TRUNCATE-TB trial

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

VISION

6 months

2 months

10 days

3 approaches to shorten treatment for TB

- New drug regimens with improved activity against dormant / persistent bacteria - “sterilising activity”
- Improve the immune response to clear persistent bacteria
- Innovative treatment strategies

Concept 1: A shorter regimen with worse outcomes in a trial may do better in a programme setting

95% cure in trials with standard 6m Rx

↓ 85% or less under programme conditions

Drop off likely due to poor adherence

A shorter regimen that has better adherence in programme conditions may provide better overall outcomes…… even if lower efficacy than standard of care regimen when tested in a clinical trial

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Concept 2: Over-treating the majority of patients

Previous trials of 3m-4m **standard treatment** show relapse rates < 10% in most cases

May do better in programme settings with **standard drugs** for 3m -4m

...

Small excess of relapses offset by better adherence to shorter regimen

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Concept 3: Strategic treatment approach

How about trading even shorter Rx for higher relapse rate?

Relapses are drug sensitive – can successfully Rx with 6m standard Rx

Can think about strategic treatment:

Treat – follow – re-treat if relapse

Strategy could be attractive to patients / programmes (convenience, QOL, costs).

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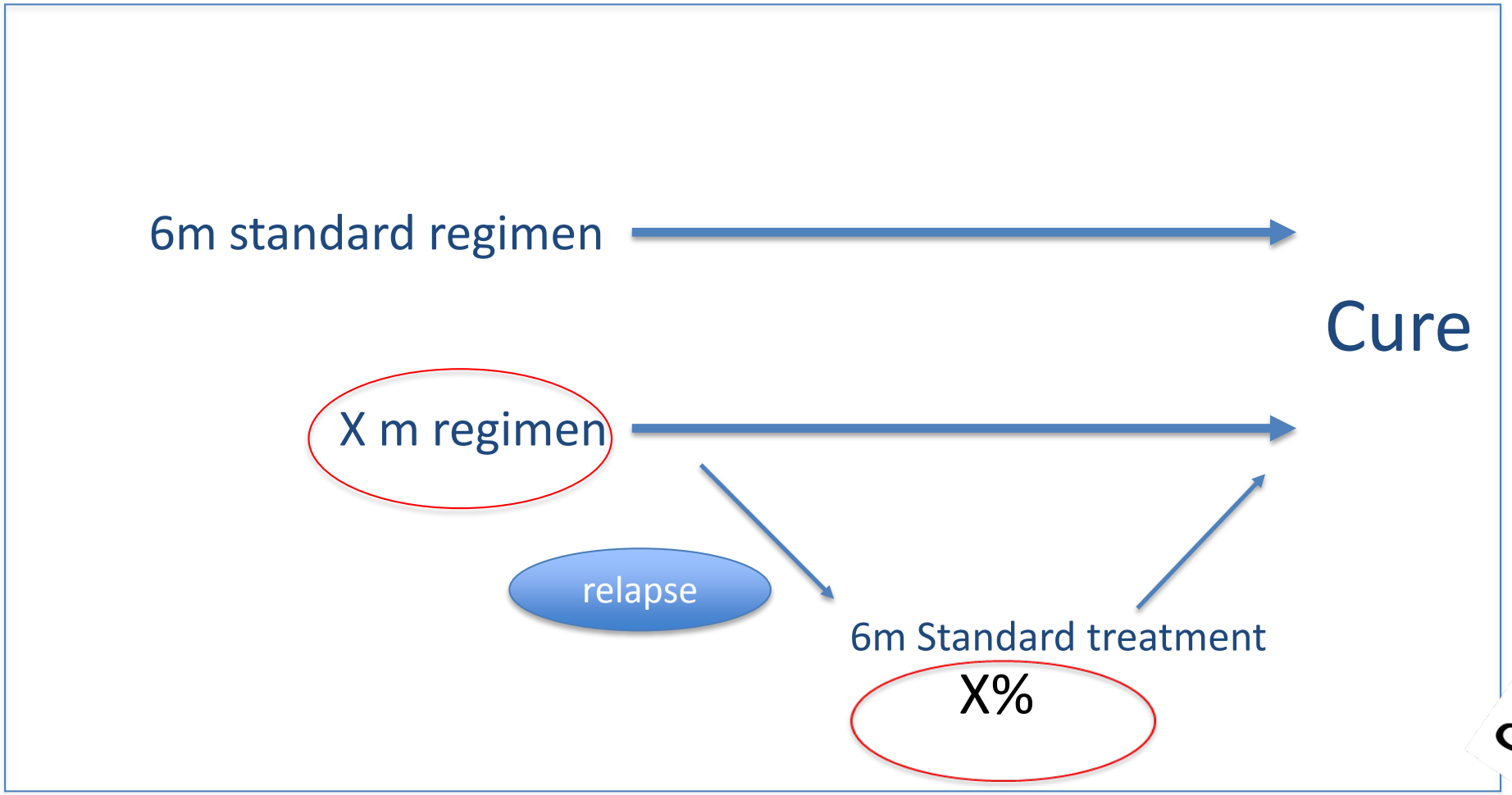
‘Treat-Follow-Relapse-Re-treat’ Strategy



