Randomized Clinical Trials

Analysis and Reporting

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Assessing and Reporting Adverse Events

- **All treatments result in some adverse events**
  - An adverse event
    - any undesirable experience to the study participants
  - An adverse event could be
    - Clinical manifestation
    - Signs and symptoms
    - Laboratory or other findings that goes in an unwanted direction
  - For an event to be adverse event (AE)
    - should occur after receiving the target intervention or
    - existed before the intervention but its frequency or severity get increased after the intervention
    - Not necessarily caused by the intervention
  - **Example:** Car accident to the participant after he/she has received the first dose of an intervention

Assessing and Reporting Adverse Events

- **Why do we worry about adverse events?**
  - The main reason is **safety of study participants**
    - Regulatory bodies require documentation and timely reporting of adverse events
    - DSMB and IRB use AEs to evaluate the level of risks to the study participants
    - Used for proper clinical management of study participants
    - They might have scientific importance
      - Some of them might be primary or secondary objectives of the trail
- **The challenges include**
  - Knowing what and how to collect these data
  - The frequency of collection
  - Potential legal issues leading to an over-collection of safety data

Assessing and Reporting Adverse Events

- **Documented adverse events should be evaluated and classified (PI or sponsor should do this) :**
  - **Serious adverse event (SAE)**
    - Resulted in Death
    - Life-threatening, or places the participant at immediate risk of death from the event as it occurred
    - Hospitalization (initial or prolonged)
    - Causes persistent or significant disability or incapacity
    - Results in congenital anomalies or birth defects
    - another condition which investigators judge to represent significant hazards
  - **Persistency**
    - **Persistent:** extends continuously without resolution
    - **Recurrent :** occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

Assessing and Reporting Adverse Events

- **Documented adverse events should be evaluated and classified (PI or sponsor should do this) :**
  - **Severity**
    - Ranges from not being sever to life-threatening
  - **Expectedness**
    - **Unexpected**: Nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or investigator brochure
    - **Expected:** It is known to be associated with the intervention or condition under study
  - **Relatedness**
    - The potential event relationship to the study intervention and/or participation
    - Rating: *definitely related, Possibly Related, Not Related*

Assessing and Reporting Adverse Events

- **In safety trials**
  - the interest is to have valid assessment of potential risk of intervention
  - primary objective is safety of study participants
- **In efficacy trials**
  - the interest is to have valid estimate of the benefit of the intervention with valid assessment of potential risk of intervention
  - primary objective is efficacy
  - safety is part of secondary objectives
- In clinical trials adequate attention needs to be paid to
  - The assessment of AEs
  - Analysis of AEs
  - Reporting of AEs

Which Participants Should Be Analysed?

Which Participants Should Be Analysed?

- **Fundamental Point**
  - Excluding randomized participants or observed outcomes from analysis and sub-grouping on the basis of outcome or other response variables can lead to biased results
  - Those biases can be of unknown magnitude or direction
- **In Practice**
  - Response variable data may be missing
  - The protocol may not be completely adhered to
  - Some participants, in retrospect, will not have met the inclusion criteria
- **Investigators do not have the same preference**
  - Analyse only those who fulfil inclusion criteria and perfectly adhere to the protocol (Per Protocol Cohort)
  - Once a participant is randomized, that participant should always be followed and included in the analysis (Intention to treat cohort – ITT)

Which Participants Should Be Analysed?

- Exclusion of participants which fulfil latter exclusion criteria described in the protocol (modified Intention to Treat – mITT)

- **Recommendation**
  - Present results of primary outcome from ITT (or mITT) and PP cohorts
    - Agreement of the two results increase the credibility of the findings
  - Minimize number of protocol violations
    - Number of participants fulfilling latter exclusion criteria
    - Number of non-adherent study participants
  - Minimize number of study participants with missing data
  - **Present study participant flow chart indicating**
    - **initial exclusions,**
    - **withdrawals with corresponding reasons, and**
    - **number of study participants included in analysis of primary outcome**

Example:

- **Efficacy and safety of fixed dose combination therapy (FDCs) compared to separate loose formulation therapy in pulmonary tuberculosis**

