Does Cochrane reviews reasonably take into account risks of type I errors and type II errors - and what can we do about it?

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What is the evidence-base?

Study (year)	Key finding regarding overestimation
Ioannidis (2002)	> 30% fluctuations before 2000 patients 10,000 patients to relieve uncertainty
Trikalinos (2005)	> 50% fluctuations before 500 patients 2000 patients to relieve uncertainty
Thorlund (2009)	1/3 of 'first statistically significance' are clinically important overestimates
Pereira (2011)	Updated estimates 0.67-fold smaller when original MA has < 300 events

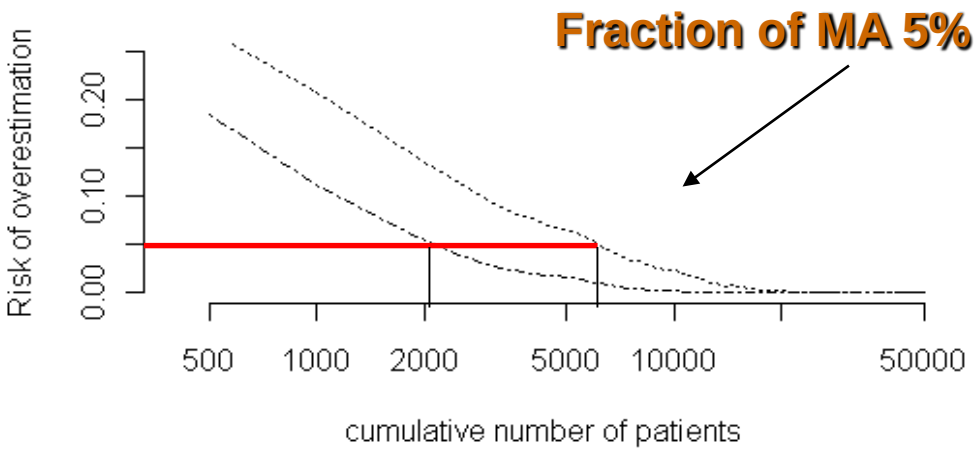
What is the evidence-base?

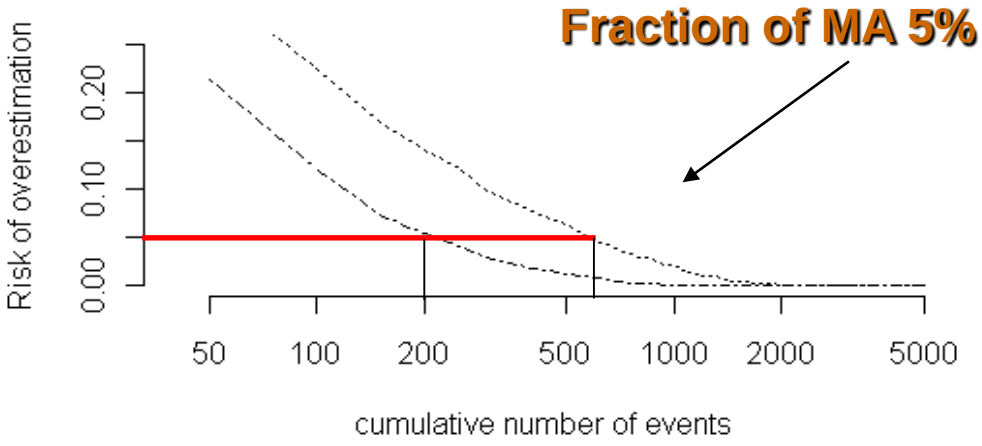
Overestimation

A simulation study has quantified the impact of random error on overestimation of meta-analysed intervention effects in relation to the cumulative number of events and patients

Thorlund et al, PLoS ONE 2011

Simulated meta-analyses with more than 20% or 30% overestimation of a truly zero effect





Scenario: RRR=0%

RRR>20% (upper curve)
RRR>30% (lower curve)

Control group risk 5%-15%

Moderate heterogeneity

Risk of overestimation plotted as a function of the cumulated number of patients and events

What is the evidence-base?

