

Practical Issues in Vaccine Trial Interim Analysis

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Outline

- what and how we test at interim times
- why we test
- decision at interim times
- what we gain/lose

Vaccine Efficacy Trial Design (Brief)

$$VE = (1 - RR) \quad \text{where } RR = I_v / I_p$$

confidence limits on RR (VE) using
conditional binomial procedures

correspondence of CI's and
hypothesis tests

$$H_0: VE = LL \quad LL = 0, 20, \dots$$

$$H_1: VE > LL$$

'super-efficacy' ? ($LL > 0$)

Possible Super-efficacy Criteria

VE	LL
90	60
80	50
70	40
60	30
50	20

Vaccine Trial Design

Determining Required Number of Cases

1. fix VE
 2. determine case split (# in placebo / # vaccine) where resulting lower limit of CI is \geq LL
 3. determine probability of this case split or better - power
-

Example

VE = 70%

split 72/28 \rightarrow 95% CI = 39, 76 \rightarrow power = 90%

Required number of cases C= 100

How Many Subjects?

depends on incidence rate (r) over follow-up time
and true VE

$$C = n * r + n * r * (1 - VE)$$

$$n = C / r * (2 - VE) \quad \text{assuming 1:1 randomization}$$

NOTE: r is over average follow-up time for a
subject

Example

VE = 70% and r = 2% over 24 month follow-up time

$$n = 100 / 0.02(2 - 0.7)$$

n ≈ 4,000 / group or 8,000 subjects in trial

Why We Want To Look Early

Safety is a Given

- unexpectedly high efficacy
- unexpectedly low efficacy
- early start/stop on development registration activities
- unexpectedly slow case accumulation – not really an interim analysis - blinded?

Unexpected High Efficacy

- Usual sequential analysis procedures

But

What should we test?

$LL_i = LL$ (final specification) or 0?

General group sequential philosophy is that interim analysis should be of the same form as the final analysis, but there are considerations for diseases with no vaccines or effective treatment. With $LL_i > 0$ have proven efficacy

Is Interim Efficacy Analysis Worth It?

Yes from power point of view

Using base case example (VE=70%, r=2%, C=100), look at $C_i = 50$ with Type 1 error of 0.005 (one sided)

		Power- for VE=		
LL_i	split	70	80	90
40	9/41	25%	68%	99%
0	15/35	91	99	99.9

Unexpected Low Efficacy - Futility

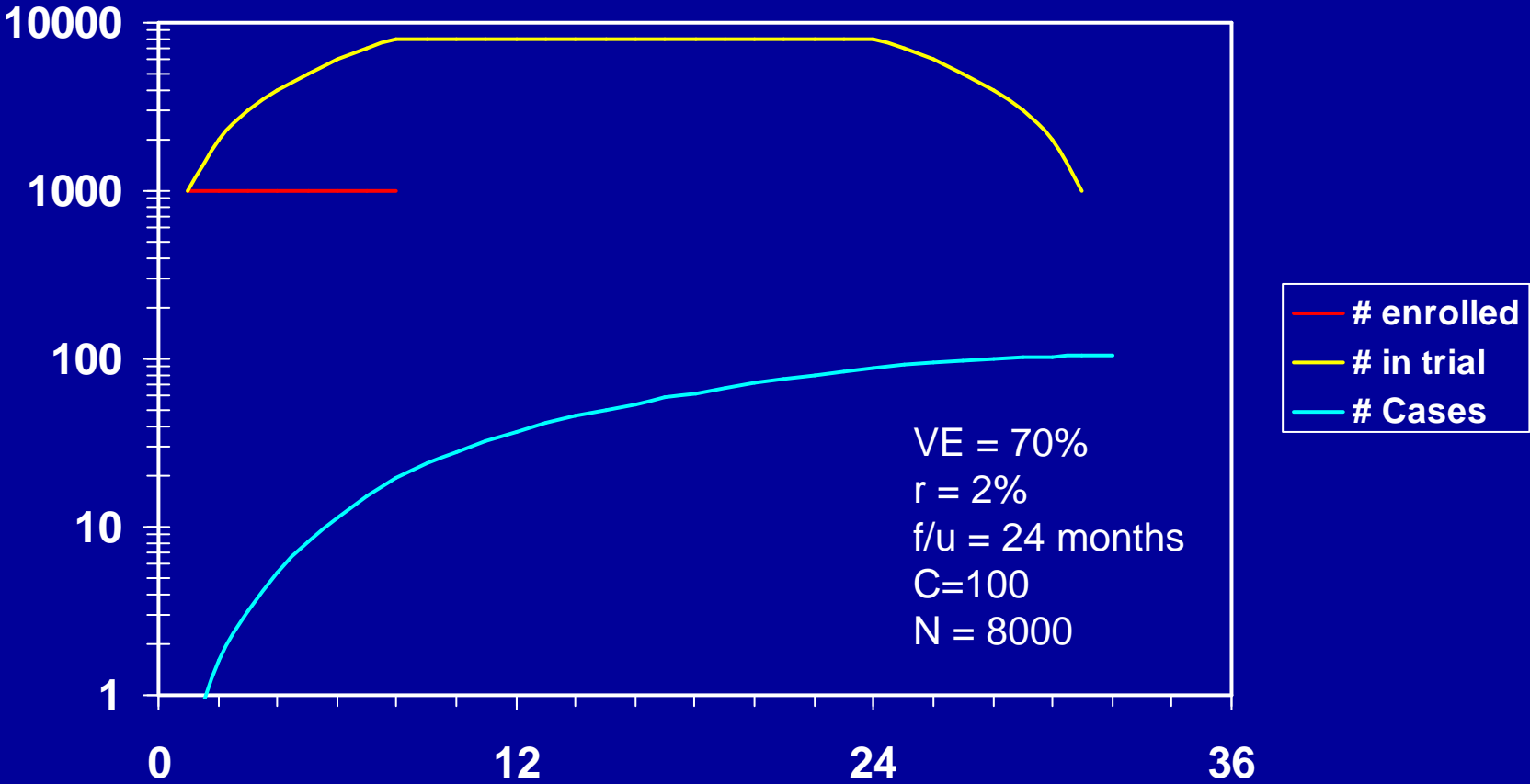
Is there any point to continuing the trial?

