Adaptive designs for developing better regimens for the treatment of TB: The PanACEA MAMS-TB trial

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Adaptive designs for clinical trials 2-day workshop
MRC BSU, Cambridge
Outline

- The global epidemic of tuberculosis (TB)
- Overview of the PanACEA MAMS-TB trial
- Experiences from the MAMS-TB trial
  - Design and Implementation
  - Challenges
- Looking forward: Adaptive design for TB drug development
TB Epidemiology, 2012

- 8.6m new TB cases
- 1.3m TB deaths
- 13% HIV co-infected
  - 63% in South Africa
- 0.5m new Multi Drug Resistant (MDR-TB) cases
Important questions for TB treatment

- Standard of care:
  - 4-drug **6-month** regimen for drug-sensitive TB

- Excellent efficacy in clinical trials (>95%) does not translate into routine practice (~65%)
  - Clinical symptoms clear up in 1-2 months
  - Considerable pill burden of daily 4-drug regimen
  - Poor adherence leads to treatment failure and drug resistance

- Particularly poor prognosis with HIV co-infection

- **Key public health need to shorten and simplify treatment.**
The PanACEA Consortium
Pan-African Consortium for the Evaluation of Anti-TB Antibiotics

- African-European TB trials consortium funded by EU (EDCTP).

- Three drug development programmes:
  - **SQ109** (Q), Novel agent
    - Phase IIA safety study completed
  - **Rifampicin** (R), Dose optimisation
    - Phase IIA maximum tolerated dose study completed
  - **Moxifloxacin** (M), Repurposed drug
    - Phase III trial with single drug substitution for treatment shortening ongoing
PanACEA MAMS-TB

• 6-month control arm:
  • HRZE 4-drug combination standard of care
• Experimental arms:
  1. HR_{35}ZE Highest dose Rifampicin (35mg/kg)
  2. HRZQ SQ109 replacing Ethambutol
  3. HR_{20}ZQ 20mg/kg Rifampicin and SQ109
  4. HR_{20}ZM 20mg/kg Rifampicin and Moxifloxacin

• Experimental regimens given for 12 weeks
  • Followed by standard of care to complete 26 week regimen
Multi-Arm Multi-Stage Design (MAMS)

- Based on Royston et al., SIM, 2003; Royston et al., Trials, 2011
- Arms stopped early only for lack of benefit
- Time to event outcomes using hazard ratios as stopping criteria
  - Time to conversion to culture negativity over 12 weeks
- Primary focus is controlling the overall pair-wise type I error rate (PWER) rather than family-wise type I error rate (FWER)
PanACEA MAMS-TB

- Maximum total sample size **372**
  - 124 on control, 62 on experimental (2:1:1:1:1 ratio)
  - Target hazard ratio **1.8**
  - Assuming **10%** loss to follow-up, overall **90% power**

- Primary endpoint:
  - Time to stable culture conversion on liquid media

- Secondary endpoints:
  - Time to stable culture conversion on solid media
  - Rate of change in MGIT days to positivity
  - Rate of change GeneXpert quantitative CT
  - Rate of change of Molecular Bacterial Load assay
  - PK/PD parameters
## Design Parameters

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th><strong>Stage 2</strong></th>
<th>Trial end</th>
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</thead>
<tbody>
<tr>
<td>Stage-wise significance level</td>
<td>40%</td>
<td>20%</td>
<td>2.5%</td>
</tr>
<tr>
<td>(one-sided)</td>
<td></td>
<td></td>
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<tr>
<td>Stage-wise power</td>
<td>95%</td>
<td>95%</td>
<td>‘90%’</td>
</tr>
<tr>
<td>Trigger for stage end</td>
<td>28 endpoints on control arm</td>
<td>50 endpoints on control arm</td>
<td></td>
</tr>
<tr>
<td>Total sample size</td>
<td>321 (estimated)</td>
<td>350-360 (estimated)</td>
<td>372</td>
</tr>
<tr>
<td>Likely date of stage end</td>
<td>DMC meet 26th February 2014</td>
<td><strong>DMC meet end March 2014?</strong></td>
<td>Recruitment complete mid-April 2014</td>
</tr>
<tr>
<td>Critical value</td>
<td>1.09</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>(hazard ratio compared to control)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Target hazard ratio (under H₁)</strong></td>
<td>1.80</td>
<td></td>
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<tr>
<td>Overall pair-wise power</td>
<td></td>
<td>87.2%</td>
<td></td>
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<tr>
<td>Overall pairwise type I error (PWER)</td>
<td></td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Overall family-wise type I error (FWER)</td>
<td></td>
<td>7.9%</td>
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PanACEA MAMS-TB: Interim Analyses (1)