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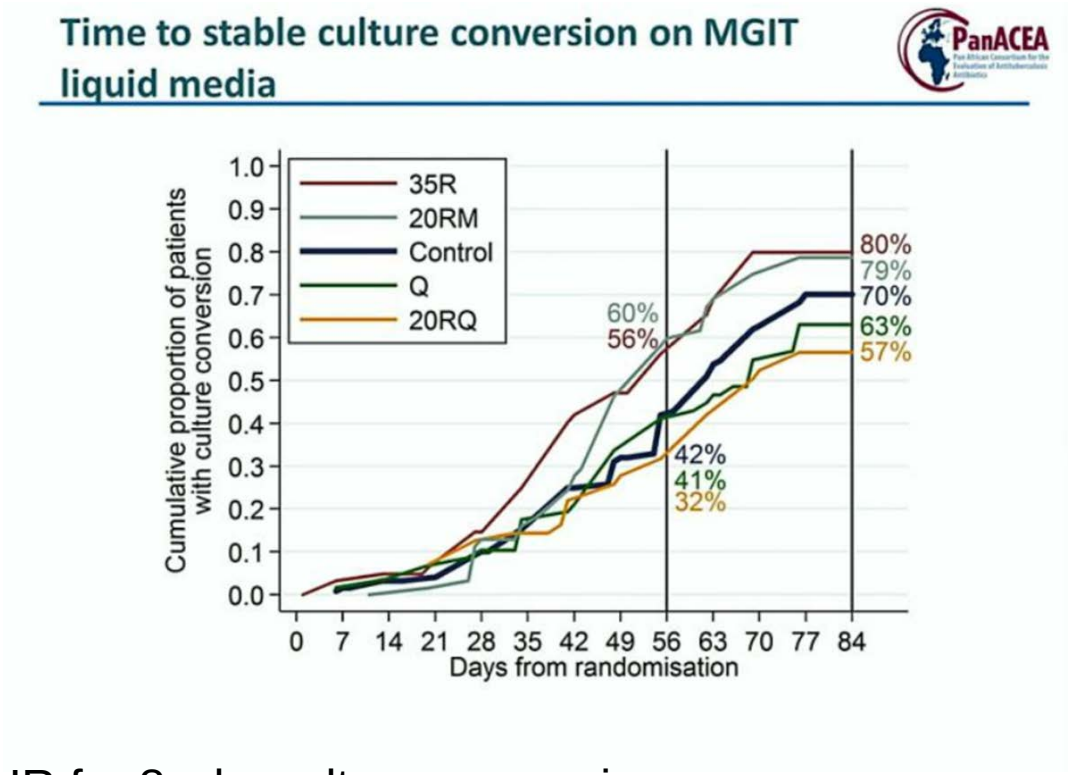
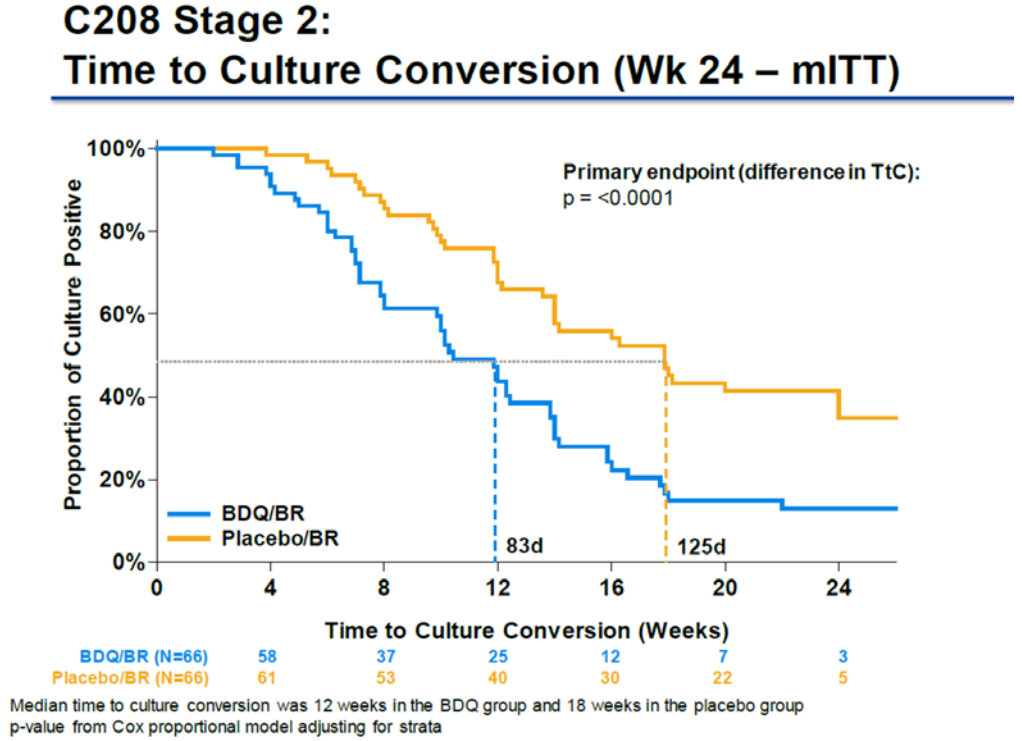
Why 2m?