Overestimation

- **The likelihood of overestimation due to random error is profound at early stages (often 20% to 30%)**
- **The risk of overestimation decreases exponentially with number of participants and outcomes**
- **Reaching the required information size provides good protection against overestimation**

Thorlund et al, PLoS ONE 2011

What is the evidence-base?

Lack of power in Cochrane reviews

Proportion of 77,237 trials in 14,886 meta-analyses of binary outcomes adequately powered to detect a relative risk reduction (RRR)

	≥ 80% power in all trials	≥ 80% power in meta-analyses
10% RRR	2.0%	ND*
30% RRR	17.0%	22.0%

Turner et al, PLoS ONE 2011

* Not determined

Houston, we have a problem!

Apollo 13

Available approaches

- The required information size

- Trial Sequential Analysis (TSA)
- Sequential Meta-Analysis (SMA)
- The Law of the Iterated Logarithm (LIL)

- Bayesian methods

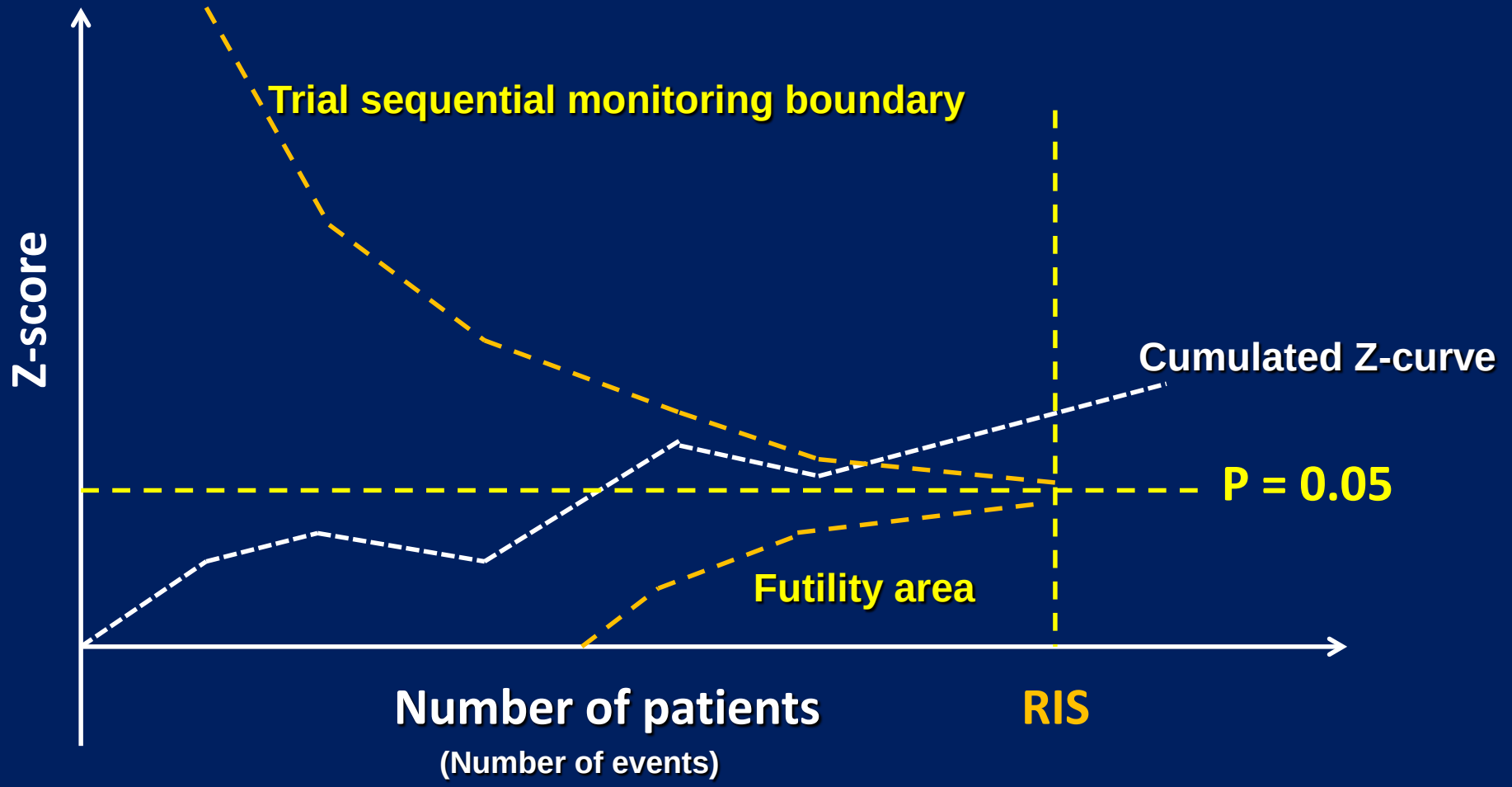
The required information size (optimal information size)

