It's all about the microbiology

- so let's make sure it's right

Prof Tim McHugh
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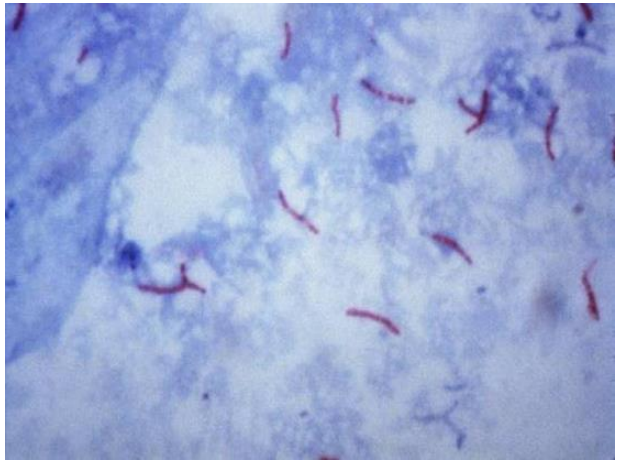
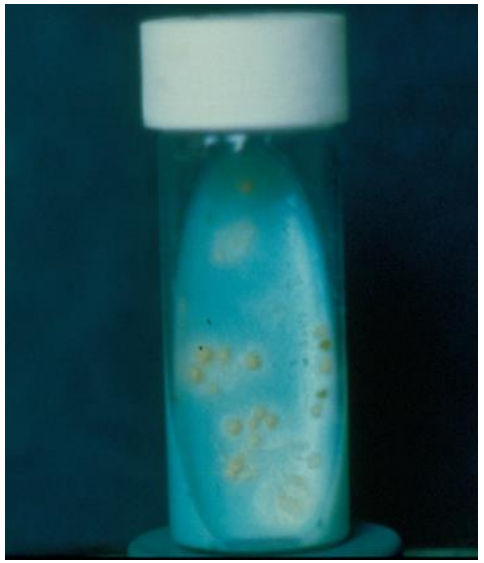
Critical end points



https://www.cdc.gov/tb/webcourses/tb101/page3294.html

Sputum Smear negativity

Culture negativity



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Both require competent microbiology

SimpliciTB: Primary and Secondary Objectives and Endpoints are based on TB Laboratory data

To evaluate the **efficacy**, safety and tolerability at 2 months, 12 months and 24 months in participants with Drug Sensitive and Drug Resistant TB

- Incidence of bacteriologic failure or relapse, or clinical failure at 24 months (104 weeks)
- Proportion of participants with sputum culture conversion to negative status in liquid culture at 4, 6, 12 and 17 weeks
- Time to culture negativity over 8 weeks

Inclusion Criteria:

- Results of AFB microscopy & molecular tests on sputum to be obtained during screening period
- If MGIT DST later shows discrepancy with molecular tests, participant may be late exclusion

What are the issues with microbiology?

- Smear
  - Missed organisms — False negative
  - Miss identified — False positive
    - Artefacts
    - Other mycobacteria
- Culture
  - No growth — False negative
    - +/-
    - Time to positivity — Under estimate of bacterial load
  - Too much growth — Indeterminate results
    - contamination

Clinical diagnosis: clinical trails: discovery research Same data - different paradigms

- All laboratories chosen are using acceptable methods for TB diagnosis
- But these methods are not necessarily standardized across laboratories
  - e.g. WHO versus American CDC reporting of smear positivity

No. of AFBs (average over 100 fields)	REMoxTB Reporting	WHO Reporting (for conversion only)
None	No AFB seen (NS)	No AFB seen (NS)
1-9 per 100 fields	+	scanty/or actual number)
1-9 per 10 fields	++	+
1-9 per field	+++	++
>9 per field	++++	+++

- Differences could introduce bias
- Limit confidence in cross-comparison of data

Rigour in delivery of microbiology

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

UCL

STAND

Protocol Ti
Tolerability
Adult Sub
Treatme

Protocol Number: NC-006-(M-Pa-Z)
Protocol Name: STAND (Shortening **T**reatments by **A**dvancing **N**ovel **D**rugs**)**
Version: 1.0; 18January2014

I hereby approve the above document and release it for appropriate amendment to make it Mycobacteriology Laboratory specific and thereafter use at the Mycobacteriology Laboratories:

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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STAND

cy, Safety and
6 months in Adult
Subjects with Drug-Sensitive Smear-Positive Pulmonary Tuberculosis and after 6 months of Treatment in Adult Subjects with Multi-Drug Resistant, Smear Positive Pulmonary Tuberculosis.