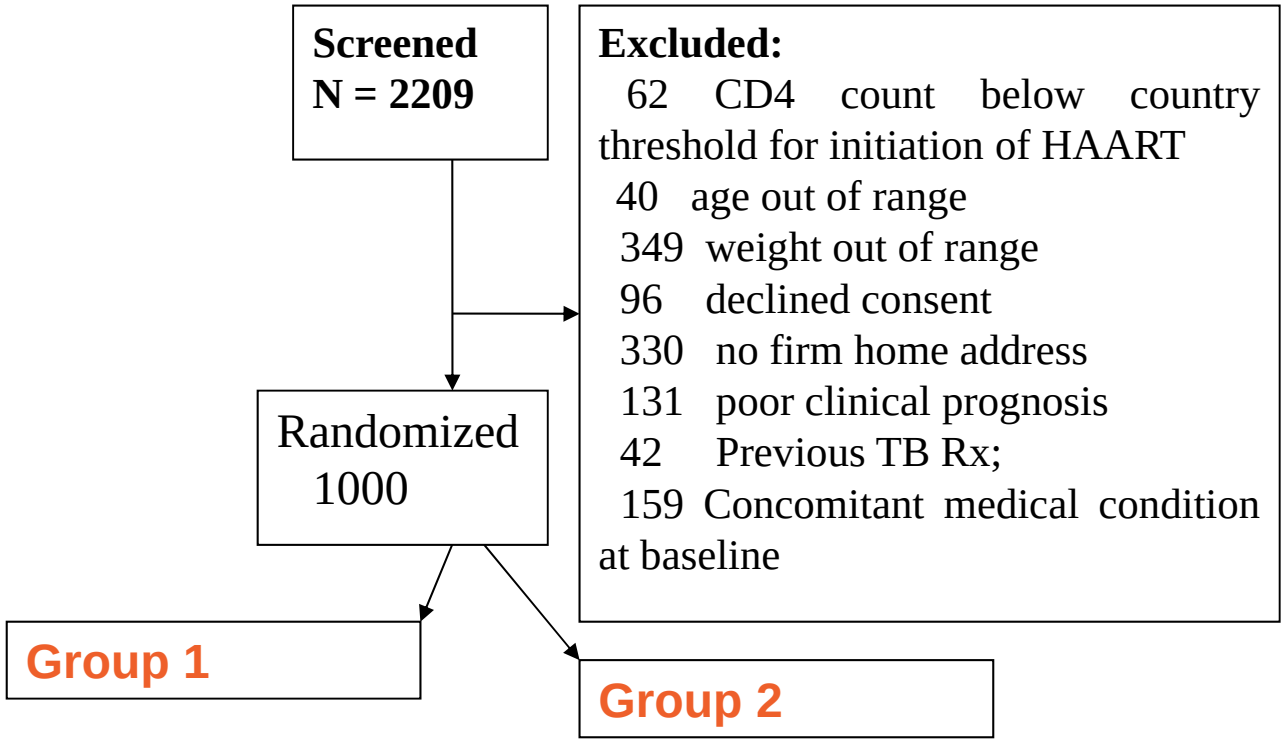
Inclusion criteria:

- **Patients with newly diagnosed pulmonary tuberculosis**
  - two sputum specimens positive for tubercle bacilli on direct smear microscopy[**to be confirmed by culture latter**]
  - no history of previous anti-tuberculosis chemotherapy, or antiretroviral therapy.
  - aged 18 years and over
  - a firm home address and intent to remain there during the entire treatment and follow up period [**for adherence**]
  - informed consent to participate in the study [**Ethics**].
  - weight between 40.00 kg and 70.00 kg inclusive [**after the start of the study there was protocol amendment to increase upper limit**].
  - acceptance of HIV counselling and testing
  - CD4 ≥ 220 (Country A) and CD4 > 350 (Country B) if the patient was HIV positive

Exclusion criteria:

- **Patients with newly diagnosed pulmonary tuberculosis**
  - Pregnancy
  - Additional extrapulmonary TB
  - Contraindications to any medications in the study regimens
  - Evidence (laboratory and/or clinical history) of pre-existing non-tuberculous disease likely to affect the response to, or assessment of, treatment
  - Requirement for hospitalisation for any reason other than directly observed treatment (DOT)
  - Concomitant immunosuppressive treatment during the whole study period.
  - Psychiatric illness, alcohol or drug abuse likely to lead to uncooperative behaviour
  - Patients on antiretroviral treatment during TB treatment period.

