TRIAL SEQUENTIAL ANALYSIS

USING TRIAL SEQUENTIAL ANALYSIS FOR ESTIMATING THE SAMPLE SIZES OF FURTHER TRIALS: EXAMPLE USING SMOKING CESSATION INTERVENTION

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INTRODUCTION

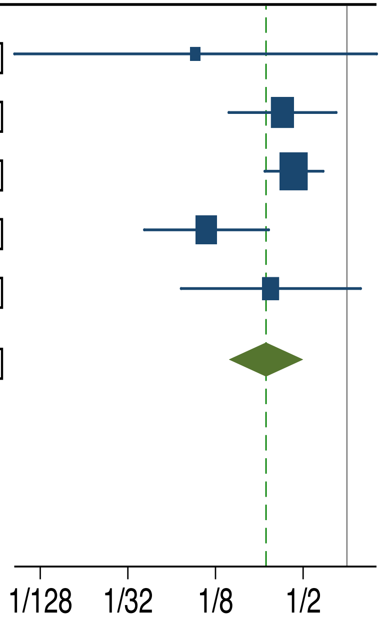
PROBLEMS

Sparse data – spurious significance

Type I (& II) error inflation

$$\Pr(H_0\ \textit{rejected}) = \Pr\left(|Z_1| \geq 1.96 \text{ or } |Z_2| \geq 1.96\right)$$
$$= \Pr\left(|Z_1| \geq 1.96\right) \cdot \Pr\left(|Z_2| \geq 1.96 \mid |Z_1| < 1.96\right)$$

Study	OM Yes	OM No	PSC Yes	PSC No	Risk ratio with 95% CI
Peña, 2003	0	44	5	39	0.09 [0.01, 1.60]
García-ureña, 2015	6	47	17	37	0.36 [0.15, 0.84]
Jairam, 2017	25	163	33	74	0.43 [0.27, 0.68]
Caro-tarrago, 2019	4	76	37	43	0.11 [0.04, 0.29]
Honig, 2021	2	30	14	53	0.30 [0.07, 1.24]
Overall					0.28 [0.15, 0.50]

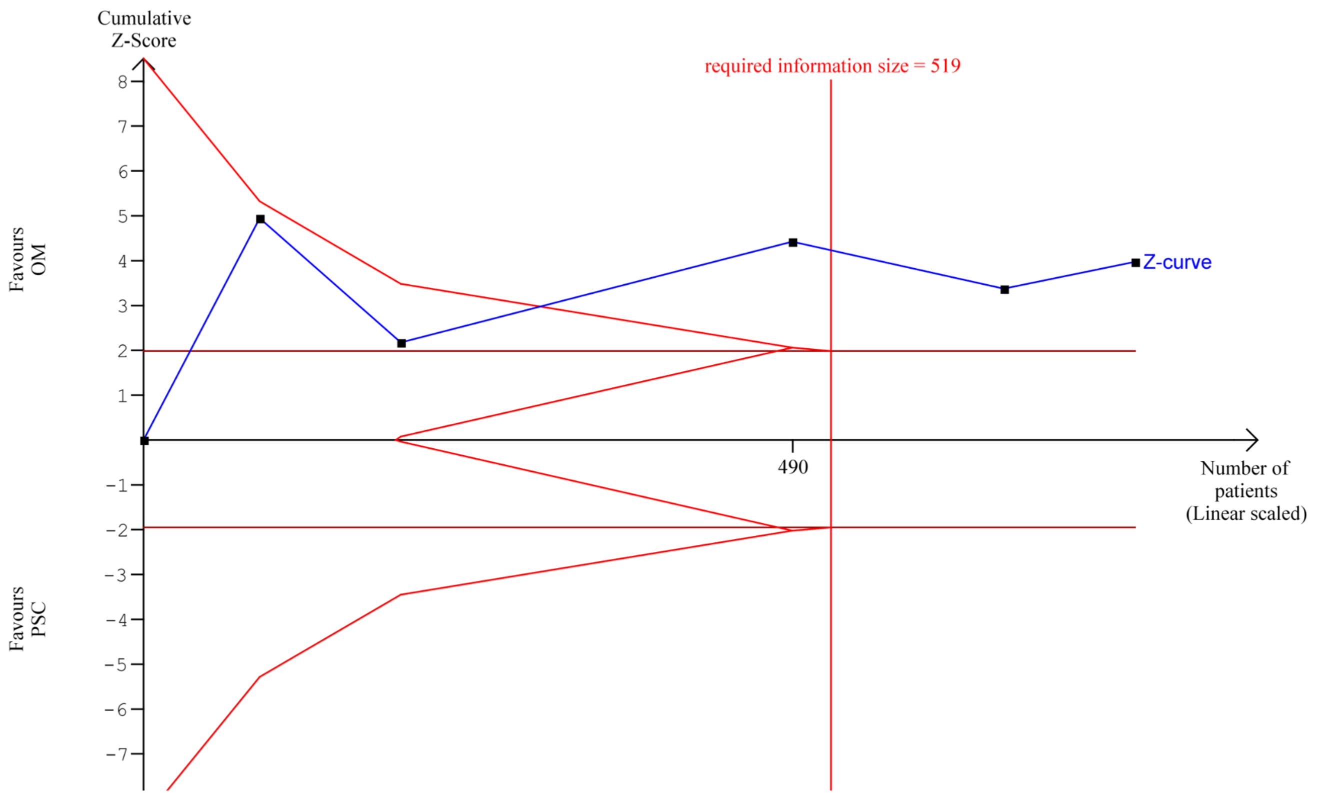


Heterogeneity: $\tau^2 = 0.18$, $I^2 = 43.36\%$, $H^2 = 1.77$

Test of $\theta_i = \theta_j$: $Q(4) = 7.06$, $p = 0.13$

Test of $\theta = 0$: $z = -4.28$, $p = 0.00$

WHAT IS TRIAL SEQUENTIAL ANALYSIS?



