

Key Issues for Pivotal Phase III trials

Part 2

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Double, single or triple blind?

Choice of control(s)

Power calculations

Determining outcome

Choosing delta

Deciding study length

Assessing surrogates

Assessing lost to follow-up

Monitoring

REMOxTB issues

- How should outcome status be defined?
- What should δ be?
- Follow-up: how long is long enough?
- What can we learn about surrogacy?

Defining an unfavourable outcome

- Historically short course chemotherapy regimens have been assessed on relapse rates in patients with a favourable response at the end of treatment.
- Even with weak, but well controlled, 4m regimens failures during treatment are very few.
- Should we be using a combined failure/relapse rate as our primary endpoint?

When failure during treatment matters

- Traditionally non-assessable patients have been excluded from all analyses.
- Should they be included? – if so how?
- A conservative approach would be to classify all those who die or default during treatment as failures?
- How would this influence the results?

Re-analysing Study R

- Study R was the first MRC/EA short course chemotherapy; four regimens of 6 months duration were studied:
 - 6SHR
 - 6SHZ
 - 6SHT
 - 6SH
- The control: 2STH/16TH

S streptomycin, H isoniazid, R rifampicin


Z pyrazinamide, T thiacetazone

Study R – the results

- The 30 month results in patients with fully sensitive (FS) organisms relapse rates were:

– 6SHR	3%
– 6SHZ	8%
– 6SHT	22%
– 6SH	29%
– 2STH/16TH	3%

S streptomycin, H isoniazid, R rifampicin
Z pyrazinamide, T thiacetazone



Even at 5 years the
6SHR relapse rate
was only 3%

Study R – two approaches to analysis

- In the original relapse analysis only patients with FS organisms who completed an adequate course of treatment were included, i.e. per protocol.
- How would the results change if we analysed by intention to treat, *and* included resistant patients?

Per protocol (FS)

6SHR 3% of 152
6SHZ 8% of 153

ITT inc resistant pts*

6SHR 4% of 185
6SHZ 8% of 196

* excluding patients with only negative cultures and those not assessable

A conservative approach

- Supposing we were to consider an unfavourable status to include not only relapse but
 - Treatment failure
 - Treatment change for drug toxicity
 - All deaths and defaulters during treatment
 - Respiratory deaths after stopping treatment
- How might this affect our results?

Analysing Study R - conservatively

	6SHR	6SHZ
Relapse	6	15
Treatment failure	2	4
Treatment change for drug toxicity	1	4
Deaths during treatment	5	5
Defaulters during treatment	3	2
Respiratory deaths post treatment	1	0
Unfavourable status	18	30
	8.3%	14.2%
Total assessed	217	211

Defining unfavourable

- Is this approach appropriate/acceptable?
- Should it also include losses in follow-up?
- What are the disadvantages?
- To note:
 - In the early short course EA studies patients were admitted for treatment, follow-up was monthly.
 - Chance differences in early deaths and treatment absconders could easily distort findings.
 - Most if not all losses in follow-up are probably due to chance

REMoxTB proposal

Unfavourable

Treatment extended, changed or restarted

Treatment changed for drug toxicity

Culture positive when last seen

Death or default during treatment

Respiratory death or death from unknown causes post treatment

Favourable

Negative when last seen (at 18, 15 or 12m)

Not assessed

Re-infection

Non-respiratory death post treatment

Lost in follow-up phase before 12 months

Choosing δ

- “The determination of the margin in a non-inferiority (δ) in a non-inferiority trial is based on both statistical and clinical judgement”

ICH E10 Choice of Control Group and Related Issues in Clinical Trials.

The statistical evidence (1)

- The control regimen 2EHRZ/4HR is well established as being highly effective with relapse rates of 3-5% under varied trial conditions.
- The intervention 2MHRZ/2MHR
 - substitutes M for E in the intensive phase
 - adds M to the continuation phase
 - reduces the continuation phase to 2 months
- It is generally accepted that ethambutol, a drug with no apparent sterilizing activity, contributes little to the intensive phase of short course regimens in patients with fully sensitive organisms

The statistical evidence (2)

- How good is the control regimen 2EHRZ/4HR if given for only 4 months? Evidence comes from 4th E African study

Regimen	Dn	N	Relapses		
2SHRZ/2HRZ	4	104	17	16%	4 th EA SCourse
2SHRZ/2HR	4	104	11	11%	
2SHRZ/4HRZ	6	55	0	0%	4 th EA SCourse
2SHRZ/4HR	6	49	3	6%	extended Rx
2SHRZ/4HR	6	166	5	3%	5 th EA SCourse

The statistical evidence (3)

..... and from Singapore.

Regimen	Dn	N	Relapses	
2SHRZ /2HRZ	4	79	9	11%
2SHRZ/2HR	4	77	6	8%
2SHRZ/4HRZ	6	78	0	0%
2SHRZ/4HR	6	80	2	2%

The statistical evidence and clinical opinion

- Because pyrazinamide contributes little or nothing after the first 2 months of treatment -

East Africa	4 month	28/208 (13%)
	6 month	8/215 (3%) non-concurrent

Singapore	4 month	15/156 (10%)
	6 month	2/158 (1%)

- Since the difference in relapse rates in the historical trials between the 6-month and 4-month regimens was around 9-10%, a delta of 6% can be justified on statistical grounds.
- In the opinion of the African PIs the benefits of reducing treatment duration to 4 months would have considerable advantages which outweighing a possible increase in relapse rate of up to 6%.

