# Trial sequential analysis

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# Problems of meta-analysis

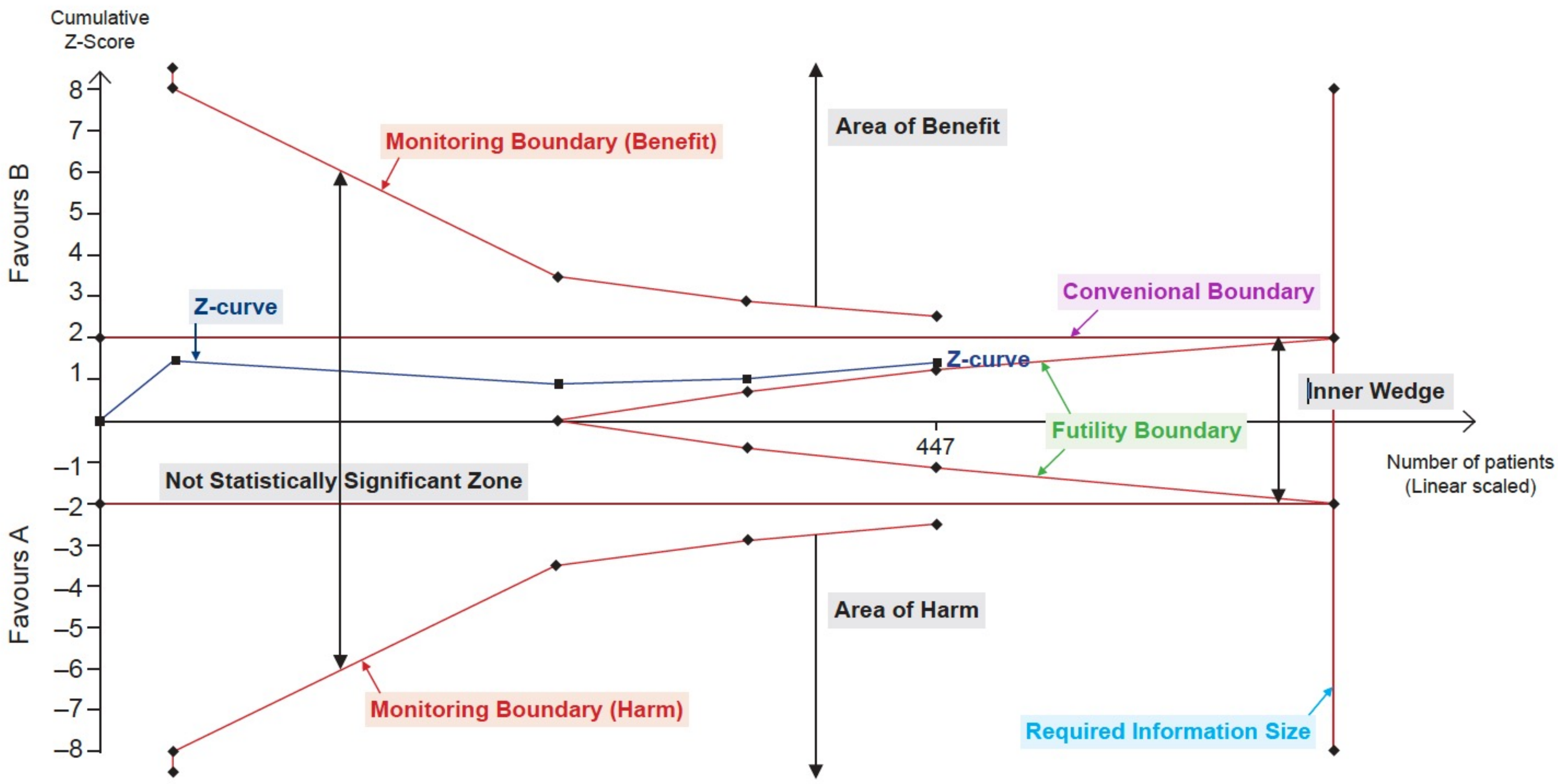
The credibility of statistical significant meta-analyses with too few participants

- spuriously overestimated (type I errors)
- spuriously underestimated (type II errors)

**Table 1** Showing the level of cumulated type 1-error risk, if a threshold of 5% is applied constantly at each sequential significance testing, on an accumulating number of trial participants

| Number of statistical significance tests | The cumulated type 1-error risk in % |
|---|---|
| 1 | 5% |
| 2 | 8% |
| 5 | 14% |
| 20 | 25% |
| 100 | 37% |
| Infinitely many | 100% |