Required information size

Adjusted monitoring boundary

- Significance
- Futility

TRIAL SEQUENTIAL ANALYSIS

Meta-analysis

Required information size

Adjusted for heterogeneity

Significance boundary &
Futility boundary

GROUP SEQUENTIAL ANALYSIS

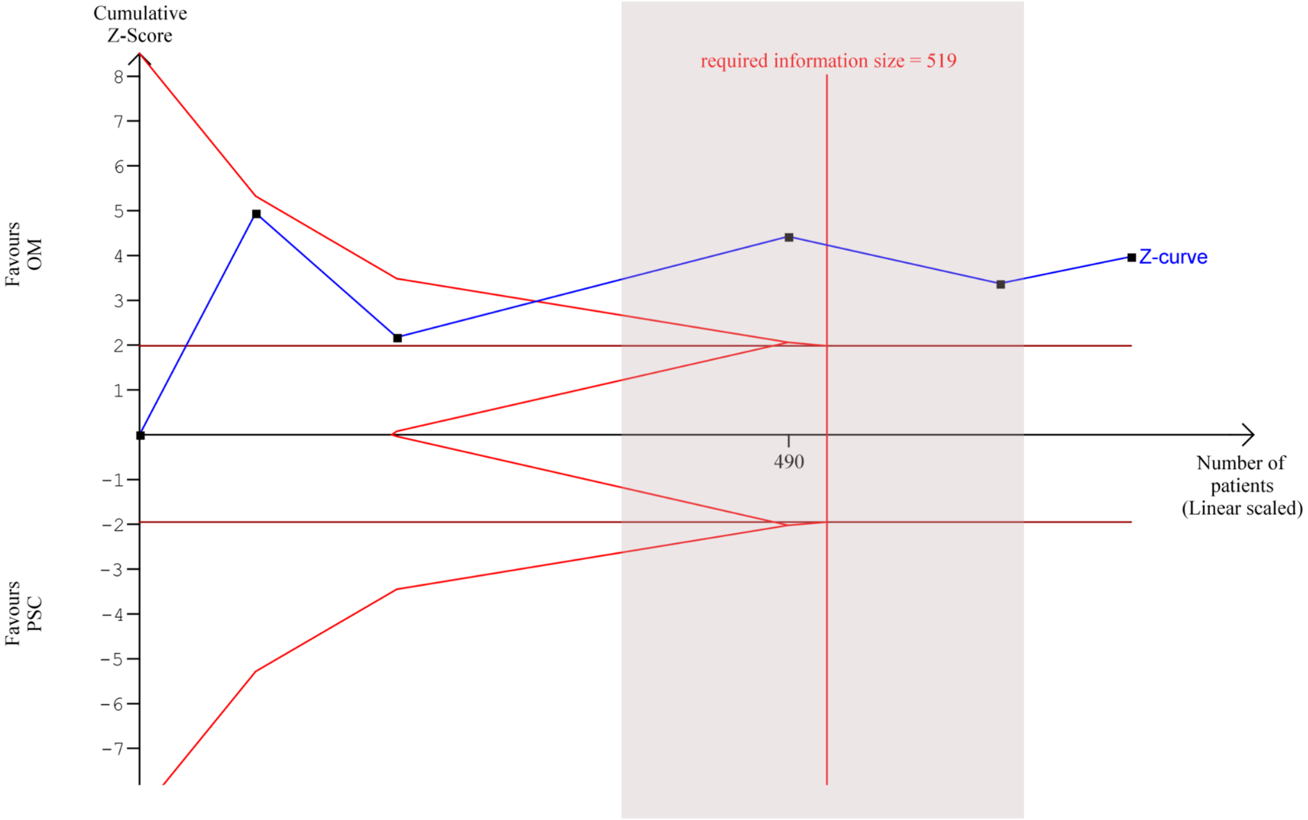
Randomized controlled trial

Sample size

Adjusted for multicenter

The same concept as an
interim analysis

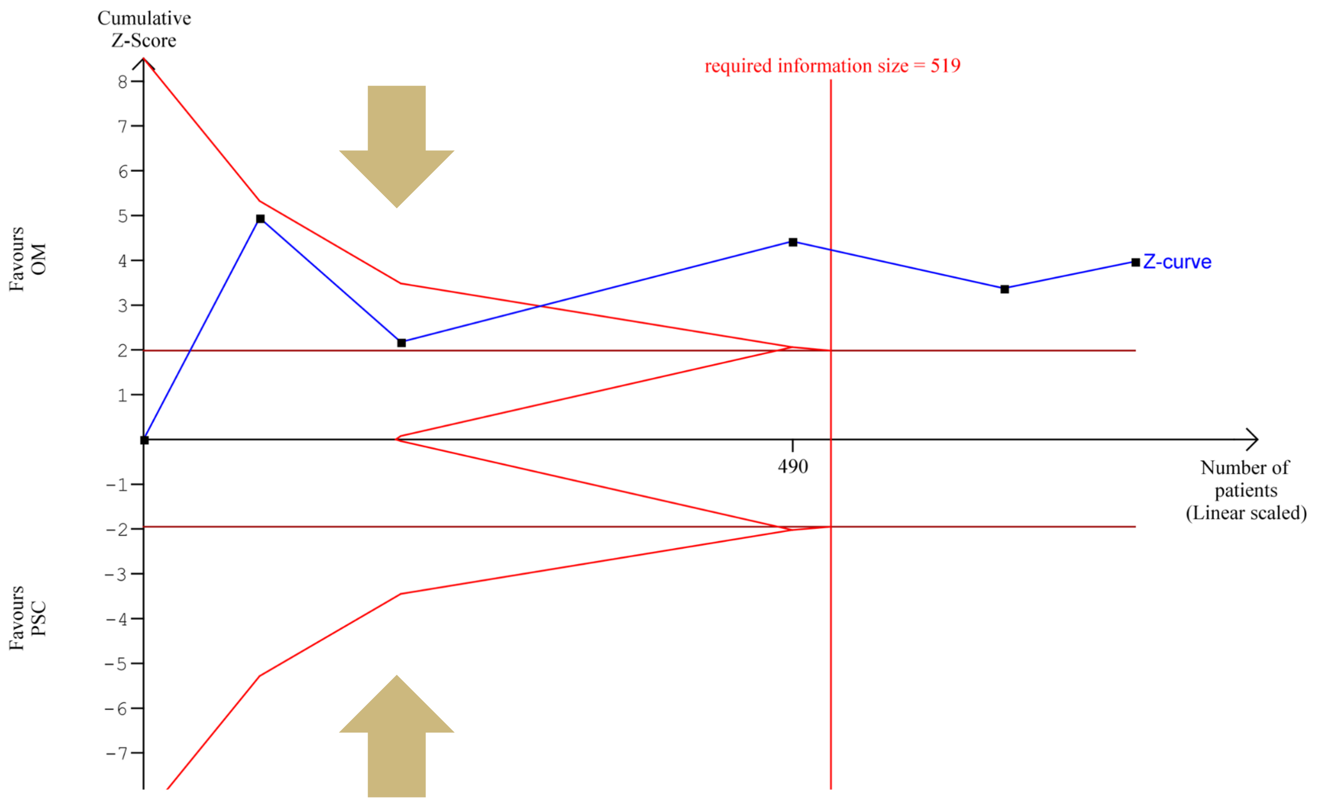
REQUIRED INFORMATION SIZE



Need *a priori*

Control event rate
Relative risk reduction
Type I error
Power

α-SPENDING FUNCTION



independent variable =
information fraction (IF)
← by dividing the accumulated information by the required information size

dependent variable =
cumulative type 1 error
→ the amount of error that should be considered the maximum when defining significance at the given IF

As IF increases, the size of 'acceptable' type 1 error also increases.

