not properly done - Indicators
    o EQA  Not always in place
  • DST
    o IQC  Not fully done
    o EQA
      • Phenotypic  Few labs
      • Genotypic  Not always implemented
      ✓ Extract DNA  Sent by central lab
DATA MANAGEMENT SYSTEM

• Request form: Transfer data lab - clinician
  o Hard copy/electronic  Clerical errors
  o Trial specific  Not always

• Registers (microscopy, culture, DST)
  o Trial specific  Difficult to harmonise
  o Hard copy  Not complete
  o Electronic  Transfer to central lab

• TAT  Meet standards
  o Smear microscopy
  o Culture
  o DST

• Review of data  Not done
CONCLUSION

Clinical Trial
- Safety
- Reliable data

Management
Human resources
DMS
QMS
Lab organisation
Infrastructures & equipment
Procurements
Lab procedures SOPs
Safety
QUESTIONS
Acknowledgments

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