# TSA diagram

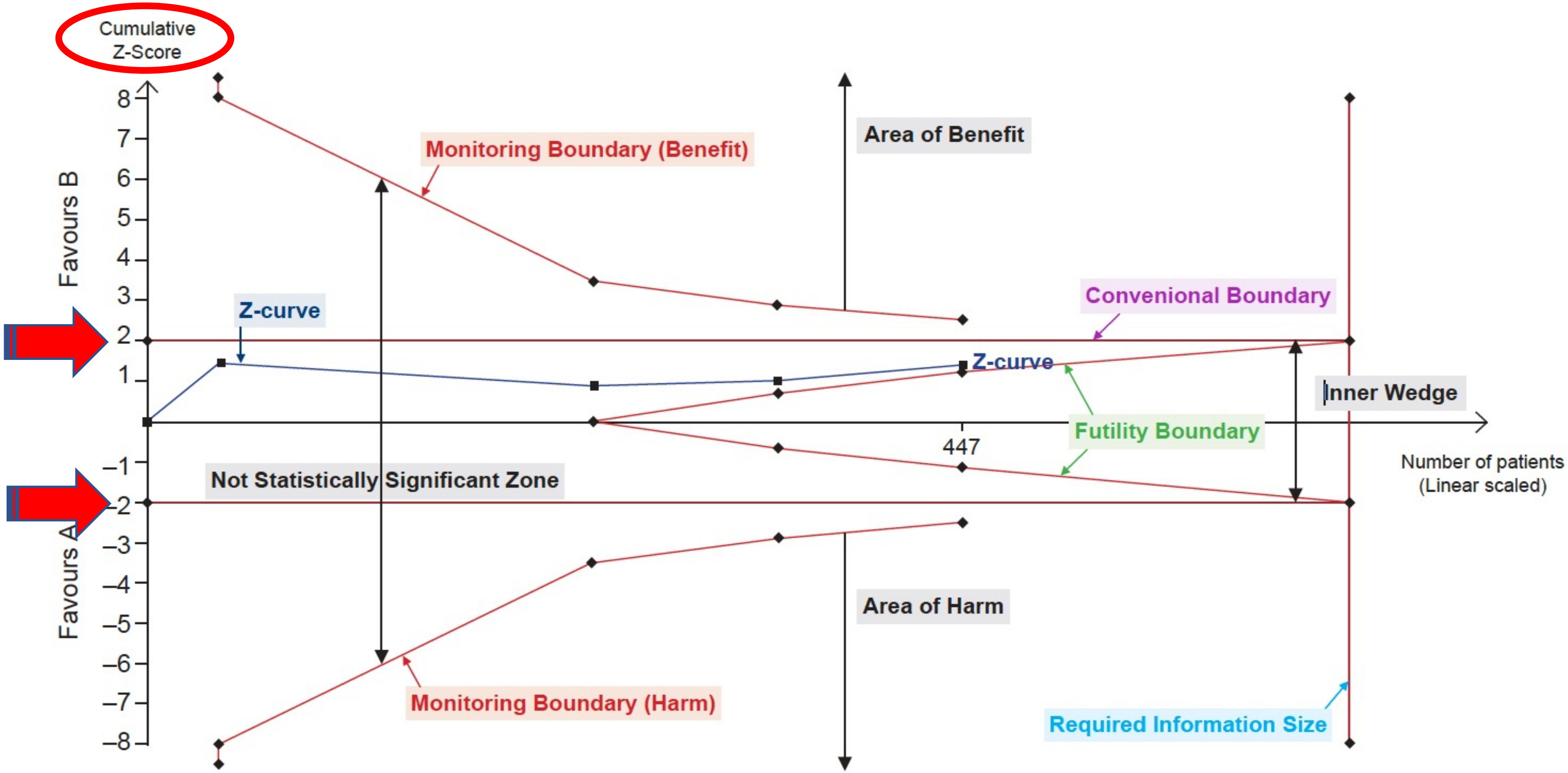



Anesth Pain Med 2021;16:138-150
Transfusion 2016;56;2918–2922

# Definition of terms used in TSA

| Term | Definition |
|---|---|
| Z score | A statistic test under the null hypothesis ($H_0$) that two interventions do not differ. |
| Cumulative Z curve | The series of Z scores plotted every time when a meta-analysis is updated. Z curve is plotted with respect to the time the new information is added (X axis). |
| Conventional meta-analysis significance boundaries | The horizontal dashed lines at Z +1.96 and −1.96 represent significant threshold given the Type I error is equal to 5% (two-sided test). The cumulative Z curve that crosses this dashed line is considered significant effect (corresponding to $p < 0.05$) in conventional meta-analysis (unadjusted significant test). |