α-SPENDING FUNCTION

$$\alpha(IF) = 2 - 2\Phi\left(Z_{\alpha/2} / \sqrt{IF}\right)$$

first proposed for equal increments of IF by O'Brien and Fleming

Lan and DeMets later proposed the above α-spending function to allow for flexible increments in IF

$$\Pr\left(|Z_1| \geq c_1\right) \leq \alpha_1 = \alpha(IF_1)$$

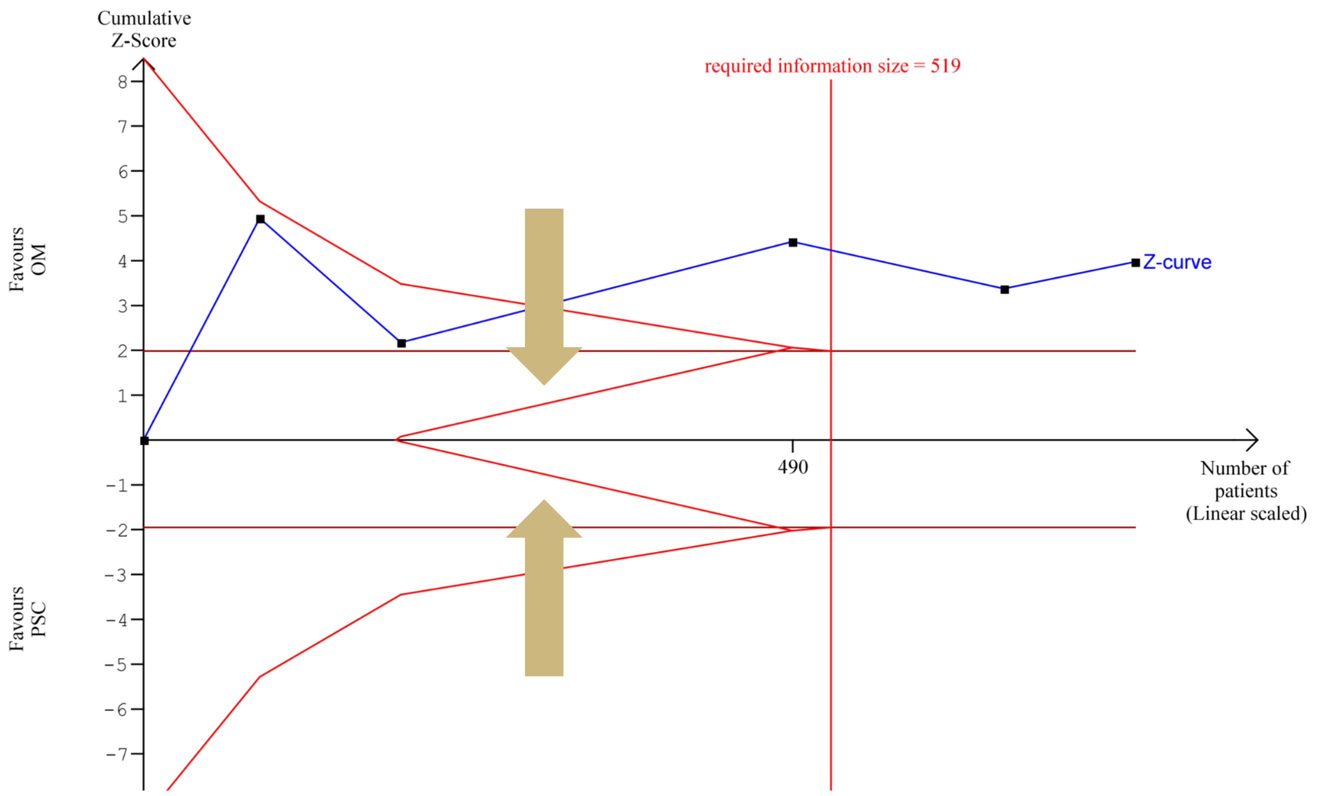
$$\Pr\left(|Z_2| \geq c_2 \;\middle|\; |Z_1| < c_1\right) \leq \alpha_2 = \alpha(IF_2) - \alpha(IF_1)$$

$$\Pr\left(|Z_3| \geq c_3 \;\middle|\; |Z_1| < c_1 \text{ and } |Z_2| < c_2\right) \leq \alpha_3 = \alpha(IF_3) - \alpha(IF_2)$$

$$\vdots$$

$$\Pr\left(|Z_k| \geq c_k \;\middle|\; |Z_1| < c_1 \text{ and } \dots \text{ and } |Z_{k-1}| < c_{k-1}\right) \leq \alpha_k = \alpha(IF_k) - \alpha(IF_{k-1})$$

β-SPENDING FUNCTION



Under the assumption that H_δ is true,
the probability of statistical significance (with the chosen α-level) is equal to the chosen power, $1-\beta$.

=

When the information size has been reached, the probability that the result will be falsely negative is equal to β.

$Pr(Z < c \mid H_\delta \text{ is true}) \leq \beta.$

β-SPENDING FUNCTION

$$\Pr\left(Z_1 < c_1\right) \le \beta_1$$

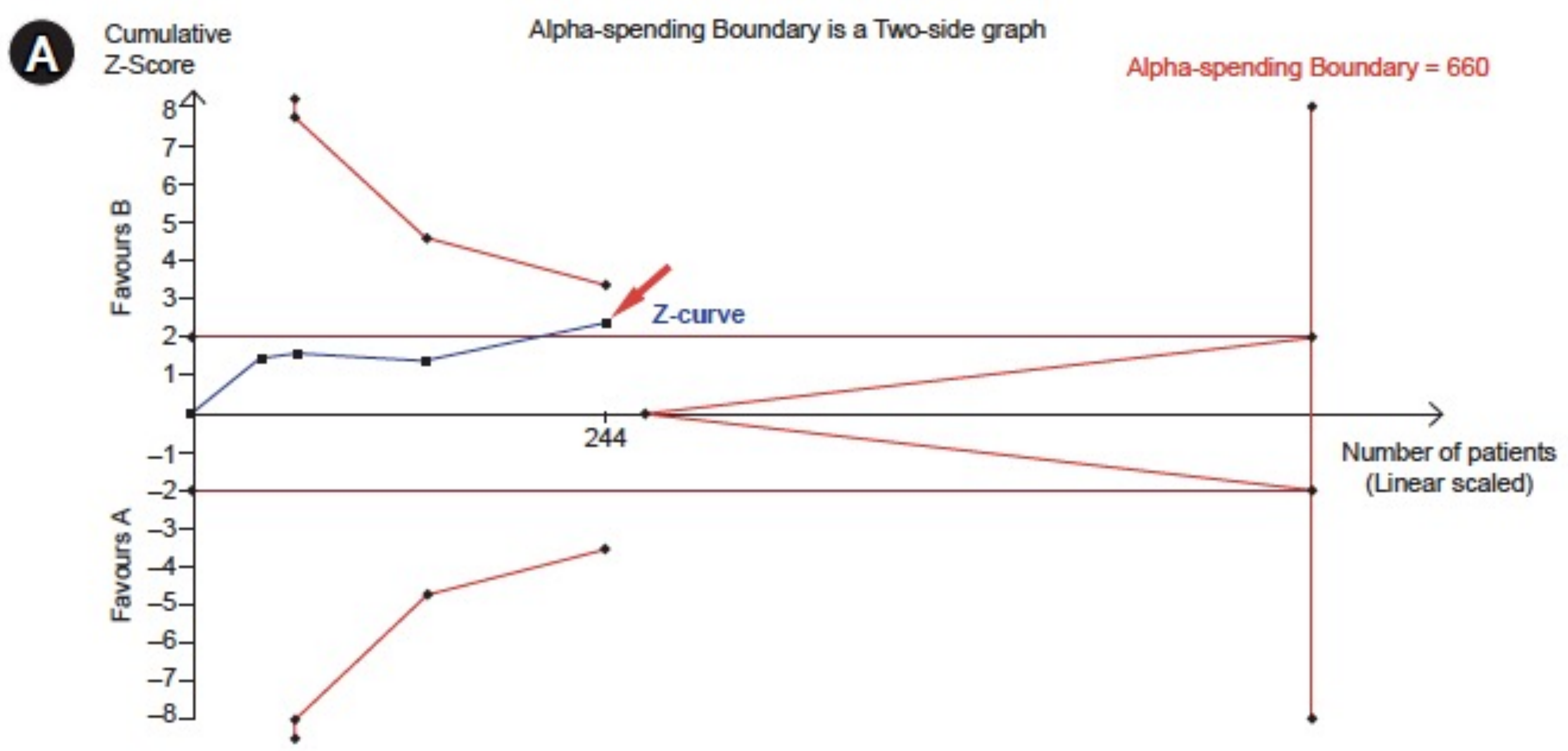
$$\Pr\left(Z_2 < c_2 \,\middle|\, Z_1 \ge c_1\right) \le \beta_2$$