The required information size (RIS) is the required meta-analysis 'sample size'

Reaching the RIS and the corresponding number of trials ensures control of type I and type II errors

Reaching the RIS also provides good protection against overestimation of the intervention effect

Trial Sequential Analysis



False-positive findings in Cochrane meta-analyses with and without TSA

TSA prevented 13 / 14 statistically significant meta-analyses (P<0.05) among cumulative meta-analyses becoming non-significant when RIS was reached

Imberger et al, BMJ OPEN 2016

Thank you

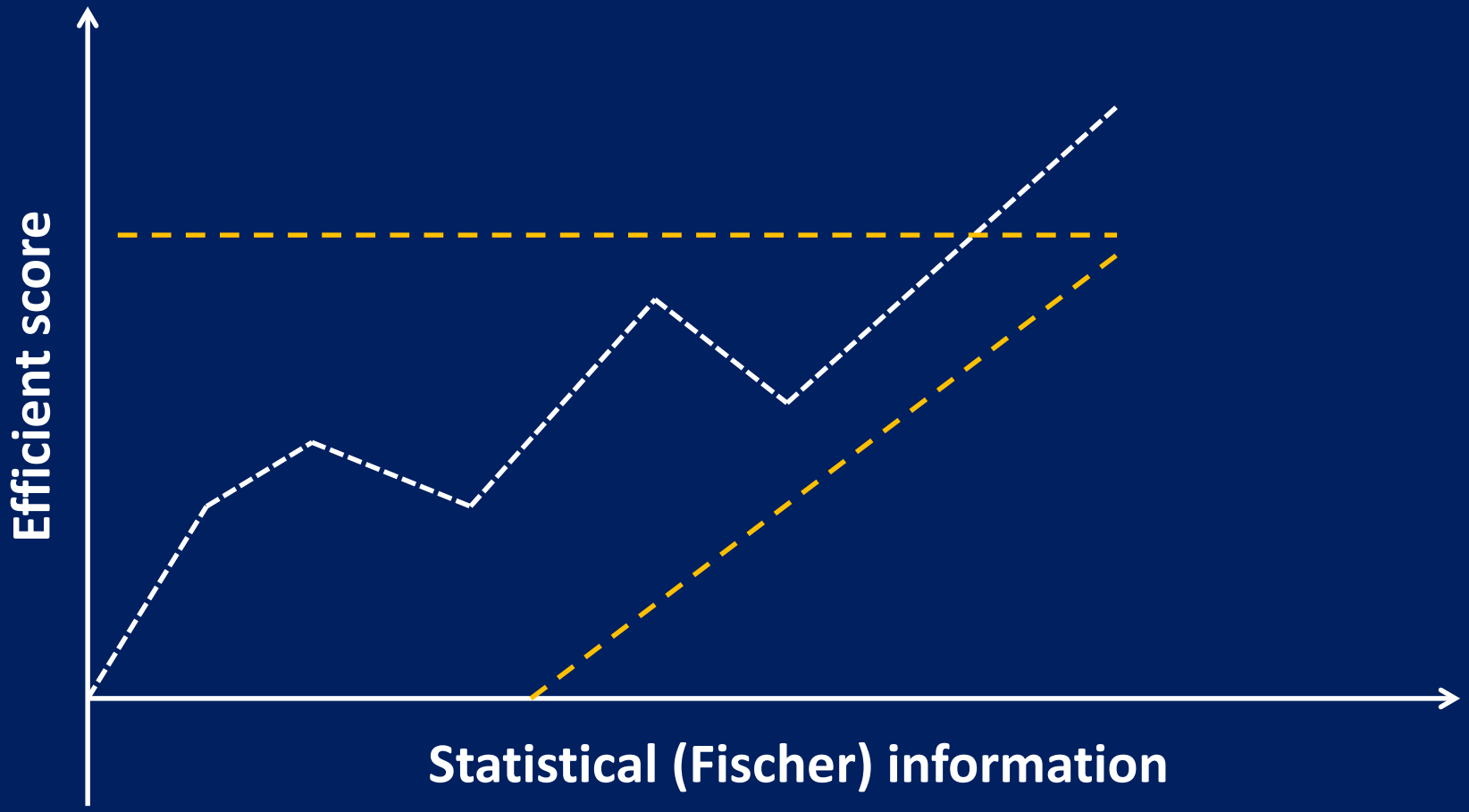
Pros & Cons of Change

PROS	CONS
Enhanced reliability of inferences about effects	Conclusions from Cochrane systematic reviews will become more conservative
Avoidance of frequent reversed statistical significance diminishing credibility	Choice of anticipated intervention effect and heterogeneity may require Bayesian methods and be perceived complicated
Yardsticks for amount of evidence required for conclusive meta-analyses (aligned with GRADE)	May discourage authors from conducting Cochrane reviews due to reduced probability of statistically significant findings
Better direction of resource use	