| Trial sequential boundaries (significance and futility boundaries) | The converged dot lines represent trial sequential boundaries (significance boundaries). The diverged dot lines represent futility boundaries. Both are adjustments to the thresholds for statistically concluding superiority or nonsuperiority and that these adjustments are made in such a way that the total Type I error (false-positive test %) and the total Type II error (false-negative test %) remain at the level prescribed in the sample size calculation once the total evidence-base reaches the calculated required sample size. |
| Required meta-analysis sample size | The vertical dot line represents required meta-analysis sample size. This sample size threshold is calculated to determine whether individual meta-analysis is able to make a conclusive inference or not. |

TRANSFUSION 2016;56;2918–2922




**Z score**:

A statistic test under the null hypothesis (H0) that two interventions do not differ.

Anesth Pain Med 2021;16:138-150
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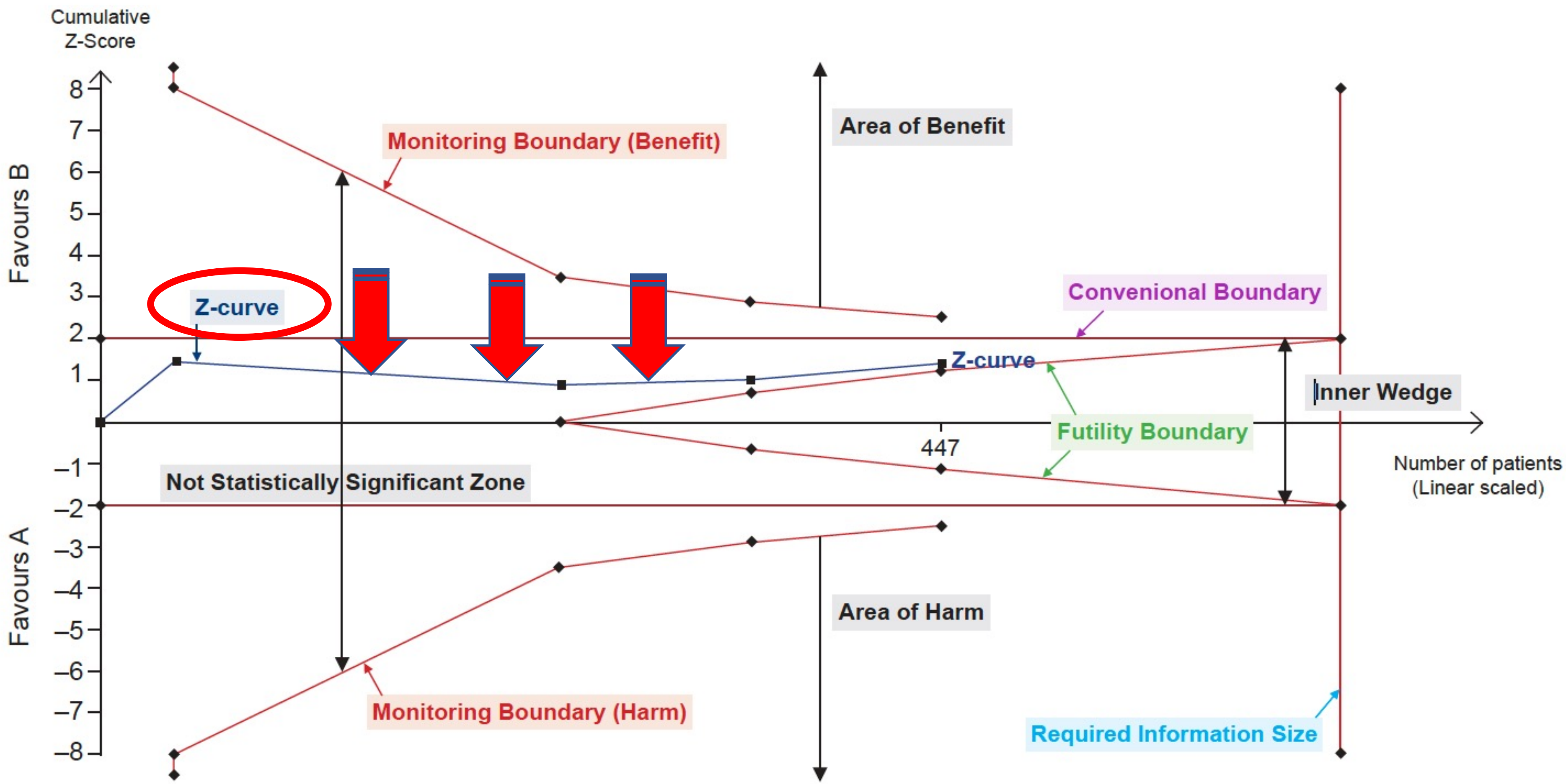