$$\Pr\left(Z_3 < c_3 \,\middle|\, Z_1 \ge c_1 \text{ and } Z_2 \ge c_2\right) \le \beta_3$$

$$\vdots$$

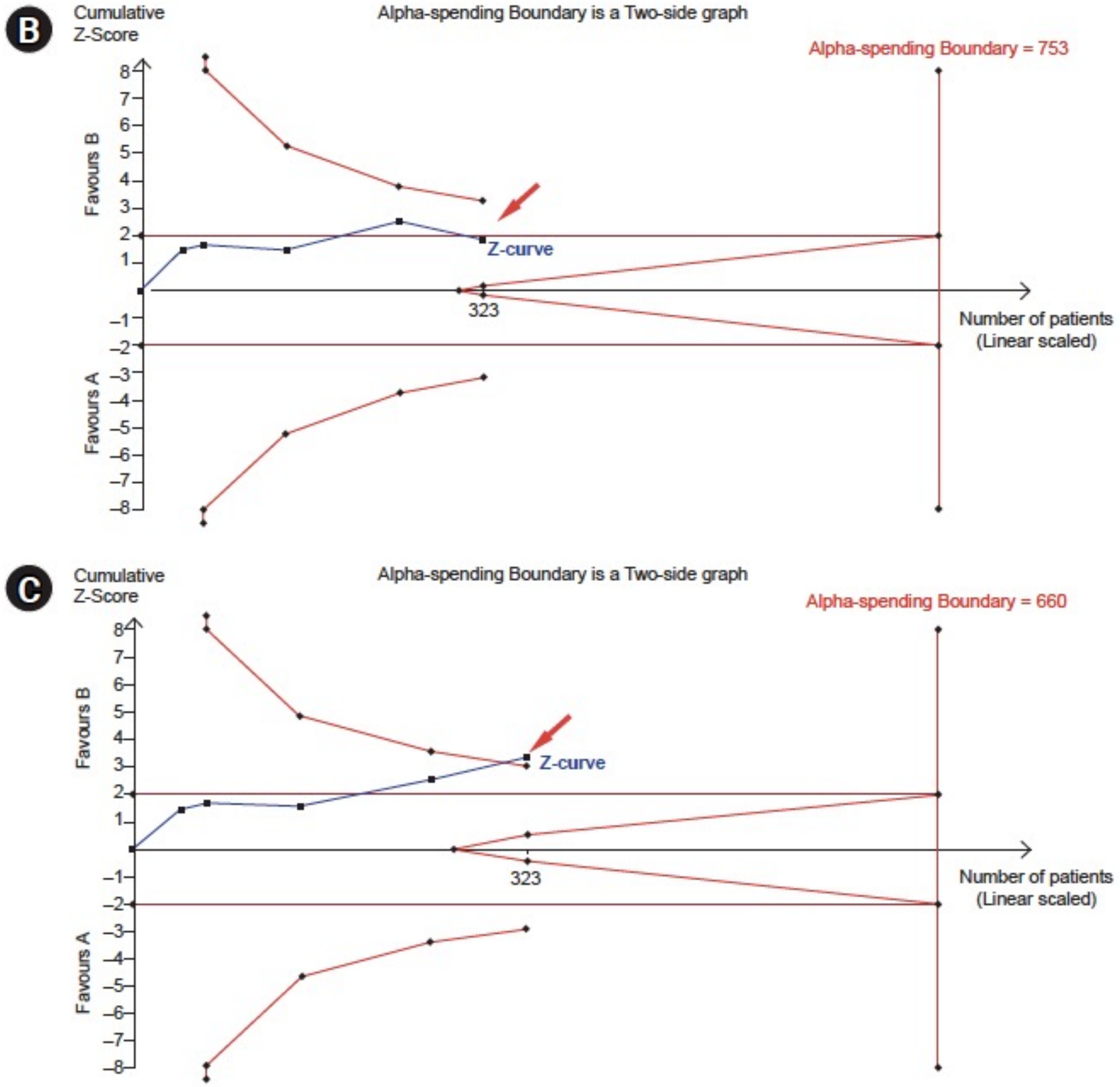
$$\Pr\left(Z_k < c_k \,\middle|\, Z_1 \ge c_1 \text{ and } \ldots \text{ and } Z_{k\text{-}1} \ge c_{k-1}\right) \le \beta_k$$

EXAMPLES



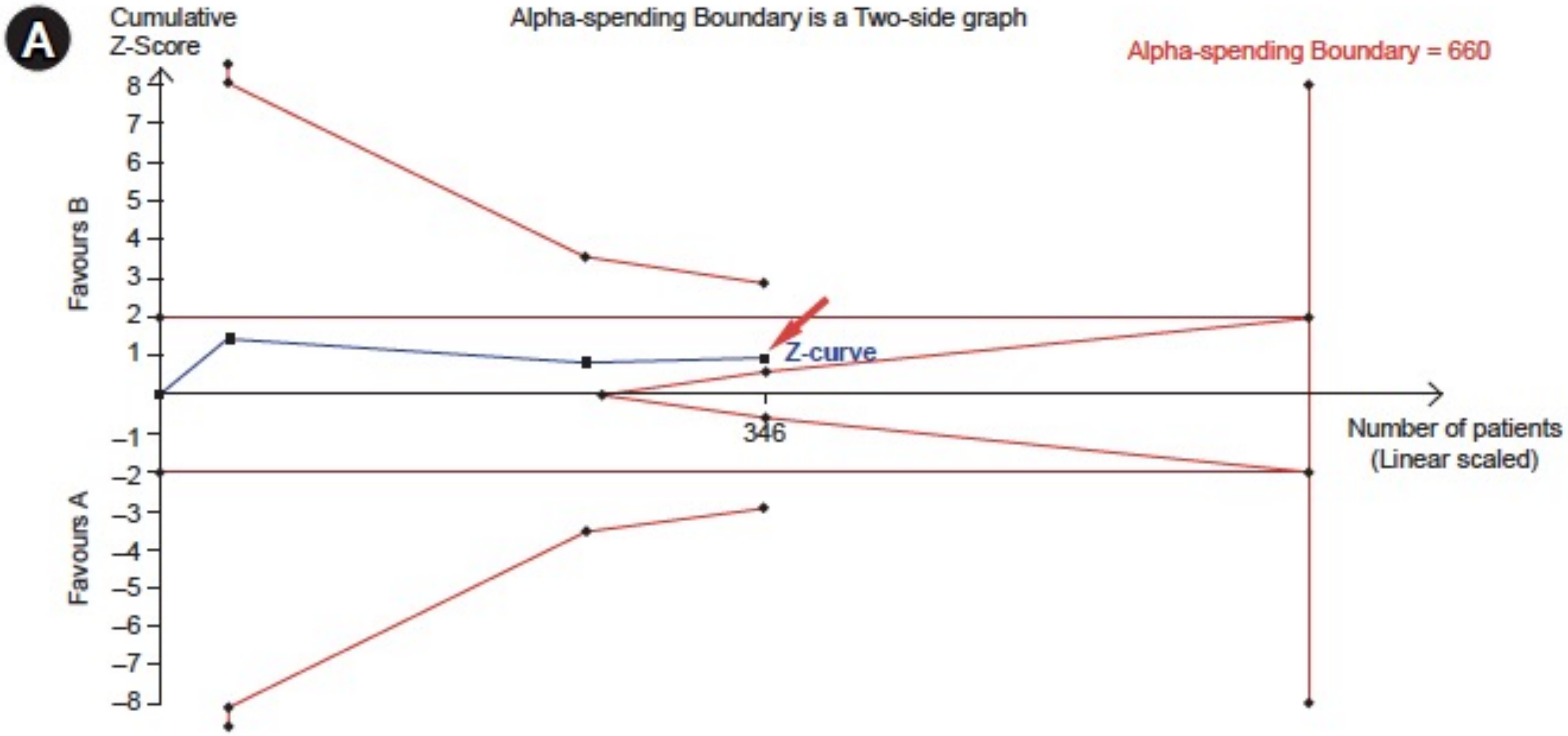
A
Cumulative
Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 660
Favours B
Favours A
8
7
6
5
4
3
2
1
−1
−2
−3
−4
−5
−6
−7
−8
Z-curve
244
Number of patients
(Linear scaled)