- Shorter the better
- Go for definitive goal – even if aspirational
- Within reach (for a moderate relapse rate)
- Sufficiently attractive to patients to offset risk of relapse
- Sufficiently cost-effective for programmes
- Fits nicely with initiation of ART in HIV+
- Reduced risk of toxicity (e.g. BDQ)

Concept 4: Possible to get a shorter regimen with modest relapse rate?





HR for 8 wks culture conversion:

Rif 35mg : 10mg/kg = 1.99 (1.21-3.29) P = 0.007

Rif 20mg : 10mg/kg = 1.69 (1.02 -2.08) P = 0.04

Boeree CROI 2015 LB

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Concept 5: Better approach to testing regimens

Selecting single combination regimen risky

Better to test several candidate regimens

Adaptive trial

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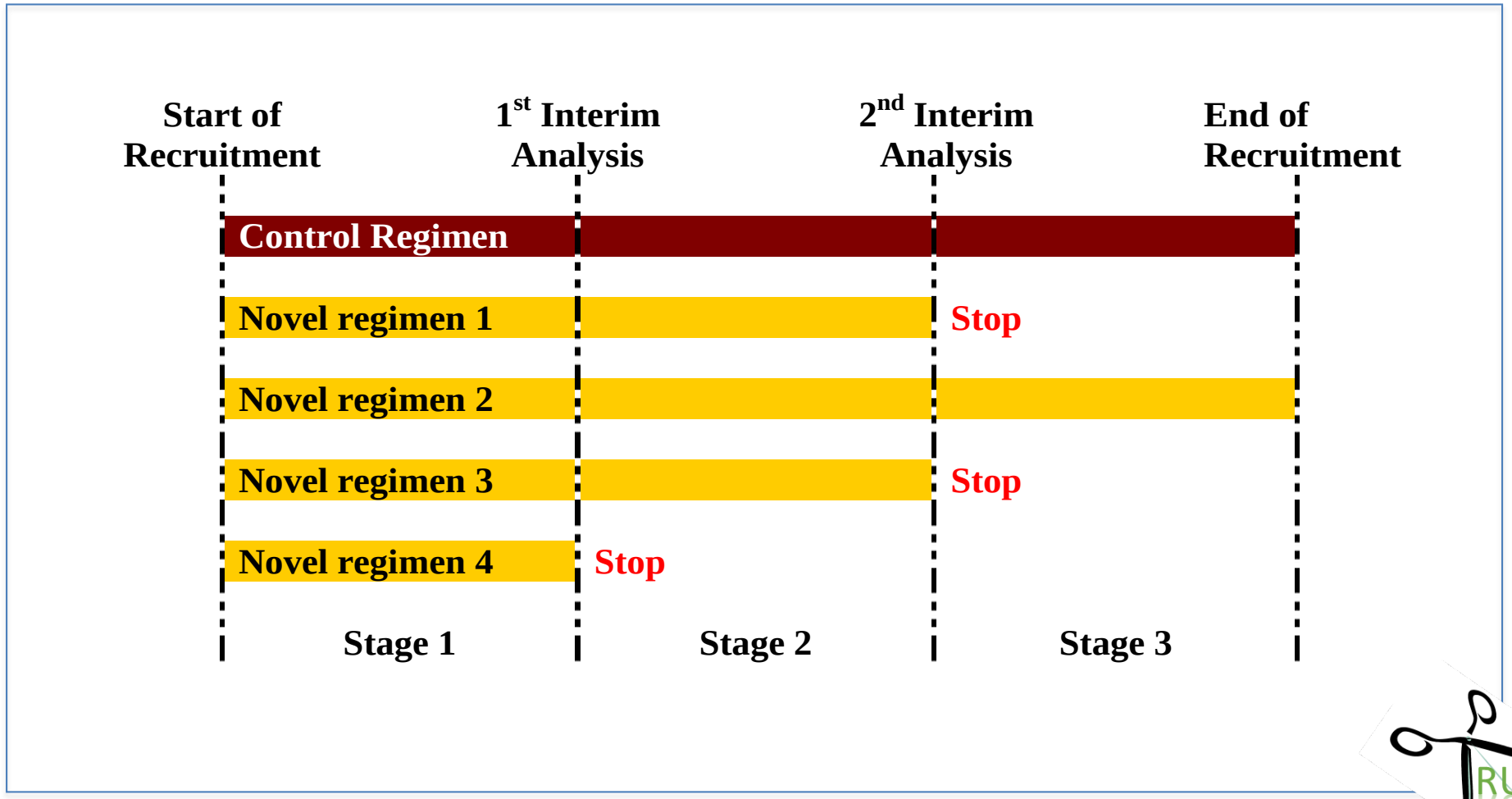
Multi arm, Multi stage trial design (MAMS)



TRUNCATE-TB

Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drug-sensitive Tuberculosis (TB):
a randomized controlled non-inferiority trial with a multi-arm multi-stage design

The “TRUNCATE-TB” Trial

AIMS

PRIMARY AIM

To determine whether a strategy of treating drug-sensitive TB for 2 months with one of a number of novel TB combination regimens and re-treating relapses with a full course of standard treatment will have non-inferior efficacy to a standard 6-month treatment regimen at 2 years (96 weeks) after randomisation.

AIMS (2)

SECONDARY AIMS

To determine the potential advantages of a 2month treatment strategy from:

- a programme perspective
  - resource use and costs
  - resistance generation
- a patient perspective
  - adherence
  - acceptability
  - quality of life
  - socioeconomic impact

AIMS (3)

ADDITIONAL AIMS

- To determine whether there are any clinical subgroups or biomarkers identifiable at baseline or early during treatment that can identify the subgroup of patients for whom 2 months treatment is not sufficient.
- To gather data to inform the design of a subsequent large pragmatic trial conducted in community TB treatment programme settings.
- To gather information on the safety, tolerability and sterilising potential (culture conversion, relapse) of new drugs and combinations

Trial design philosophy

- Strategy is intended as a pragmatic strategy for programmes (acceptability to programmes and patients is a key outcome)
- Insufficient data to guarantee the safety of the strategy and the regimens, so close monitoring needed for this trial
- Need to strike a balance between ensuring safety (patient selection and monitoring) and ultimate generalisability to programmes….[if effective, recognize that will need a subsequent large scale trial with optimal strategy informed by this trial]

Main Inclusion criteria

1. Age 18 years or more.
2. Clinical symptoms consistent with pulmonary TB.
3. Sputum molecular test (GeneXpert) positive.
4. Resident at a fixed address that is within feasible travelling distance to the site and likely to remain resident there for the foreseeable future.