- First interim analysis after **28 control patients culture converted to negative**
- Each experimental arm will be compared with the control in pairwise comparisons
  - Hazard ratio ≥ **1.09**
    - Evidence for sufficient efficacy → Continue
  - Hazard ratio < **1.09**
    - Insufficient evidence for efficacy → Cease enrolment
    - \( P(\text{Continue effective arm}) = 0.95 \)
      - Stage-wise power
    - \( P(\text{Continue ineffective arm}) = 0.40 \)
      - ‘Stage-wise Type I error’
- Estimated to be after **200-250** patients recruited
PanACEA MAMS-TB: Interim Analyses (2)

- Second interim analysis after **50 control patients culture converted to negative**
  - Hazard ratio ≥ **1.23**
    - Evidence for sufficient efficacy → Continue
  - Hazard ratio < **1.23**
    - Insufficient evidence for efficacy → Cease enrolment
- P(Continue effective arm) = **0.95**
  - Stage-wise power
- P(Continue ineffective arm) = **0.20**
  - ‘Stage-wise Type I error’

- Recruitment should be sufficiently rapid that the second interim analysis will convey no benefit and will therefore be cancelled.
PanACEA MAMS-TB: Interim Analyses

At an interim analysis, data monitoring committee (DMC) has three options for each experimental arm:

1. **Evidence of sufficient efficacy**
   - No change. Continue arm

2. **Insufficient evidence of efficacy and no safety concerns**
   - Cease enrolment to arm. All patients complete allocated treatment and follow-up.

3. **Very poor efficacy or safety concerns**
   - Cease enrolment to arm. Withdraw patients from treatment and transfer to standard therapy
Experiences from PanACEA MAMS-TB

- MAMS in the context of TB drug development
- Design and Implementation
- Challenges
- Looking forward
MAMS in the context of TB drug development
Global TB Drug Pipeline

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GLP Tox.

Phase I

Phase II

Phase III

Cyclopeptides
Diarylquinoline
DprE Inhibitors
InhA Inhibitor
LeuRS Inhibitor
Macrolides
Mycobacterial Gyrase Inhibitors
Pyrazinamide Analogs
Ruthenium(II) Complexes
Spectinamides
Translocase-1 Inhibitor

CPZEN-45
DC-159a
Q203
SQ609
SQ641
TBI-166

PBTZ169
TBA-354

AZD5847
Bedaquiline (TMC-207)
Linezolid
Novel Regimens

PA-824
Rifapentine
SQ-109
Sutezolid (PNU-100480)

Delamanid (OPC-67683)
Gatifloxacin
Moxifloxacin
Rifapentine

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

1 Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline.php](http://www.newtbdrugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline-discovery.php](http://www.newtbdrugs.org/pipeline-discovery.php).

2 Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, NCT01215851; NC-002 -(M-Pa-Z), phase 2b, NCT01498419; NC-003 -(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01 -(H-R-Z-E-Q-M), phase 2b, NCT01785186.

www.newtbdrugs.org

Updated: June 2013
Moving from drug development to combination regimen development

- Due to acquisition of drug-resistance, it is necessary to treat TB with 3-4 drug combination regimens.

- **Regulatory approval** for a drug is not enough:
  - How should the new drug be used in combination with other existing and new drugs?

- Inherent conflict between:
  - Commercial interests and
  - Public health priorities

- A MAMS designs asks: *Which are the best regimens to improve the treatment of TB?*,
  - While yielding evidence to support licensing application for a drug or combination.
PanACEA MAMS-TB

- Three drug development programmes

SQ109 (Q) Novel compound
- Phase IIA dose-ranging study

Rifampicin (R) Existing drug
- Phase IIA maximum tolerated dose study

Moxifloxacin (M) Repurposed drug
- Phase III with single substitution

\[
\text{HR}_{10}^\text{ZE} - \text{Standard of care (Control)}
\]

1. \[
\text{HR}_{35}^\text{ZE} - \text{35mg/kg dose of Rifampicin}
\]

2. \[
\text{HR}_{10}^\text{ZQ} - \text{SQ109 substitution}
\]