EXAMPLES



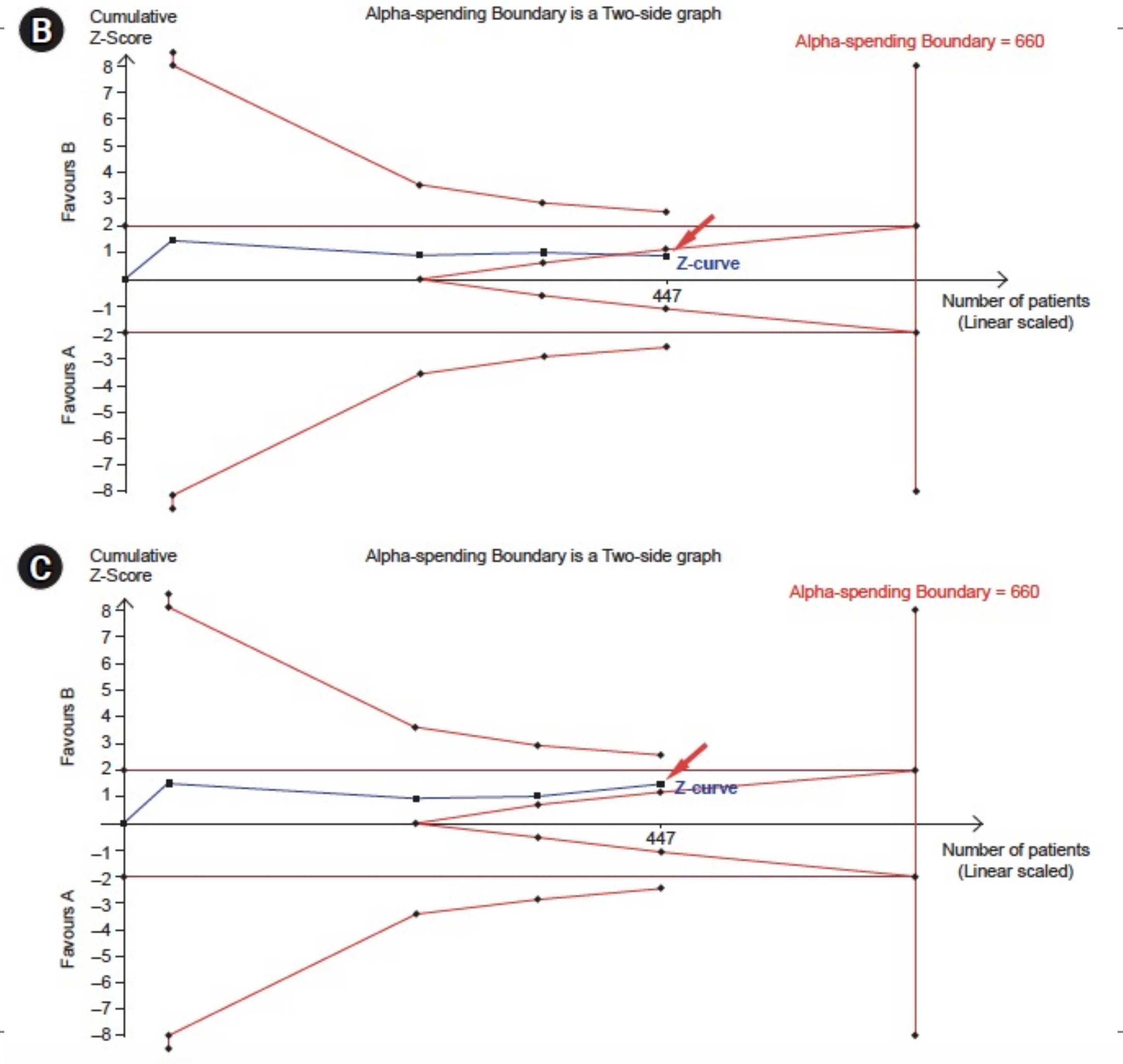
B
Cumulative Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 753
Favours B
Favours A
Z-curve
323
Number of patients (Linear scaled)
C
Cumulative Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 660
Favours B
Favours A
Z-curve
323
Number of patients (Linear scaled)

EXAMPLES



A
Cumulative
Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 660
8
7
6
5
4
3
2
1
−1
−2
−3
−4
−5
−6
−7
−8
Favours B
Favours A
Z-curve
346
Number of patients
(Linear scaled)

EXAMPLES



B
Cumulative Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 660
Favours B
Favours A
Z-curve
447
Number of patients (Linear scaled)
C
Cumulative Z-Score
Alpha-spending Boundary is a Two-side graph
Alpha-spending Boundary = 660
Favours B
Favours A
Z-curve
447
Number of patients (Linear scaled)

TRIAL SEQUENTIAL ANALYSIS

USING TRIAL SEQUENTIAL ANALYSIS FOR ESTIMATING THE SAMPLE SIZES OF FURTHER TRIALS: EXAMPLE USING SMOKING CESSATION INTERVENTION

INTRODUCTION

Meta-analyses often influence future research

- If all available RCTs are included, systematic reviews with meta-analyses are considered the best available evidence

INTRODUCTION

However, this does not necessarily mean that the available evidence is either sufficient or strong

- Often overvalued, particularly where sparse data (number of events and participants) or repetitive analyses (type I errors) are employed
- intervention effects that are not statistically significant are often interpreted as showing that the intervention has no effect, and it is assumed that no more evidence is required (type II errors)

INTRODUCTION

In the examples , the authors show how the Trial Sequential Analysis can be used to estimate the sample size required for one or more new trials to add further data to a meta-analysis to provide more firm evidence for an intervention either having or not having the postulated effect.