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Main Exclusion criteria

1. > 7 days of treatment for TB prior to randomisation.
2. Treatment for previous active TB
3. Extra-pulmonary TB (lymphadenopathy alone is not an exclusion).
4. Rifampicin resistance on Gene Xpert
5. Underlying serious chronic diseases (such as liver or kidney disease, active malignancy, poorly-controlled diabetes), HBV/HCV carrier, pregnancy etc
6. HIV + (may be allowed in definitive stage if CD4 > 200, not on ART, can start after 8 weeks)
7. Sputum smear 4+ (may be allowed in definitive stage)
8. Cavities > 4cm (may be allowed in definitive stage)

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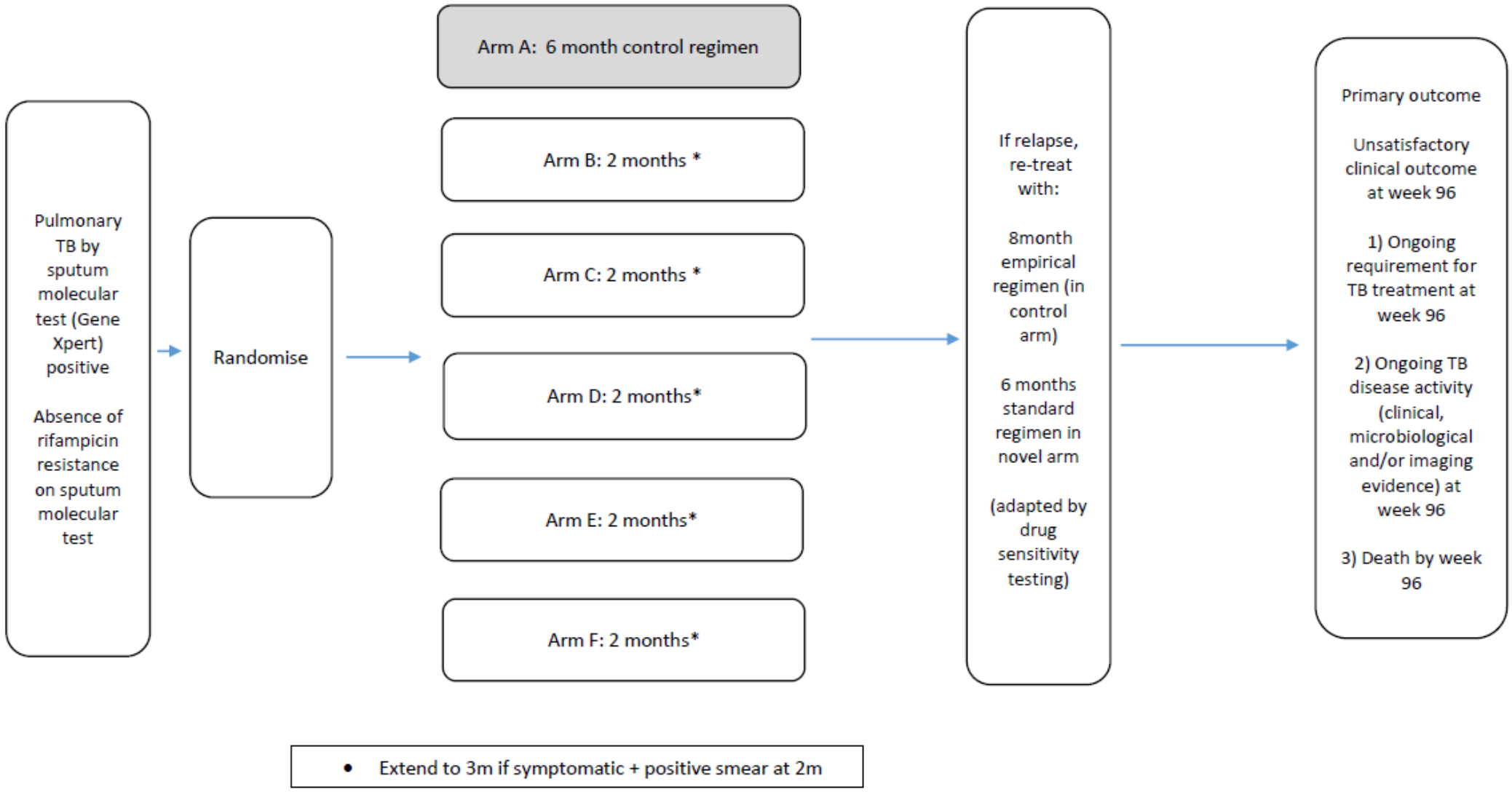