- after safety may be the most important test
- $C_i = 50$ the 21/29 → stop, impossible to get 72/28 at final analysis
- stochastic curtailment / conditional power
- should not waste economic resources

Too Slow Case Accumulation Blinded – and not a true interim analysis

- when to make decision and decision reached depends on:
 - enrollment rates
 - follow-up time
 - # cases achieved
- case accumulation will also influence
 - when the interim analysis should be scheduled
 - what actions to take
 - value of the interim analysis
 - cost
 - time

Case Accumulation

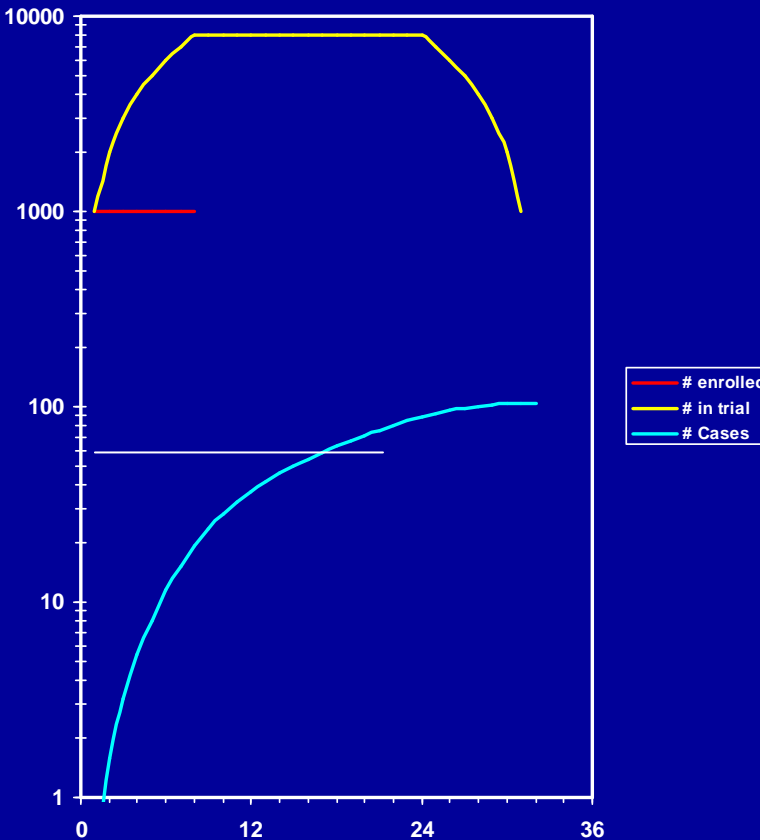
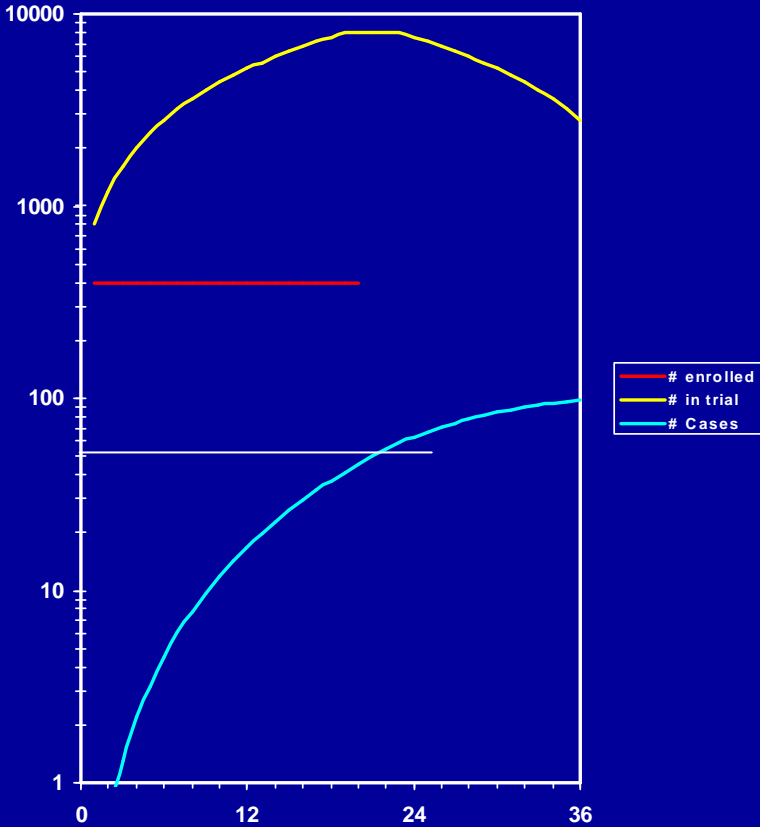