DATA USED

- MiQuit: Pregnancy; intervention = individually-tailored text messages
- MiQuit feasibility RCT
  - N = 207
  - 7-day cessation 12 weeks after randomization (biochemically validated)
  - OR 1.68 (0.66, 4.31)
- MiQuit pilot RCT
  - N = 407
  - Self-reported abstinence from 4 weeks post randomization until late pregnancy follow-up (2% (control) & 5.4% (experimental) biochemically validated)
  - OR 2.70 (0.93, 9.35)

DATA USED

From now on, I will call

- MiQuit feasibility RCT → study I
- MiQuit pilot RCT → study II

Considered at lower risk of bias than study I

Used for sample size calculation

RESULTS

- Conventional meta-analysis
  - OR 2.26 (1.04, 4.93)
  - $I^2 = 0\%$

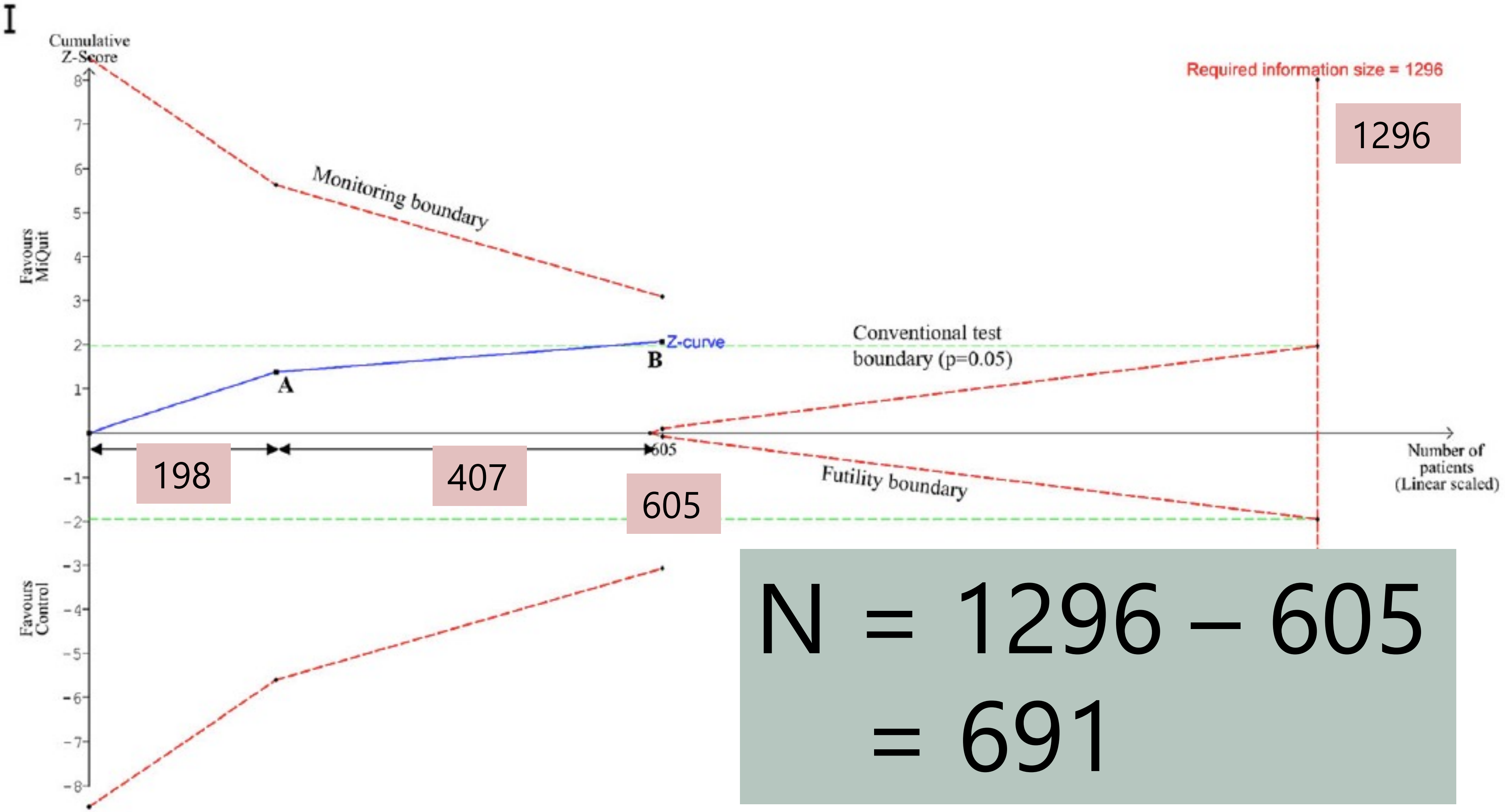
RESULTS

- Conventional sample size calculation
  - 5.4% vs 2% of abstinence
  - Power 90%
  - 2-side type I error 5%