Pulmonary TB by sputum molecular test (Gene Xpert) positive
Absence of rifampicin resistance on sputum molecular test
Randomise
Arm A: 6 month control regimen
Arm B: 2 months *
Arm C: 2 months *
Arm D: 2 months*
Arm E: 2 months*
Arm F: 2 months*
If relapse, re-treat with:
8month empirical regimen (in control arm)
6 months standard regimen in novel arm
(adapted by drug sensitivity testing)
Primary outcome
Unsatisfactory clinical outcome at week 96
1) Ongoing requirement for TB treatment at week 96
2) Ongoing TB disease activity (clinical, microbiological and/or imaging evidence) at week 96
3) Death by week 96
• Extend to 3m if symptomatic + positive smear at 2m

“Boosted”treatment regimens (proposed)

Arm B: Rifampicin, (35mg/kg), Isoniazid, Pyrazinamide, Ethambutol, Linezolid (600mg daily)

Arm C: Rifampicin (35mg/kg), Isoniazid, Pyrazinamide, Ethambutol, Clofazimine (100mg daily)

Arm D: Isoniazid, Pyrazinamide, Ethambutol, Linezolid, Bedaquiline (400mg daily for 2 weeks then 200mg three times weekly)

Arm E: Rifapentine (1200mg daily), Isoniazid, Pyrazinamide, Linezolid, Levofloxacin (1000mg) daily

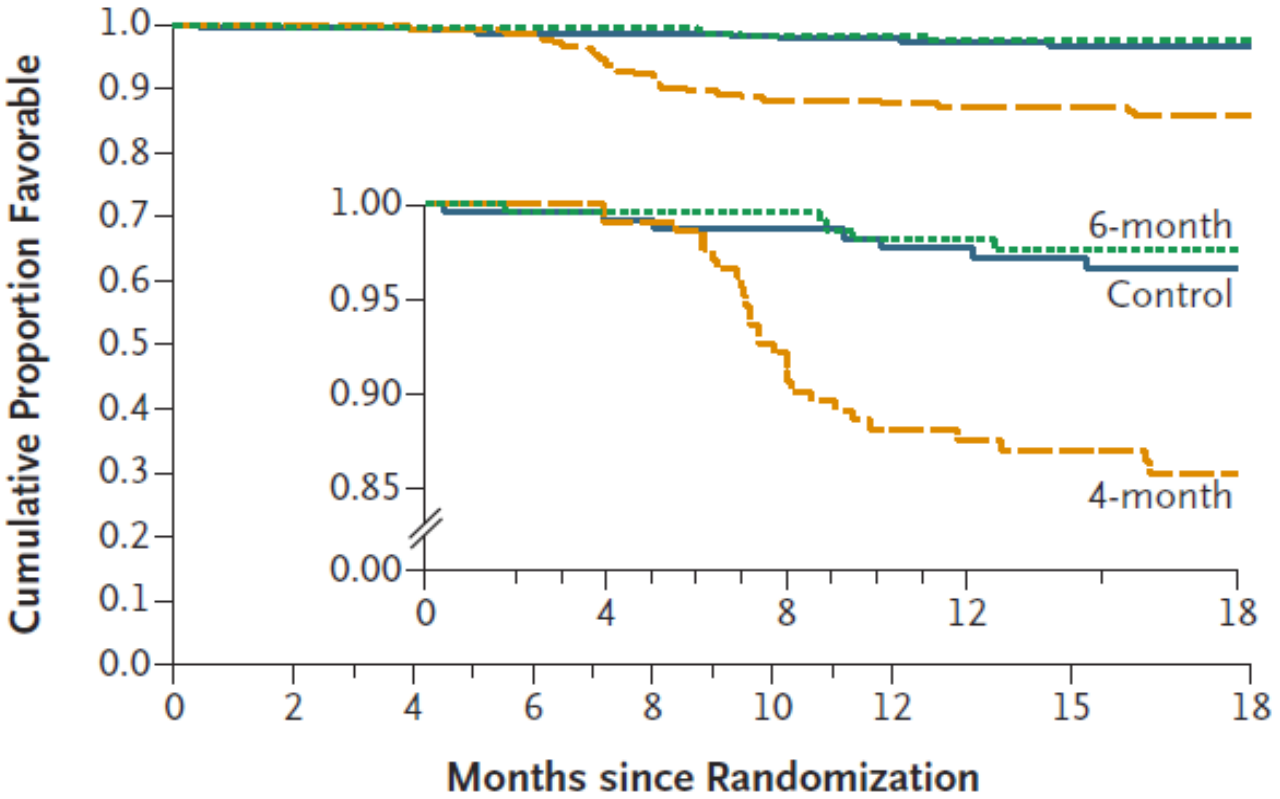
Arm F: Isoniazid, Pyrazinamide, Linezolid, Levofloxacin, Delamanid (100mg twice daily)