Initial screening of TB treatment study



Excluding large and diverse group of TB patients at recruitment

- **Is likely to affect external validity of the findings**
- **Does not affect internal validity of the findings**

Study withdrawals :

- **Withdrawal from analysis**
  - **Refer to participants who have been randomized but deliberately excluded from analysis**
  - **Exclusion of randomized participants will potentially bias the finding**
- **Withdrawal could be due to**
  - **ineligibility**
    - **This leads to modified intention to treat (mITT) analysis**
  - **Nonadherence**
    - **Taking unintended treatment for various reasons(intentional or unintentional; caused by patient himself or by Investigators)**
    - **not taking the full course of intended intervention as per the protocol**
    - **This leads to Per Protocol (PP) analysis**

Study withdrawals :

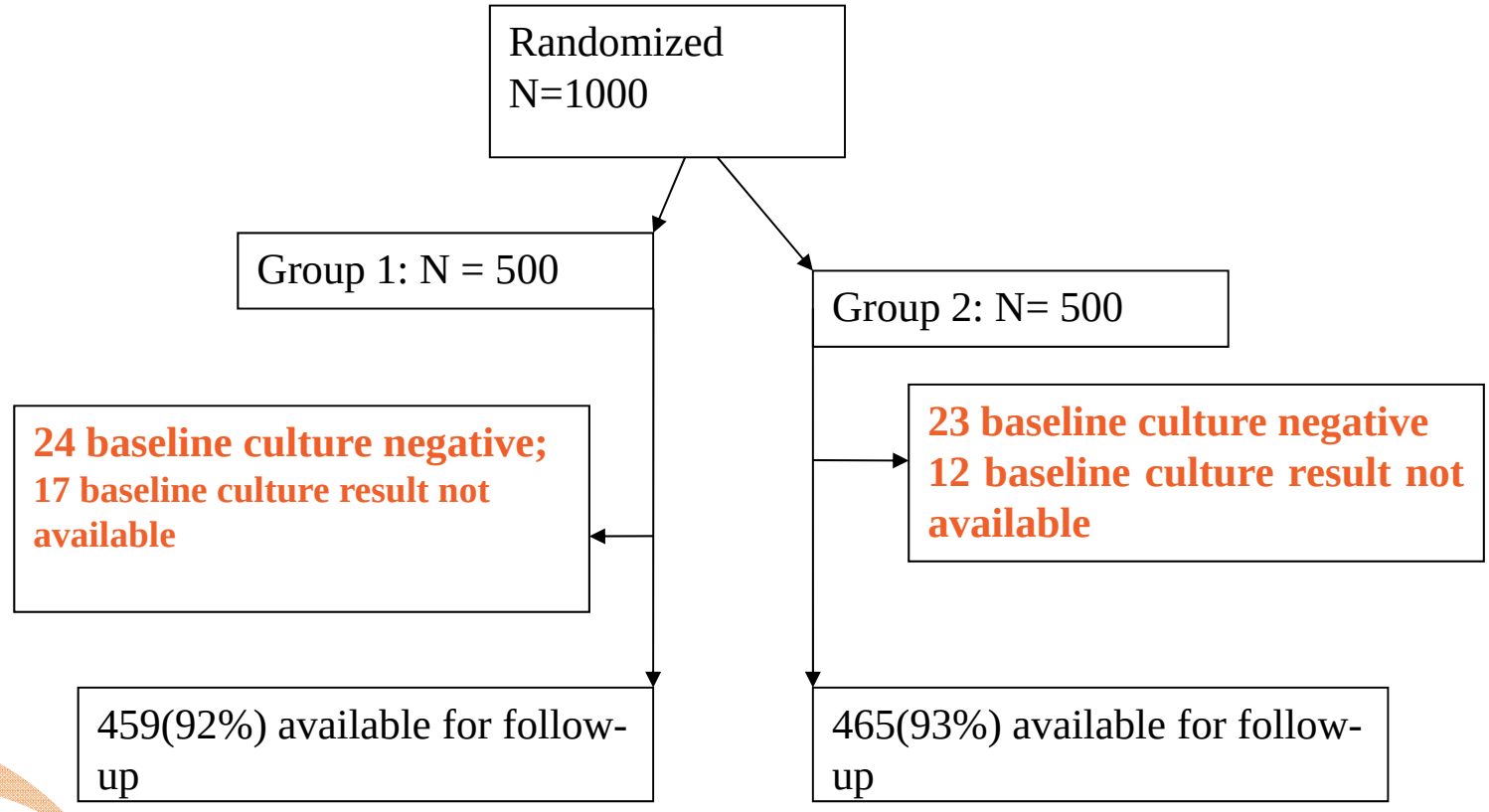
- **Obtaining Complete Data on every one (i.e. No withdrawal for any reason) is an ideal situation**