N = 1292

RESULTS

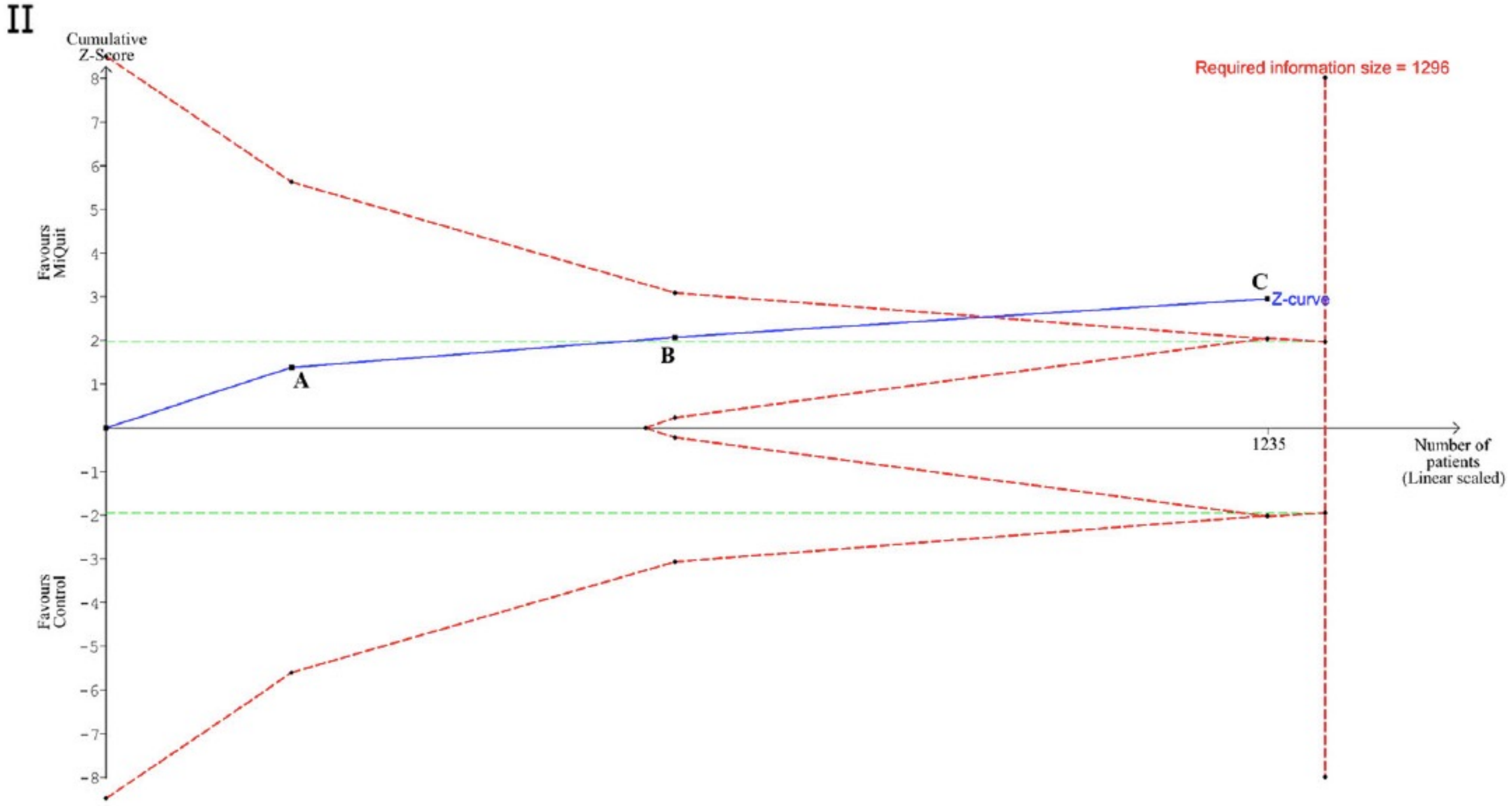
- Using TSA



$$N = 1296 - 605 = 691$$

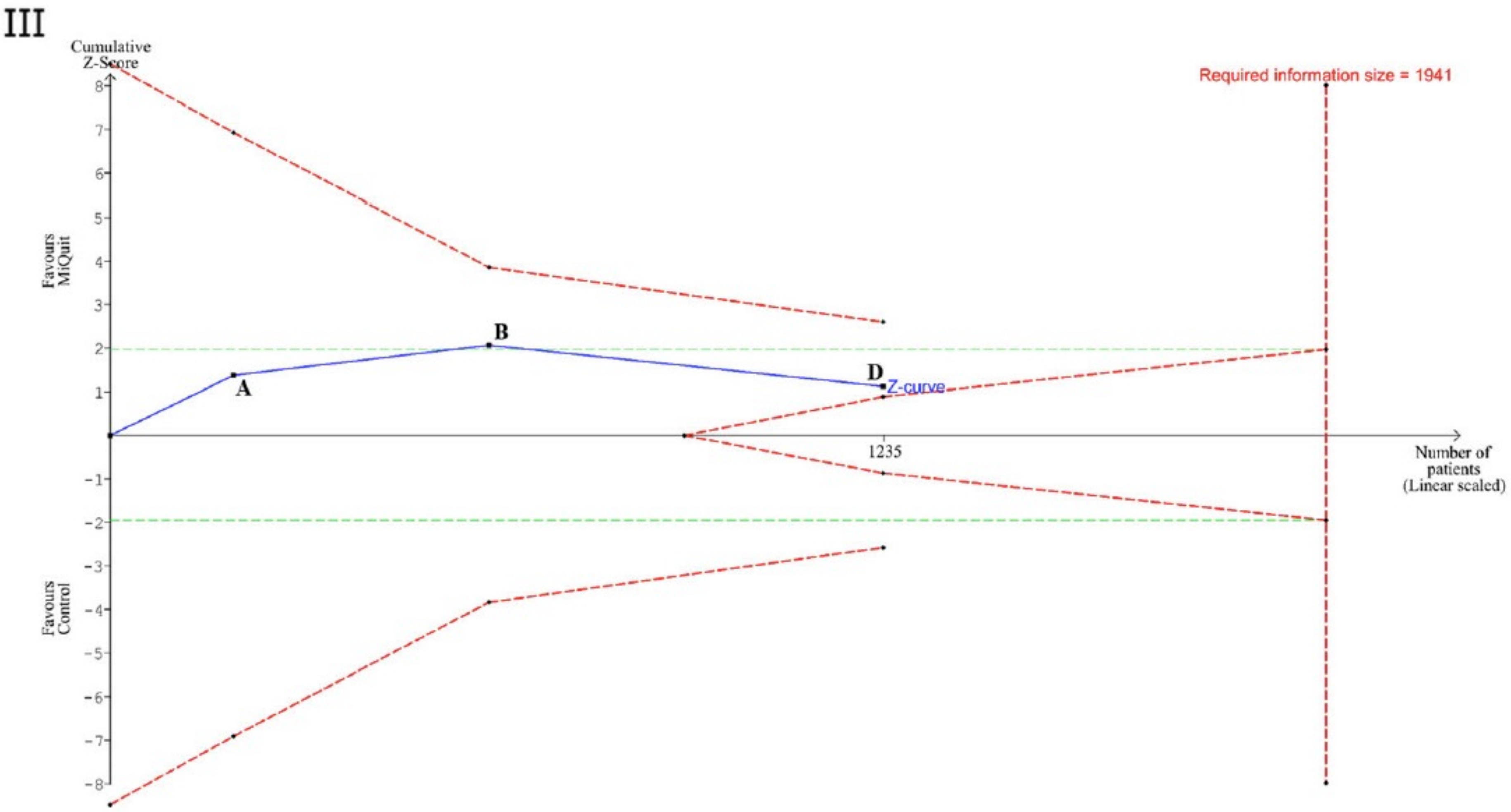
RESULTS

- Adding theoretical 3rd trial
  - N = 630
  - 3.17% difference favoring experimental group