Boosted regimen given for 8 weeks, extended to 12 if persistent TB symptoms and +ve smear

Treatment supervision and follow-up

- DOT throughout (2m or 6m) using locally-feasible approach
- Study visits: weeks , 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96
- Telephone visits: weeks 30, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92 (maintains contact ≈ monthly).
- Systems to remind patients of coming visits (e.g. calls, SMS).
- Prompt trace / re-call patients who do not attend on expected day.
- If cannot contact patient, contact named friends/relatives (consent and contacts obtained at trial recruitment) and do home visits

Timing of relapses



No. at Risk

Control	240	232	227	213	210	203	195	175	142
4-month	239	223	211	202	185	172	169	147	127
6-month	251	234	224	217	212	207	205	180	153

Jindani et al NEJM 2014

Intermediate analyses / stopping rules

Stopping criteria for IDMC ….either of

1. Standard treatment reintroduction

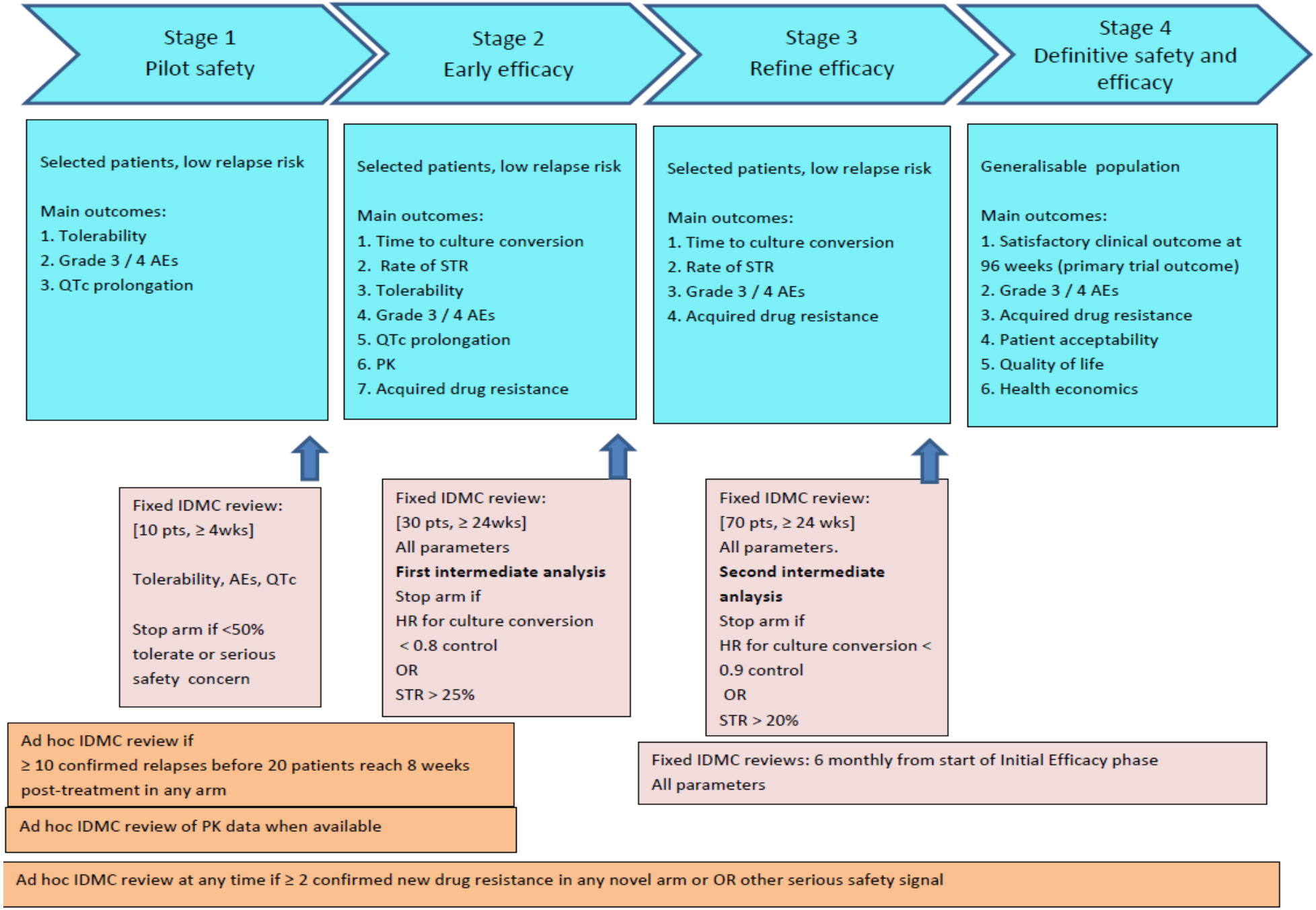
> 20% (>25% at first analysis)

for toxicity, tolerability, treatment interruption, treatment failure (after week 12), relapse

2. HR for time to culture conversion

<0.9 control (<0.8 at 1st analysis)

[+ safety data, and any combination of signals on the above]


Stage 1
Pilot safety
Stage 2
Early efficacy
Stage 3
Refine efficacy
Stage 4
Definitive safety and efficacy
Selected patients, low relapse risk