- **If we mange to generate complete data for every study participants**
  - **Intention to treat (ITT) analysis becomes meaningful**
  - **The finding from ITT analysis is expected to be unbiased**

Study withdrawals :

- **Protocol defined withdrawals of TB medication Trial**
  - AFB smear positive patients found to be culture negative.
    - These patients will be withdrawn from the study but they will be assessed clinically to see if treatment should be continued or not.
    - **What is the meaning of "withdrawn from the study "**
    - **Shouldn't the outcome of "these withdrawals" be monitored?**

Withdrawals because of baseline ineligibility



Study withdrawals :

- **<u>Protocol defined</u> withdrawals of TB medication Trial**
  - Patients withdrawing consent in the course of the trial
    - This is a key issue for the right of participants
  - Antiretroviral therapy initiation within the first six months of anti-TB medication (**SAE**).
  - AFB smear positive patients at week 20 whose sputum culture and DST confirm resistant to isoniazid and rifampicin (**MDR TB**)
  - Drug toxicity necessitating interruption of treatment (**SAE)**

Outcomes in RCT of TB treatment formulation

- **Primary Outcome**
  - Proportion cured at the end of treatment (6 months):
- **Definition of primary outcome**
  - A **cure** is defined as one negative sputum culture in patients who did not **fail treatment**
  - **Treatment failed:**
    - Persistently smear positive by five months of treatment, or
    - Becomes smear negative but positive again at or after five months of treatment
- **Question**
  - **What will be the value for primary outcome for participants whose**
    - **baseline culture is negative, or**
    - **baseline culture result is unknown (i.e. contaminated or sputum sample was small to be cultured)**

Time frame for the trial

Study procedures	Screening	Enrolment Study Drug T=0h	Week 8 (end of intensive phase)	Week 20	Week 24 (end of continuation phase)	(Weeks 36,48,72 and 96)
Medical History	X					
Physical Examination	X		X	X	X	X
Sputum for AFB smear	X		X	X	X	X
Sputum for culture		X	X	X[a]	X	X[a]
Sensitivity testing				X[b]		
Informed consent	X					
Haematology and Clinical chemistry	X	X	X	X	X	X
Urine analysis	X	X				
Pregnancy test	X					
HIV testing CD4 test	X X[d]				X[d]	X[d]
Randomisation		X				
Drug administration		X	X	X	X[e]	
Adverse Events		Symptom checklist	X	X	X	X

X[a] If the sputum smear is positive ; X[b] Sensitivity testing of screening smear and 5 month smear if sputum is positive.
X[d] CD4 testing only for HIV positive TB patients. Repeat CD4 test on weeks 24, 48, 72 and 96. Not indicated at week 36.
X[e] By the end of week 24, treatment should be completed.