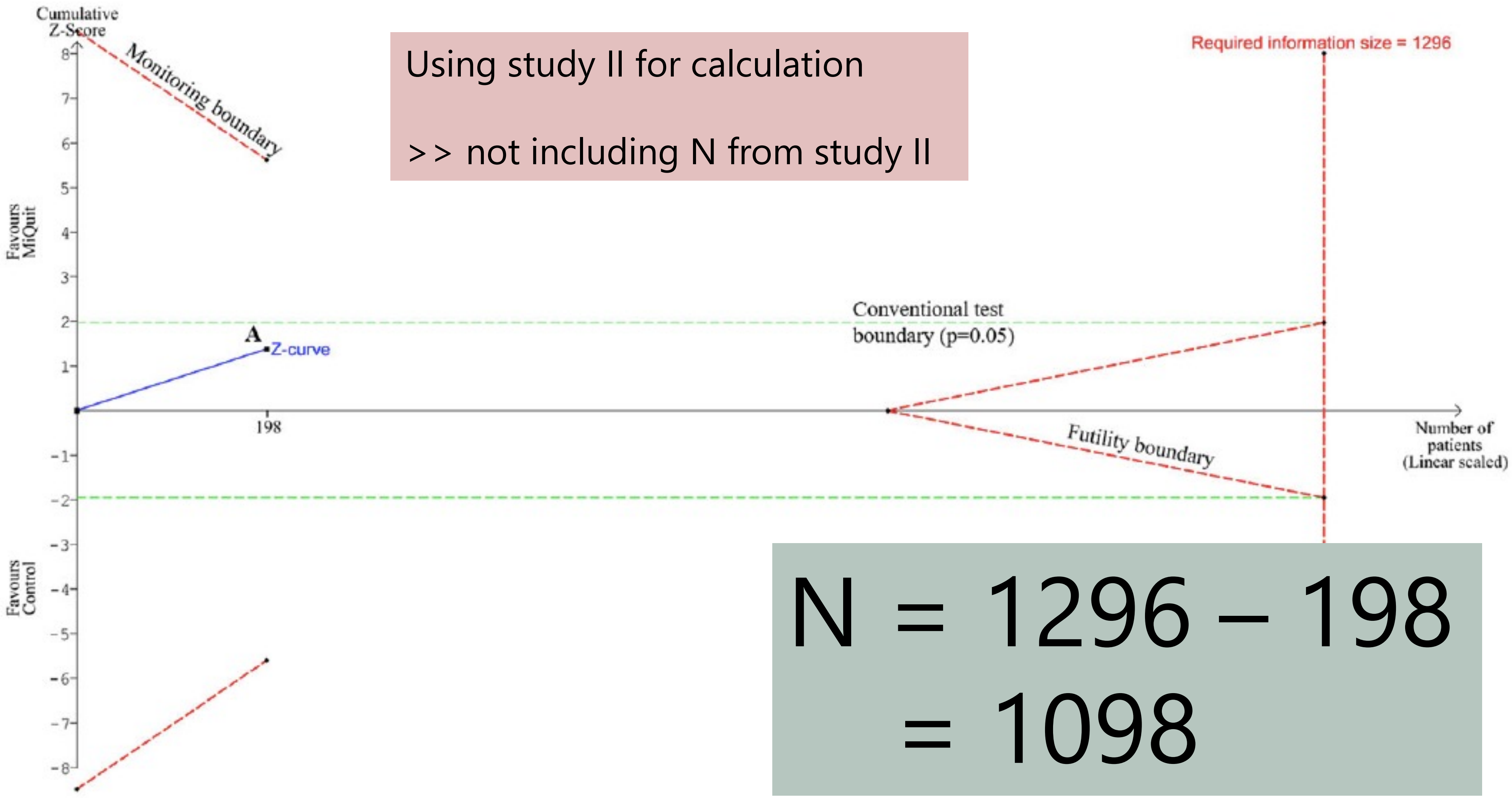


RESULTS

- Adding theoretical 3rd trial
  - N = 630
  - -0.63% difference favoring control group



RESULTS



Using study II for calculation

>> not including N from study II

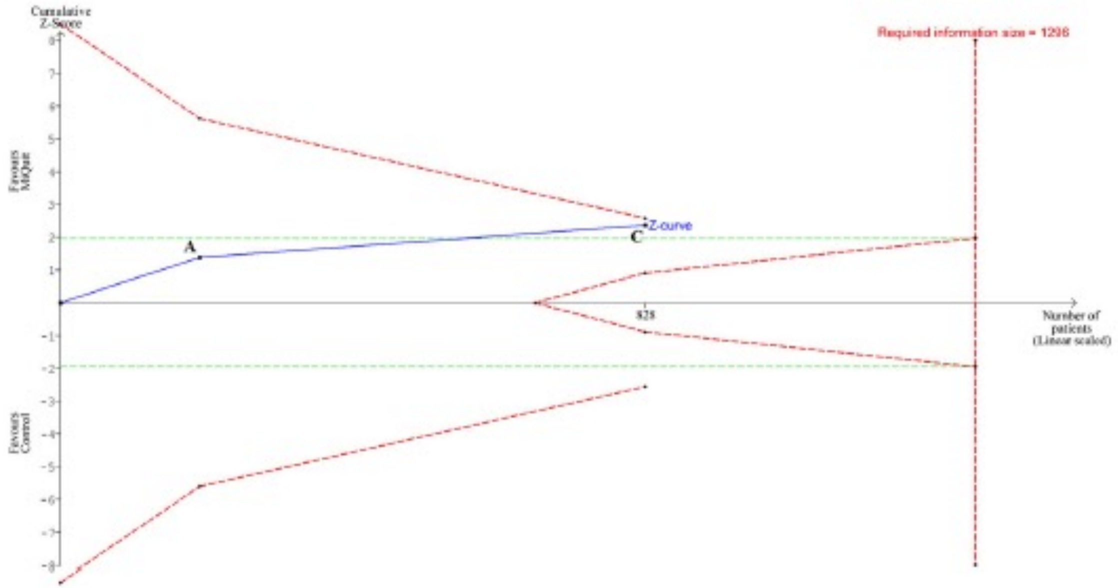
N = 1296 – 198

= 1098

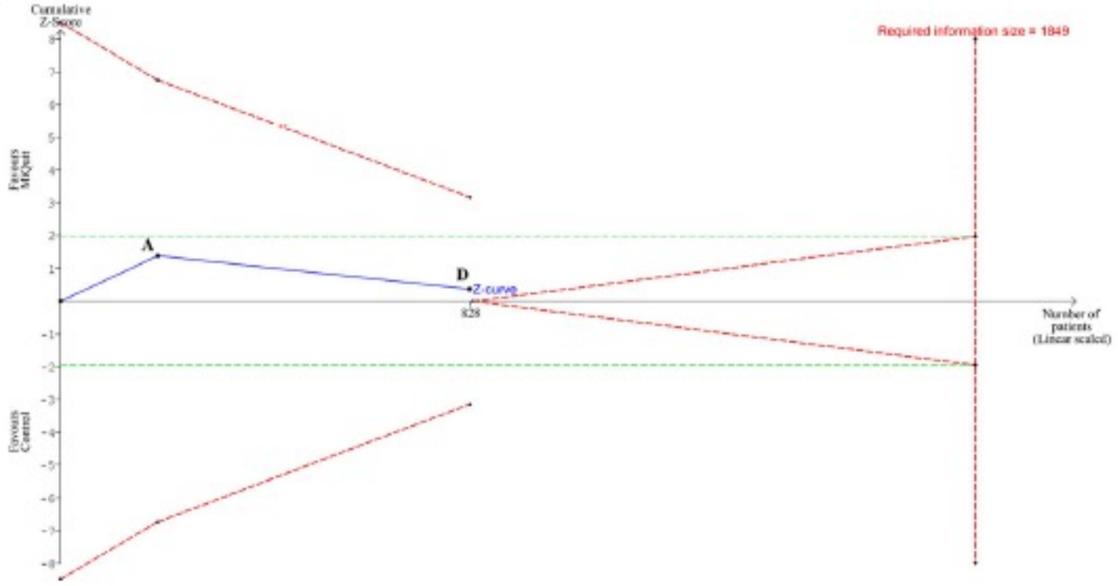
RESULTS

- Adding theoretical trial

II



III



DISCUSSION

The example demonstrates how Trial Sequential Analysis can be used to determine the required sample size for one or more additional RCTs to make a meta-analysis more conclusive.

Future trials could be planned using significantly fewer resources and with less cost than trials planned using traditional sample size calculations.

DISCUSSION

The meta-analysis of the existing two MiQuit trials quantified heterogeneity as 0%.

However, it is unlikely that this will be the case for meta-analyses of other interventions; therefore, trial sequential analysis methods have been developed to account for this.

DISCUSSION

Using multiple trials to reach the required information size may be beneficial in meta-analyses where heterogeneity occurs.
Smaller trials have more imprecise estimates of intervention effects; hence heterogeneity is reduced in the meta-analysis of such trials.

However, setting up more than one trial can be more expensive and may not be realistic in practice.

DISCUSSION

Cochrane's guidance

- should not be used in primary analyses or to draw conclusions, but could be used as secondary analyses
- interpretations of evidence should be based on estimated magnitude of effect of an intervention and its uncertainty rather than drawing binary conclusions,
- and decisions should not be influenced by plans for future updates of meta-analyses
- a meta-analyst does not have any control over designing trials that are eligible for meta-analysis. It would therefore be impossible to construct a set of stopping rules.
- there are methodological limitations to sequential methods when heterogeneity is present

LET’S PRACTICE