Value of Interim Efficacy Analysis

$$VE = 70\% \quad r = 2\%$$

- Recruit 1000/month for 8 months (8,000)
 - C = 100 at 28 months
 - C = 50 at 15 months
- Recruit 400/month for 20 months (8,000)
 - C = 100 at 37 months
 - C = 50 at 21 months
- Faster enrollment → shorter trial, but maybe not as much as you would think. Somewhat lower time savings for interim
- Interim saves little money if major cost driver is charge per subject. Some savings in follow-up costs and opportunity costs of time.

Case Accumulation



Timing of Interim Efficacy Analysis

	Power VE=	
C_i	70	90
25	14%	81%
50	25	99

BUT

VE	70		90	
C_i	25	50	25	50
n	mn-ave. f/u			
400	15-8.0	21-11.5	16-8.5	23-13.8
1000	9-5.6	15-15.0	10-6.9	17-19.1

Timing of Interim Efficacy Analysis

$C_i = 50$

VE	70%		90%	
n	end month	savings	end month	savings
400	38	17	>48	15
1000	28	13	>36	9

Conclude

- savings is in time
- savings depends on enrollment rates
- although savings in cases = 50%, savings in time \approx 25% @ VE=90%
- worth it? Yes, but perhaps marginal

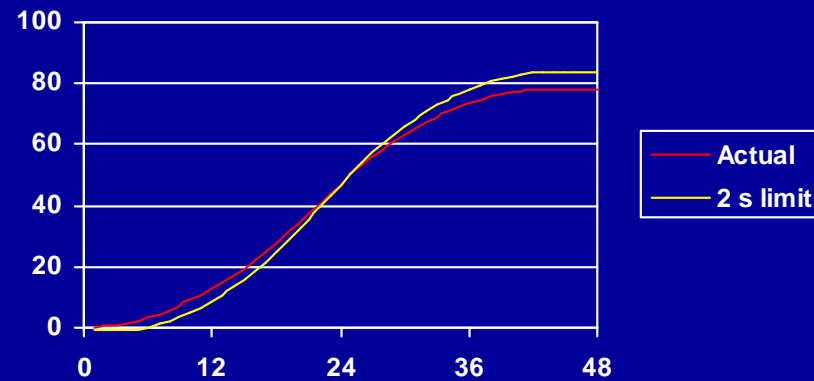
Slow Case Accumulation Sample Size Re-estimation ?