Outcomes in RCT of TB treatment formulation

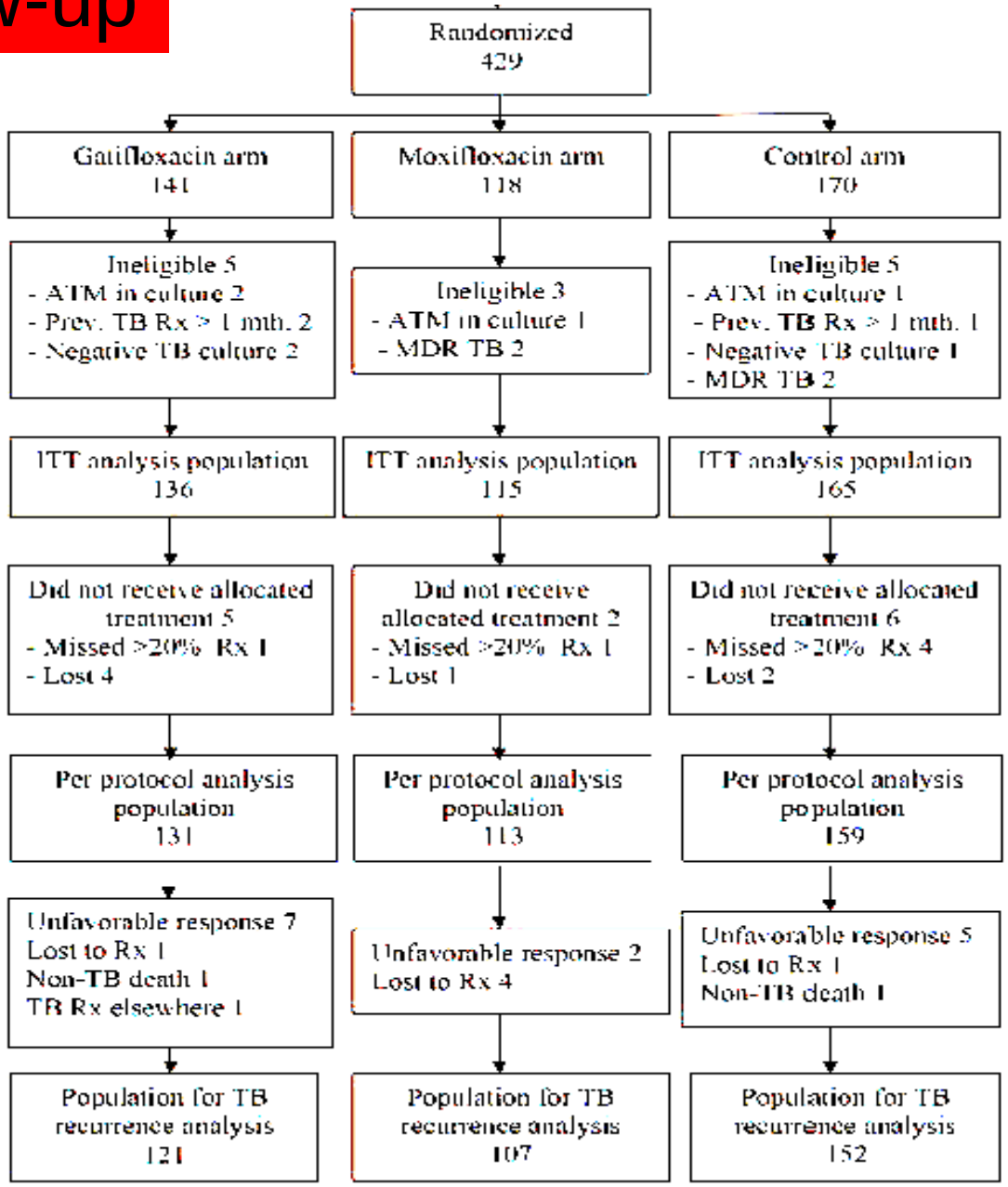
- **Secondary Outcomes**
  - **Efficacy**
    - **Early response:** proportion of patients with negative culture results at 8 weeks after initiation of therapy
    - Proportion of patients who developed MDR-TB
  - **Adherence**
    - Proportion of patients **completing treatment** **[Protocol defined]**
  - **Subgroup analysis**
    - Proportion of patients with relapse during 72 weeks follow up period after the end of treatment.
    - Proportion cured in HIV positive TB patients

Outcomes in RCT of TB treatment formulation

- **Secondary Outcomes**

  - **Safety monitoring**
    - Proportion of patients with **any adverse event** during chemotherapy
    - Proportion of patients with ***serious* adverse event** any time during chemotherapy
      - Proportion of patients with clinical deterioration of pulmonary tuberculosis with **the need for hospitalisation**
      - Proportion of patients **died** any time during chemotherapy

Patient Follow-up



Jawahar M.S. et. al. PLOS ONE 2013. *doi:10.1371/journal.pone.0067030.g001*

Missing data

- **Missing data is not avoidable**
  - Withdrawal of randomized study participants for various reasons (consent, lost-to-follow-up, safety issues, etc)
  - Data recording errors
  - Incomplete patient assessment (interview, laboratory results, clinical evaluation, etc)
  - Missed scheduled appointments
  - Absorbing outcomes (e.g. mortality)
- **Different mechanisms of missing**
  - Missing completely at random (MCAR)
    - Not related to the observed data or the value that would be recorded if it was not missing
  - Missing at random (MAR)
    - Related to the observed data but not related to the value that would be recorded if it was not missing
  - Missing not at random (informative missing) (MNAR)
    - Related to the value that would be recorded if it was not missing

Missing data

- **Any missing data will affect the principle of ITT analysis**
  - The remaining subset may no longer be representative of the randomized population
  - There is no guarantee that the validity of the randomization has been maintained in this process
  - **Example: TB treatment trial**
    - 85.6% in group 1 and 86.0% in group 2 have **results for primary outcome**
    - What do we know about the missing data mechanism?
    - Is it reasonable to assume that data missing mechanism is MCAR?
    - Complete case analysis is unbiased only if the assumption of MCAR is valid
- **The following paper is a good reference on how to handle missing outcome data**

Groenwold, Rolf H.H. et. al. American Journal of Epidemiology. 2012. 175(3): 210-217