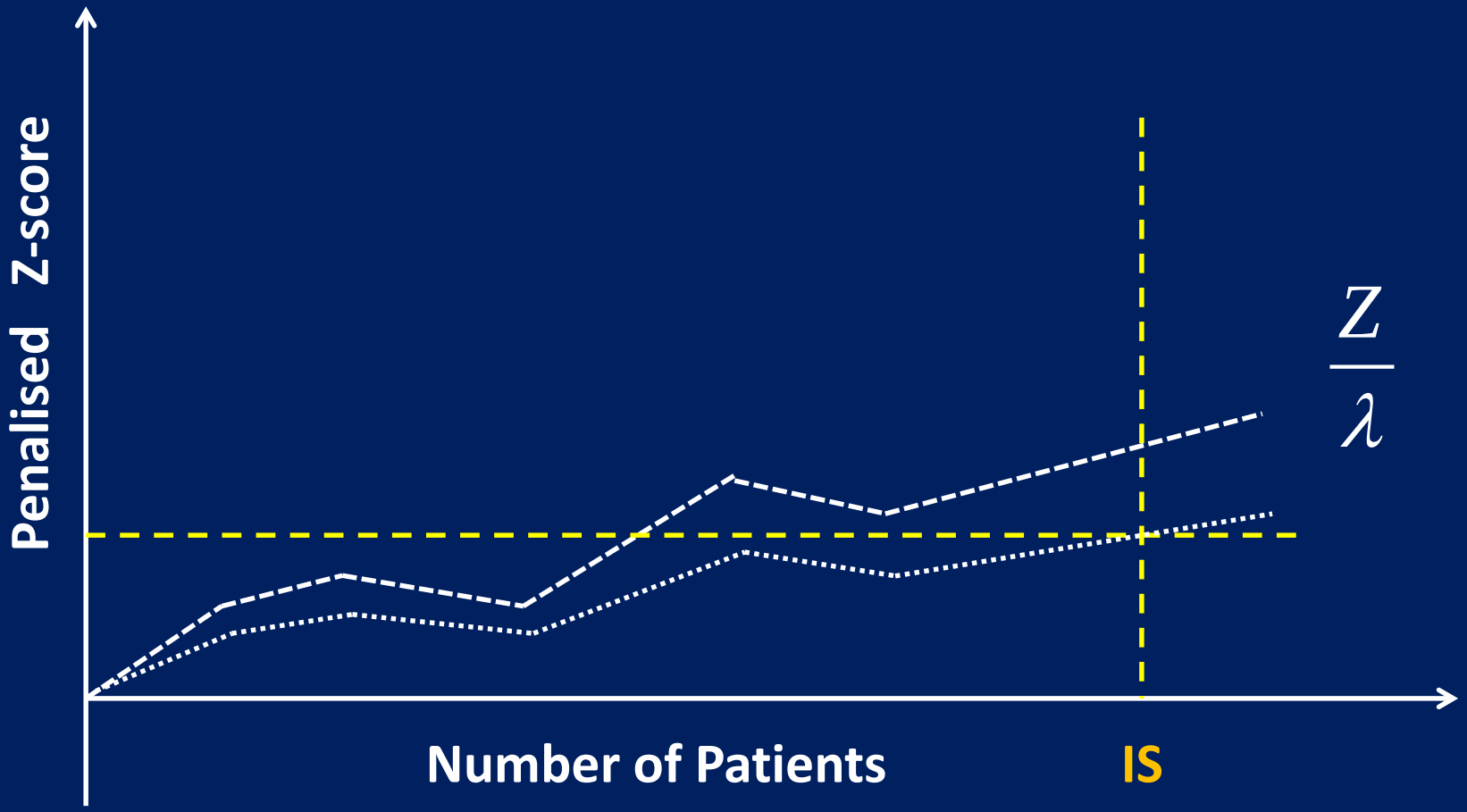
PROS & CONS

Approach	PROS	CONS
TSA	Known from trials Adjusted CIs before RIS Information=patients Futility boundaries	RIS assumptions may be challenging
SMA	Known from trials Adjusted CIs Semi-Bayesian (full distribution of heterogeneity) Futility boundaries	RIS assumptions may be challenging Information=Fisher
LIL	Can obtain adjusted P-values	Arbitrary (or simulation) determined fixed Z-penalisation values required

Sequential Meta-Analysis



Law of the iterated logarithm



Outline

Random errors in meta-analysis - how big a problem?

Approaches for dealing with random errors

Current practice versus change of practice

Before reaching RIS…

In the light of the available evidence, it seems sensible to employ methods that will provide more reliable inferences about the ‘statistical significance’, the magnitude of the intervention effect, and the associated confidence interval

Available frquentist approaches

- **Trial Sequential Analysis (TSA)**
  O'Brien-Fleming type alpha-spending adjusted thresholds for significance (Z-score)

- **Sequential meta-analysis (SMA)**
  O'Brien-Fleming type Whitehead adjusted thresholds for significance (efficient score)

- **Law of the iterated logarithm (LIL): penalisation (adjustments) of Z-score**

Performance of the approaches

TSA and SMA have theoretically identical backgrounds

Simulation studies have demonstrated that SMA and LIL generally provide good control of the type I error

Empirical evidence suggests that TSA provide adequate protection against false positives and clinically important overestimates

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Current practice versus change of practice

Current practice vs change

What are the PROS and CONS of implementing either of these methods?

What impact will the more conservative nature of these methods have on Cochrane systematic reviews and The Cochrane Collaboration?

Recap

Random error, in concert with repeated testing, causes increased risks of false statistically significant findings (spurious $P < 0.05$ results)

Random error is likely to cause important intervention effect overestimates in meta-analyses with sparse data

What is the evidence-base?

Repeated testing

Three empirical studies have explored the probability of 'early' false positive results

In two, 20% to 25% of meta-analyses had at least one temporary instance of false statistical significance (P < 0.05)

In one study, the probability of reversed statistical significance after one update was 16% to 37%

What is the evidence-base?

Repeated testing

5 simulation studies have investigated increase of type I error under repeated testing

Depending on the simulated scenario and number of repeated tests, the overall type I error can be anywhere between 10% and 40%

What is the evidence-base?

Overestimation

4 empirical studies explored ‘early’ fluctuations in intervention effects estimates and the probability of ‘clinically important’ overestimation

Outline

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