TREAT TB
DR-TB Clinical Trials Capacity Building Webinar Series

Challenges with MDR-TB Clinical Trials Implementation – Site Perspectives

Setting up a Trial Site

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Outline

- Strategies, Challenges, and Lessons Learned
  - DR TB research challenges
  - Human Resources
  - Ethics and Regulatory Approvals
  - Communication with NTP/MoH/Others
  - Patient Identification/Enrolment/Retention
  - Community Engagement
- Conclusions

DR TB research challenges (1)

- Under resourced (until recently)
- DR TB tends to occur more in regions with more constraints on resources

	Cases of RR/MDR TB per 100 000*	GDP trillion USD**
Swaziland	49(25–73)	4,409
South Africa	34(22–45)	349,419
USA	0.05(0.04–0.07)	19,390,604

*WHO TB report 2017

** *"GDP (current US$)". World Development Indicators. World Bank. Retrieved 3 July 2018.*

DR TB research challenges (2)

- Individuals with DR TB face a number of challenges including
  - Socio-economic
  - Food insecurity
  - Co-morbidities e.g. Diabetes, HIV
  - Stigma and marginalisation
  - Substance abuse
  - Often DR TB is the least of the participant’s problems

Human Resources
Requirements for key personnel (1)

Principal investigator:

Overall responsibility for the whole trial rests on this individual

- General requirements
  - Qualified by education, training, and experience
  - Aware of and comply with GCP
  - Delegate responsibilities to suitably qualified staff
  - Ensure adequate medical care is provided to a subject for their condition and any adverse events during the trial
- Specific DR TB trial requirements
  - Skilled in the treatment of DR TB patients
  - Aware of standard guidelines
  - Aware of adverse events associated with DR TB medication

Human Resources
Requirements for key personnel (2)

Investigator:

- "Second in charge"
- General requirements
  - Qualified by education, training, and experience
  - Aware of and comply with GCP
- Specific DR TB trial requirements
  - Skilled in the treatment of DR TB patients
  - Aware of standard guidelines
  - Aware of adverse events associated with DR TB medication

Human Resources
Requirements for key personnel (3)

Study Coordinator/ Study nurse/ Trial manager

One of the keys to the success of a trial and need to have excellent attention to detail.

Must understand

- Protocol compliance
- Clinical Trials–Related Communication
- Informed Consent Process
- Management of Clinical Trial Patients including the schedule of events, scheduling of visits, timing of procedures
- Documentation
- Patient Recruitment

Human Resources
Requirements for key personnel (4)

Study Pharmacist

- Accountable for
  - ordering
  - receipt
  - storage
  - dispensing
  - Drug accountability
  - destruction of trial medication if need be.
- Research pharmacist needs different skills from routine pharmacist
- Key is attention to detail.

Identification, training, recruitment and retention of suitable candidates (1)

Identification of suitable candidates

- One of the most difficult aspect in DR TB trials
- To complete a trial, there is a need for dedicated/full time staff
- DR TB treatment knowledge is scarce
- Few people interested in research
- Once process of staff recruitment is complete, try to ensure retention
- Often need to address concerns about infection control

Most research is donor funded

- Dependent of the availably of funds and performance.
- Often fixed term contracts are offered to employees
- Balance funding stream with job security
- If possible, try to obtain more than on funding stream

Identification, training, recruitment and retention of suitable candidates

Training

- Education appropriate to staff level e.g. investigators are usually MDs
- Good Clinical Practice GCP (training) deals with interalia
  - Ethical issues (autonomy, beneficences, lack of maleficence‘ and justice)
  - Aware of issues around informed consent
  - Practical aspects of conducting a trial e.g. Investigators Site File
  - Requirement of source documents
  - Training needs to be renewed periodically (refresher training)
  - Online options with multiple choice questions for assessment
  - Can be provided by sponsor or local training agency
  - Proof of appropriate training usually needed for approval by IRB/ Regulatory agency
- Attendance at protocol specific training.

Ethics and Regulatory Approvals and Reporting

- Each country has its own policies and procedures (and peculiarities)
- Parallel submission to the independent review committee and the medicines regulator may be permissible
- Notoriously slow can take weeks to months
- EMEA/FDA timelines: 60 days from submission
- Be aware that once ethics and regulatory approvals are in place, there are often other approvals needed e.g. facility, provincial approvals

Engaging with the National TB Program

Treatment of TB is under the mandate of National TB Program

- Flow of data to NTP for reporting internationally to WHO, Stop TB partnership etc.
- Trust relationship must be established
  - Any major issues with the trial should communicated with the NTP
  - Report the findings of the trial to the NTP first
  - Disruptions in the trust relationship will hamper if not stop research
- Research should be a “value add” to the NTP
  - Assist where possible in policy change discussions
- Useful to have a Key Opinion Leader on board

Engaging the Community around research and DR TB

- Parallels with the community engagement in HIV in the early nineties
  - Stigmatised disease
  - Few treatment options but with a robust research agenda
  - Need for increased community awareness of research principles and current DR TB treatment
- Need a long term commitment from researchers
- Who to engage:
  - National TB program
  - Local treatment facilities (district and provincial)
  - Patients and their families infected with DR TB
  - Interested community members
  - Health advocates

Engaging the Community around research and DR TB

Patient Identification

- DR TB is a lab based diagnosis
  - GeneXpert, Culture, LPA
- Ethically, referral however must be from the treating clinicians
- Good communication between referring site and research site
  - Ensure that the referring site is aware of major inclusion and exclusion criteria e.g. age, MDR TB, HIV status, CD4+
  - Referring site to be kept in to loop as to the status of the patient
  - If patients not successfully screened, ensure referring site is aware why

Enrolment and retention.

- In most MDR TB programs, loss to follow is common (up to 20%)
- To reduce loss to follow up in clinical trial
  - Potential participants must be contactable via more than one route
  - Assessment of potential adherence ability during screening process e.g. attendance at clinic visits, prior treatment adherence e.g. HIV, diabetes or TB medication
  - Exclude ‘active’ substance abuse prior to enrolment
  - Adequate and timeous management of adverse events
  - Be aware of possible patients’ migration due to work or family commitments

Conclusions

- DR-TB Clinical Trials Implementation at a site level have number of challenges
- These include
  - The nature of the disease
  - Local site staffing capacity
  - Regulatory framework
  - Lack of community awareness of DR TB and research principles
  - Need to interact with the National Department of Health or Ministry

Questions