Main outcomes:
1. Tolerability
2. Grade 3 / 4 AEs
3. QTc prolongation
Selected patients, low relapse risk
Main outcomes:
1. Time to culture conversion
2. Rate of STR
3. Tolerability
4. Grade 3 / 4 AEs
5. QTc prolongation
6. PK
7. Acquired drug resistance
Selected patients, low relapse risk
Main outcomes:
1. Time to culture conversion
2. Rate of STR
3. Grade 3 / 4 AEs
4. Acquired drug resistance
Generalisable population
Main outcomes:
1. Satisfactory clinical outcome at 96 weeks (primary trial outcome)
2. Grade 3 / 4 AEs
3. Acquired drug resistance
4. Patient acceptability
5. Quality of life
6. Health economics
Fixed IDMC review:
[10 pts, ≥ 4wks]
Tolerability, AEs, QTc
Stop arm if <50% tolerate or serious safety concern
Fixed IDMC review:
[30 pts, ≥ 24wks]
All parameters
First intermediate analysis
Stop arm if
HR for culture conversion < 0.8 control
OR
STR > 25%
Fixed IDMC review:
[70 pts, ≥ 24 wks]
All parameters.
Second intermediate anlaysis
Stop arm if
HR for culture conversion < 0.9 control
OR
STR > 20%
Ad hoc IDMC review if
≥ 10 confirmed relapses before 20 patients reach 8 weeks post-treatment in any arm
Ad hoc IDMC review of PK data when available
Fixed IDMC reviews: 6 monthly from start of Initial Efficacy phase
All parameters
Ad hoc IDMC review at any time if ≥ 2 confirmed new drug resistance in any novel arm or OR other serious safety signal

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