3. \[
\text{HR}_{20}^\text{ZQ} - \text{20mg/kg Rifampicin + SQ109}
\]

4. \[
\text{HR}_{20}^\text{ZM} - \text{20mg/kg Rifampicin + Moxifloxacin}
\]

- One multi-arm clinical trial
Design and Implementation
Design Parameters
Target hazard ratio (alternative hypothesis, $H^1$)

- **Single arm trial:**
  - Tendency to choose smallest effect size that budget/sample size will allow
  - ‘All your eggs in one basket’

- **MAMS trial:**
  - Flexibility to select genuine minimum effect size that is likely to result in clinical benefit
  - Evidence-based approach to identify what reduction in time to culture conversion will allow treatment shortening.
Design Parameters
Threshold for decision making at interim analysis

- Royston, 2011, recommends first stage-wise alpha at 50%
  - First threshold at hazard ratio = 1.0
  - Interventions must be at least as good as control to pass

- With only time expected for one interim analysis:
  - Investigators felt that more evidence was required to pass a regimen
  - Decided on first stage-wise alpha at 40% with threshold of HR=1.09.
  - After around 70% of patients randomised.
Design Parameters
Threshold for decision making at interim analysis

- Second interim analysis planned
  - Stage-wise significance of 20%, threshold HR=1.23.
  - Likely to occur after end of recruitment
  - ‘Protection against slow recruitment’
Study Implementation
Rapid data entry

- Rapid data entry, management, query resolution essential to respond quickly in an adaptive design.

- Central database system using eSource with tablet computers.
Electronic Source Document: SureSource®

- 11.6” Screen
- Windows Operating System
- ‘Fast Start’ Powerup
- +5 Hour Battery
- 0.75kg
- Digitizer Stylus pen
- Handwriting recognition
Challenges
Challenges
Limitations of tablet data entry

- Capturing data from restricted-access laboratories
- Training for site staff
- Connectivity issues

- Site experiences:
  - “Our telephone cables were stolen twice during a period of two weeks”
  - “The more tablets you have and the more files you need to download the slower the speed of the tablets.”
  - “When tablets are switched on they often show that it is not registered with Clinical Ink and therefore have to be rebooted. Long process”
  - “Is faster recruitment not jeopardizing the chance to close arms?”
Challenges
Complex data management system

Data
Clinical Data (eSource)
CLS TB Lab
STE TB Lab
Tanzanian TB and Safety Labs
Quintiles Q-Lab (SA)
Quintiles CSS for ECG (all sites)

Databases
Clinical Ink
Sponsor Database

Data Validation
Queries raised in Clinical Ink Web portal
Data Validation at DM level
Queries raised for lab data

Data is transferred weekly

E=Electronic Transfer, M=Manual Data Entry by Data management
Challenges
Delayed culture-based endpoint

- Primary endpoint is time to culture conversion:
  - up to 12 weeks follow-up from randomisation
  - 6 weeks required for evidence of absence of culture growth (negative culture)
  - ~4 weeks for data entry, flow, analysis and DMC meeting
  - =10 weeks from last result, 22 weeks for last patient randomised
Challenges
Delayed culture-based endpoint

- Maximum sample size: 372
- Projected total at DMC meeting: 321

Visit data not included in interim (10 week lag)

Recruitment to date
Target
Further Challenges

- Complex pharmacy plan
  - 5 different tablets in different combinations across 5 regimens
  - Weight-based dosing

- DMC members from Tanzania, Zambia, Arkansas, London
  - Timing of interim depended on number of events.
  - Challenging coordinating diaries for a meeting as soon as possible (but not before!) the required events.
Looking forward
Looking forward

- Drug/regimen development in TB is a setting well suited to use of adaptive designs – in particular MAMS
  - Combination treatment
  - Increasing number of new compounds, repurposed drugs, or outstanding questions around dosing
  - Major public health need with much public investment in research
Looking forward

- MAMS and other adaptive designs will continue to be used by research groups conducting clinical trials in TB:
  - Flexibility, standardised protocol
  - Obvious benefits of multi-arm studies evaluating multiple regimens simultaneously
  - Potential control for slow recruitment which is appealing
  - Conceptually appealing to investigators/site staff
  - More drugs / better biomarkers would lead to more efficiency
  - Can test new biomarkers within study

- **Challenges to conducting global health trials with adaptive designs are many, but not insurmountable.**
Further reading