## Cumulative Z curve:

The series of Z scores plotted every time when a meta-analysis is updated.

Z curve is plotted with respect to the time the new information is added (X axis).

Anesth Pain Med 2021;16:138-150
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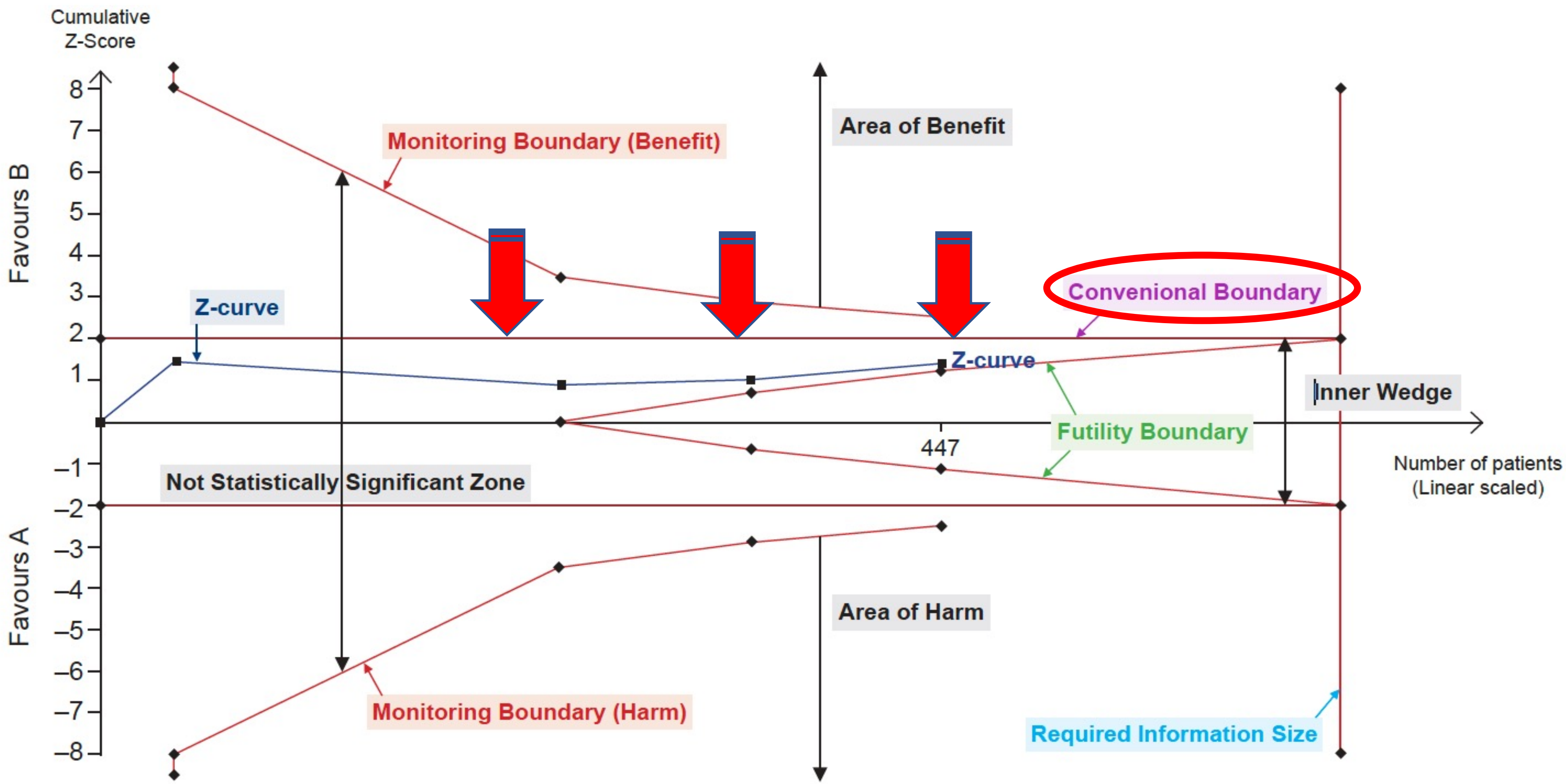