Implications for power

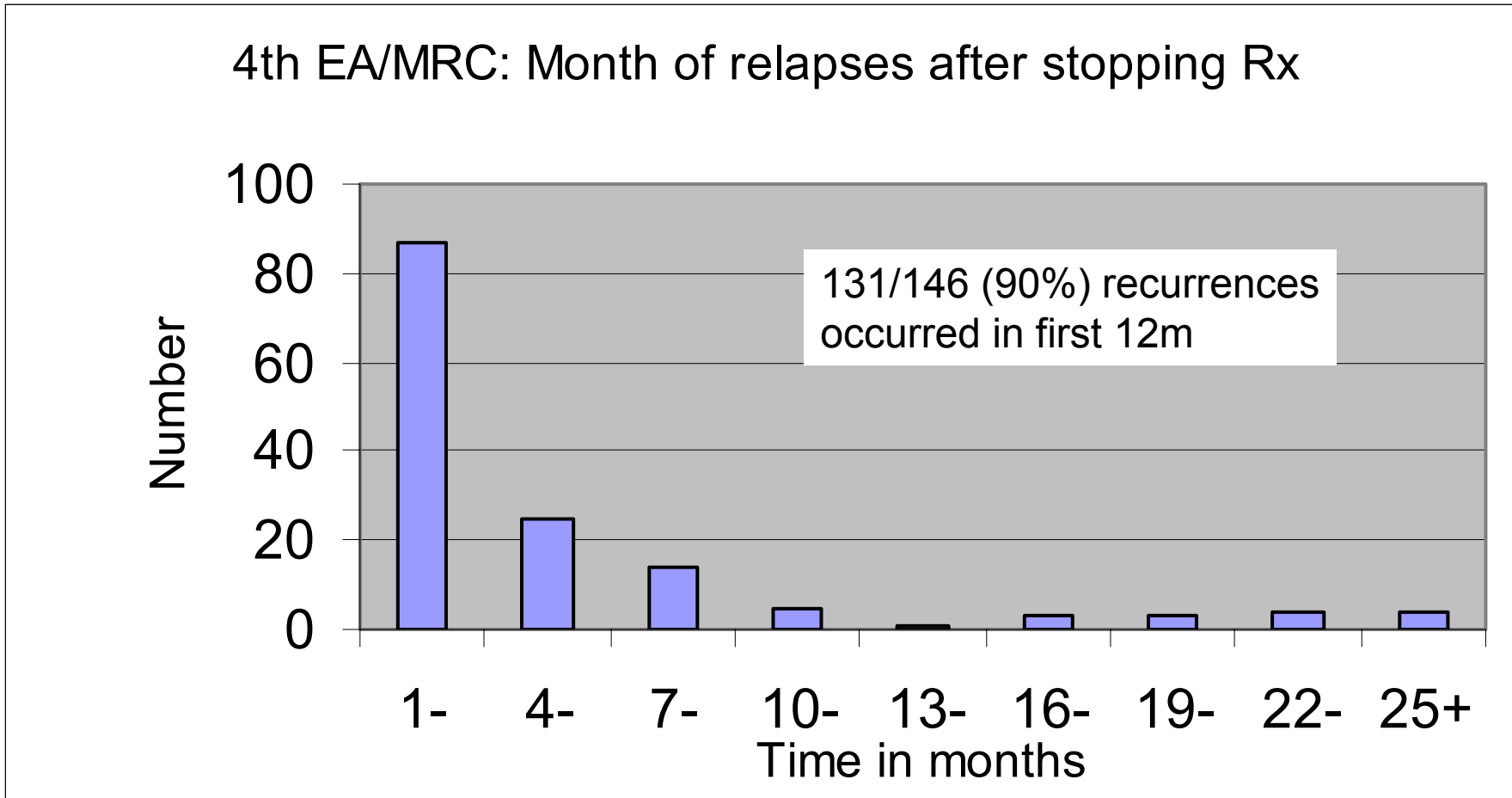
Control failure/ relapse	N/group for given delta and power*					
	4%		5%		6%	
	80%	90%	80%	90%	80%	90%
4%	377	505	242	323	168	225
10%	883	1183	566	757	393	526
15%	1251	1675	801	1072	556	745

* Using one sided 97.5% confidence interval

Power problem

- Currently it has been assumed that the 6m standard regimen and the 4m regimen are equally effective.
- But what if we assume that the 4m regimen will be 2% less effective while retaining the current levels of δ ?
- This would more than double the number of participants required in an RCT.

Follow-up – for how long?



A point to remember – the limitation of early biomarkers

- The 3rd East African SC study shows clearly the limitation of the 2m culture result in predicting relapse.

Regimen	2m cul	Relapse
1SHRZ/7TH	67%	7%
2SHRZ/4TH	87%	13%

The duration of the continuation phase was more important than 2m culture result

What will REMox tell us about possible surrogacy?

- Between regimens – probably rather little.
 - Both 6 month regimens are likely to have low relapse rates
 - If the 4m regimen is successful it too will have very few relapses
- However, a moderate to high failure rate in the 4m regimen will provide an excellent opportunity to assess alternative measures of change in bacterial load and possible other biomarkers.

Conclusion

- 12m follow-up is probably adequate
- Increased rates of unfavourable outcomes, however defined, reduces power
- It is essential to minimise losses (from death or default) during treatment
- δ needs to be justified on both statistical and clinical grounds.

Postscript

- REMox can be seen as proof of concept trial asking the question is it possible for a 4m regimen in which moxifloxacin is substituted for ethambutol to give acceptably low failure/relapse rates.
- It will be important to ensure that the study regimen has the best chance of success by enrolling patients who are likely to be adherent and unlikely to die early.