Protocol Number: NC-006-(M-Pa-Z)
Protocol Name: STAND (Shortening Treatments by **A**dvancing **N**ovel **D**rugs**)**
Version: 2.0: 09February2015

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Date:	13 Feb 2015

Shift in zeitgeist

‘Too difficult’ becomes essential

Quality framework

- A comprehensive Mycobacteriology Laboratory Manual provided by the sponsor must be followed to ensure the same procedures are used across all laboratories.
  - Essential for the **strength** and **integrity** of the trial data

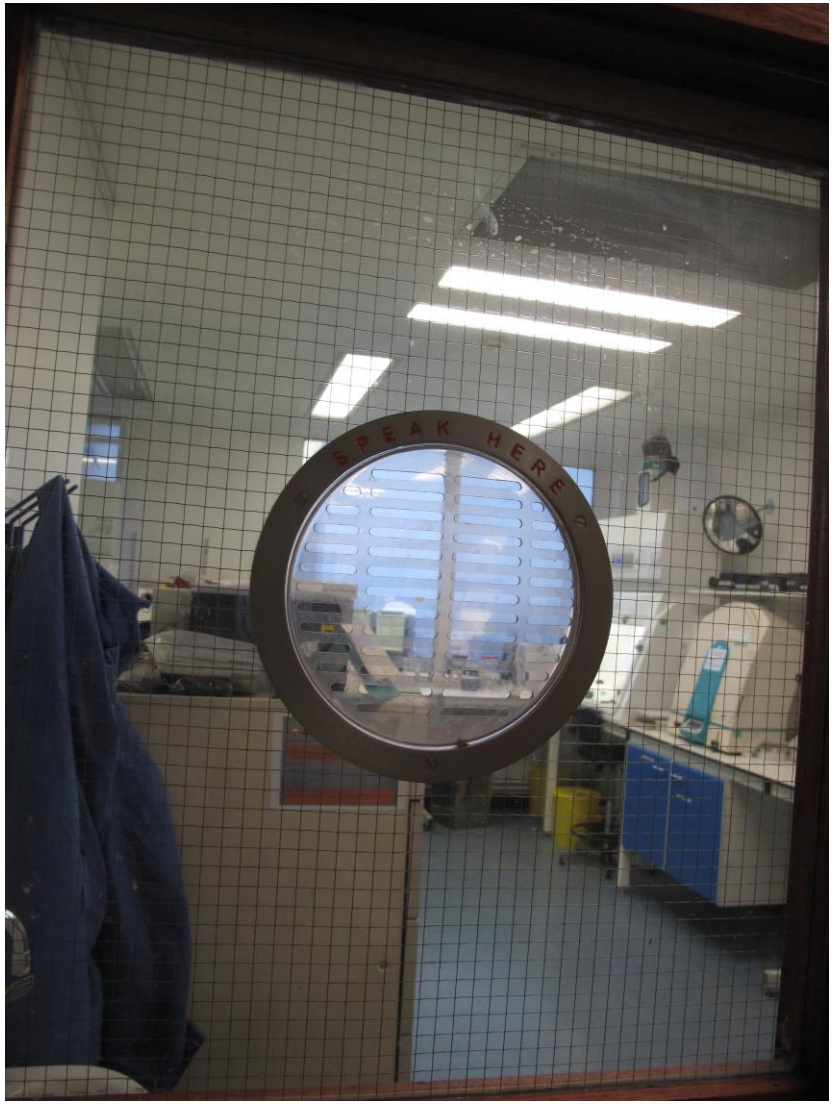
The results generated by the laboratory must be unquestionable for the study to be a success

  - Essential to ensure the **consistency** and **validity** of the results obtained

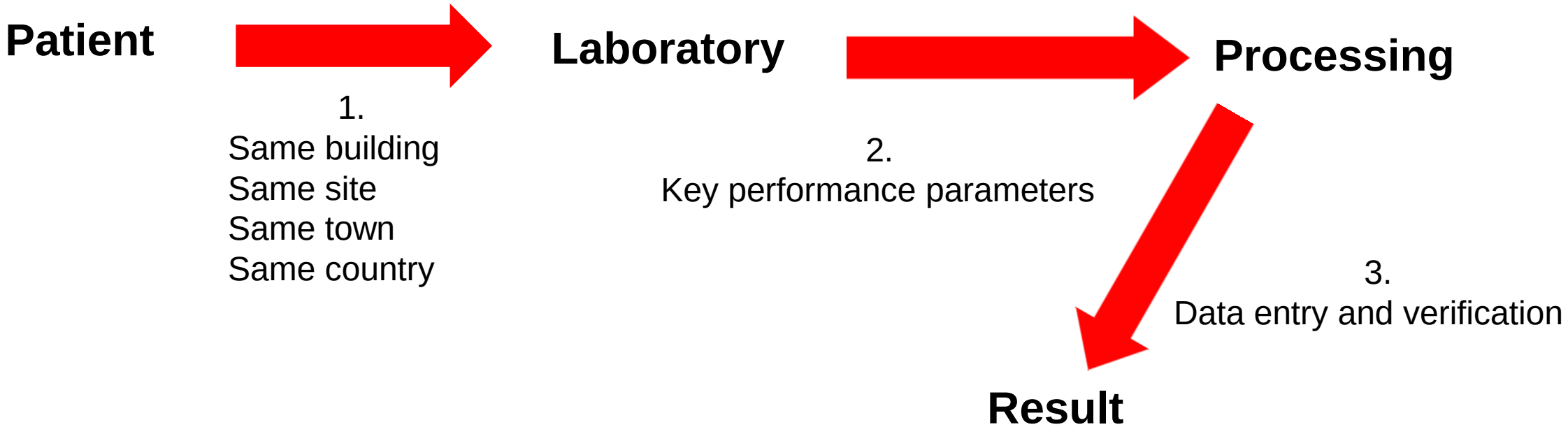
- Rigorous assessment, set-up and monitoring of labs, as well as periodic data reviews (remote monitoring) are performed by the sponsor representatives