- different from usual SSR → C is 'sample size'.
Changing N and/or follow-up
- do we have enough information to decide?
- both too much change and too little change not optimal
- consider decision rule:
adjust if actual cases (C_t) is $2\sigma < C$ -expected
will assume case accumulation is Poisson

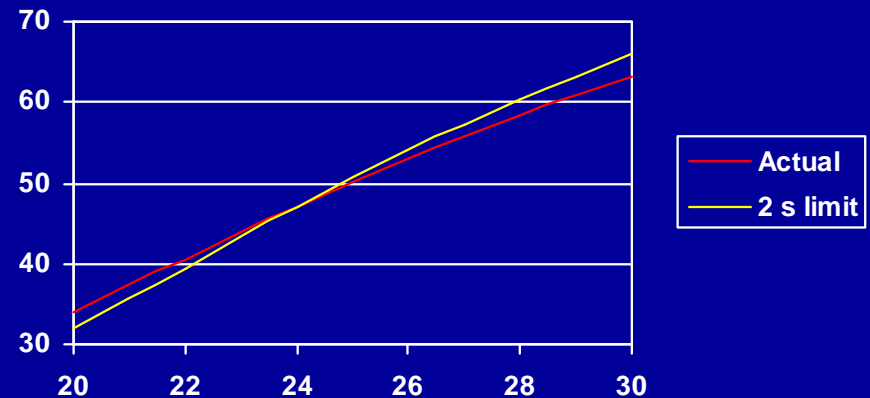
Case Accumulation

VE =70% $r(\text{expected}) = 2.0$ $r(\text{actual}) = 1.5$
400 enrolled / month for 20 months

Detection at 25 months
End enroll at 20 months
Final number of cases =
78 at 48 months



At month 25, extend follow-up
from 24 to 30 months
Final number of cases=
97 at 48 months



Case Accumulation

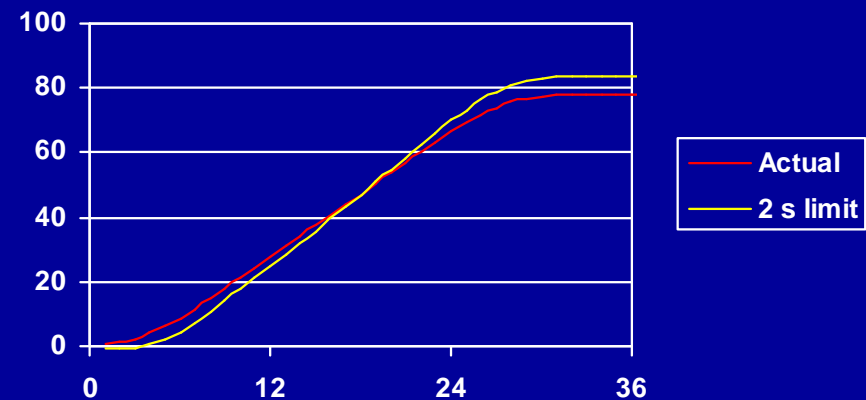
VE =70% $r(\text{expected}) = 2.0$ $r(\text{actual}) =1.5$
1,000 enrolled / month for 8 months

Detection at 19 months

End enroll at 8 months

Final number of cases =

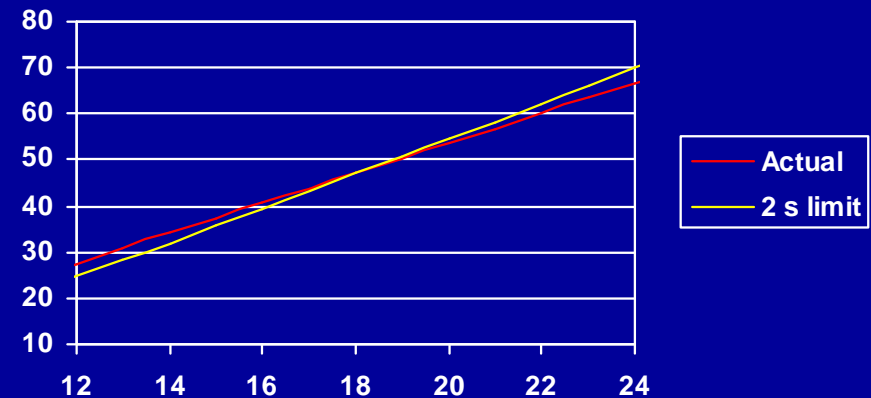
78 at 36 months



At month 19, extend follow-up
from 24 to 30 months

Final number of cases=

97 at 36 months



Interim Administrative Decision

If promising then proceed with further planning
Issue: exact results remain blinded, but actions
give an indication of efficacy.

Promising: if conditional power is sufficiently high

Actions: manufacturing, dossier, future trials.

Perhaps could blind actions in some sense

Are the time savings worth the integrity of the trial
question?

Conclusions -1

- enrollment rates and follow-up times are a key part of designing an interim analysis
- safety and futility are the most important issues in an interim analysis
- interim efficacy analysis results can easily be overridden by considerations of duration of protection and long term safety

Conclusions -2

- consideration should be given to designing on number enrolled rather than number of cases
- in situations of low case accumulation, extending follow-up more likely than extending enrollment unless enrollment is continuous or can be stopped/re-started
- slower enrollment leads to greater savings in interim analysis but longer expected trial times.

Some References

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