Elements of a quality framework

- Reliability of data
- Safety
- Training



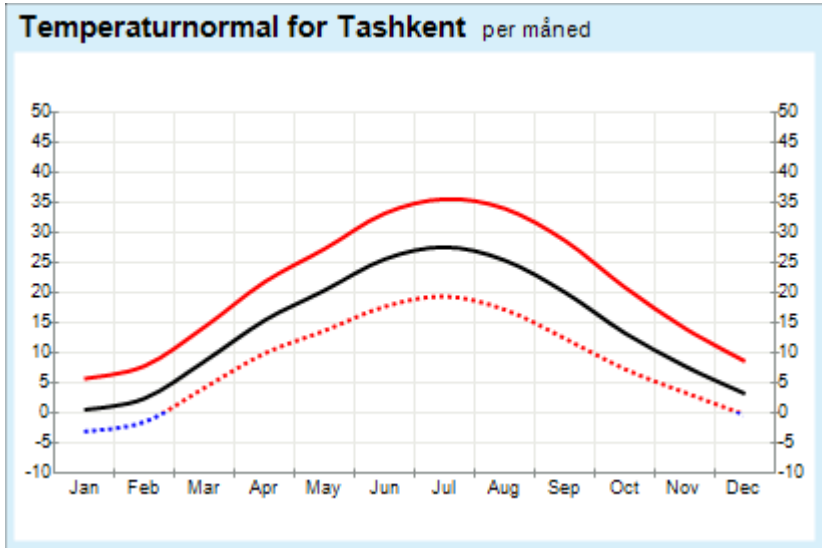
The sample journey



Each step represents a challenge to reliability of results

Key performance parameters:
1. Sample transfer & receipt

- Temperature range for sample transfer



- Time from collection to processing

Consequences:

1. No growth
2. Contamination
3. Sample lost

Key performance parameters: 2. Sample processing

- Time to Zn
- Time to molecular test
- Time to inoculation in MGIT

- Flag positive
  - Time to Zn
  - Time to blood culture result
  - Time to MGIT speciation

Consequences:

1. Operational
   - Workload accumulation
   - Late exclusion of patient
2. Microbiological
   - Failure to identify contamination

Contamination rates

Acceptable range: 3 – 8%

- Contamination rates reflect the overall performance of a laboratory
- They are multi-factorial:
  - Sample handling
  - Sample type
  - Laboratory environment
  - Staff competence and professionalism
- Too low – depleting mycobacteria in the sputum, false negatives
- Too high – lost data points due to contaminated cultures

Key performance parameters: 3. Results – resolving discrepancies

- Operational
  - Data entry
  - Data verification

- Microbiological
  - Laboratory errors
  - Biological artefacts
  - Unexpected biological observations

- Missing data
  - Redundancy, more samples collected than required for ultimate analysis

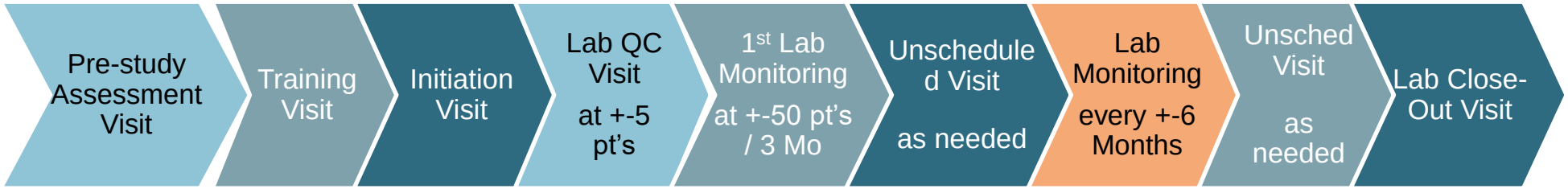
Monitoring of laboratory data

- Regular standardised review of all mycobacterial data in database – undertaken remotely

- Output of this review:
  - To direct onsite laboratory monitoring
    - provides overview of laboratory performance
    - identifies areas of concern that may require additional site visits/additional training needs
  - Identify data queries (mistakes with data entry into eCRF)
  - Identify clinical sites that are not recalling patients for additional sputum sampling as required in the protocol

'Cradle to grave' site supervison

Example overview of laboratory visit schedule from selection to study closeout



Data to prove my point?

No

Processes designed for Quality Improvement

Data incursions result in:

- Investigation of cause
- Plan for correction
- Monitored implementation

Success demonstrated by lack of trace in the study database

Rigorous quality management of laboratory procedures minimises uncertainty in the data

Acknowledgments

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