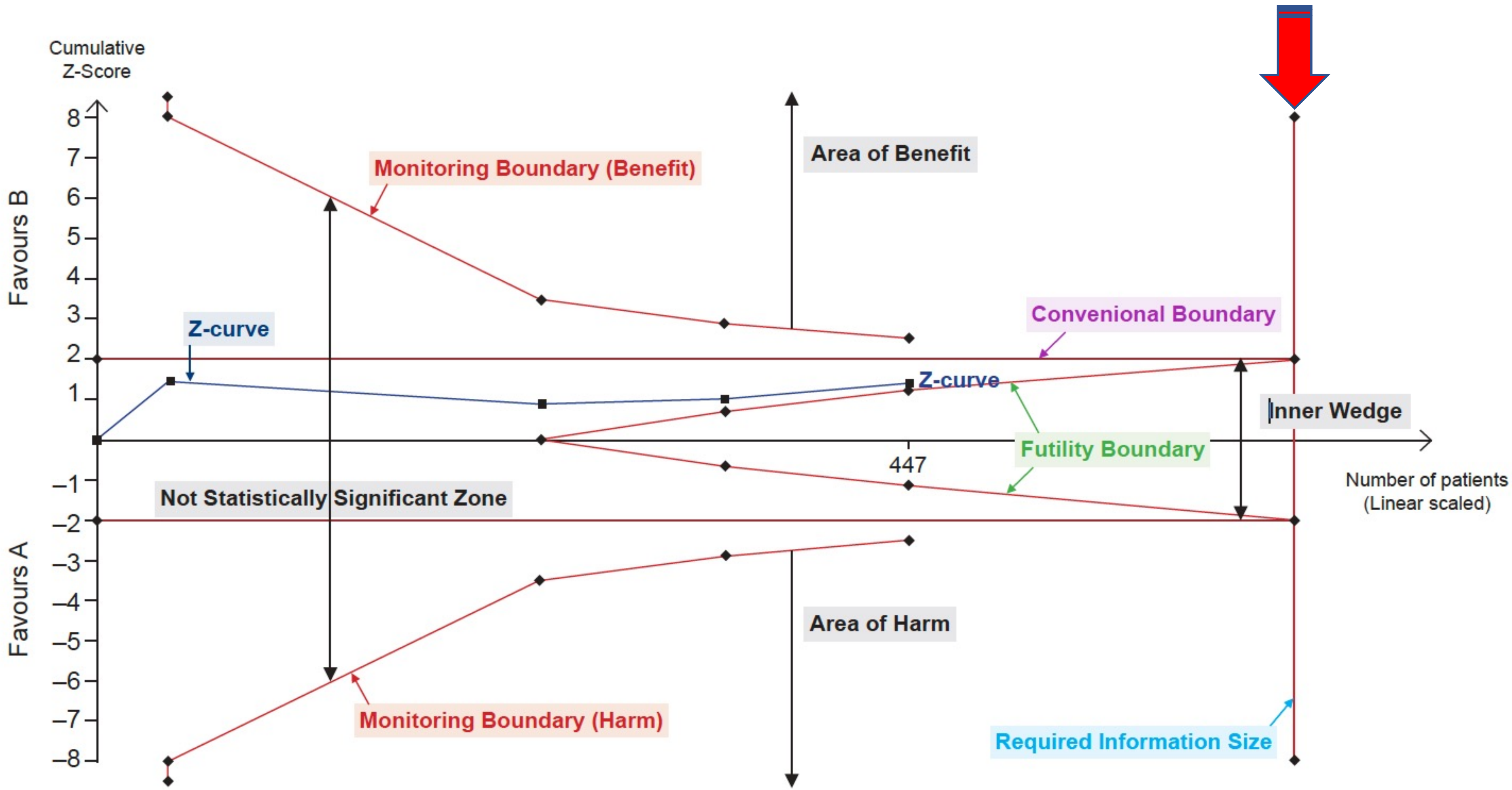



## Conventional meta-analysis significance boundaries :

The horizontal dashed lines at Z + 1.96 and - 1.96 represent significant threshold given the Type I error is equal to 5% (two-sided test).

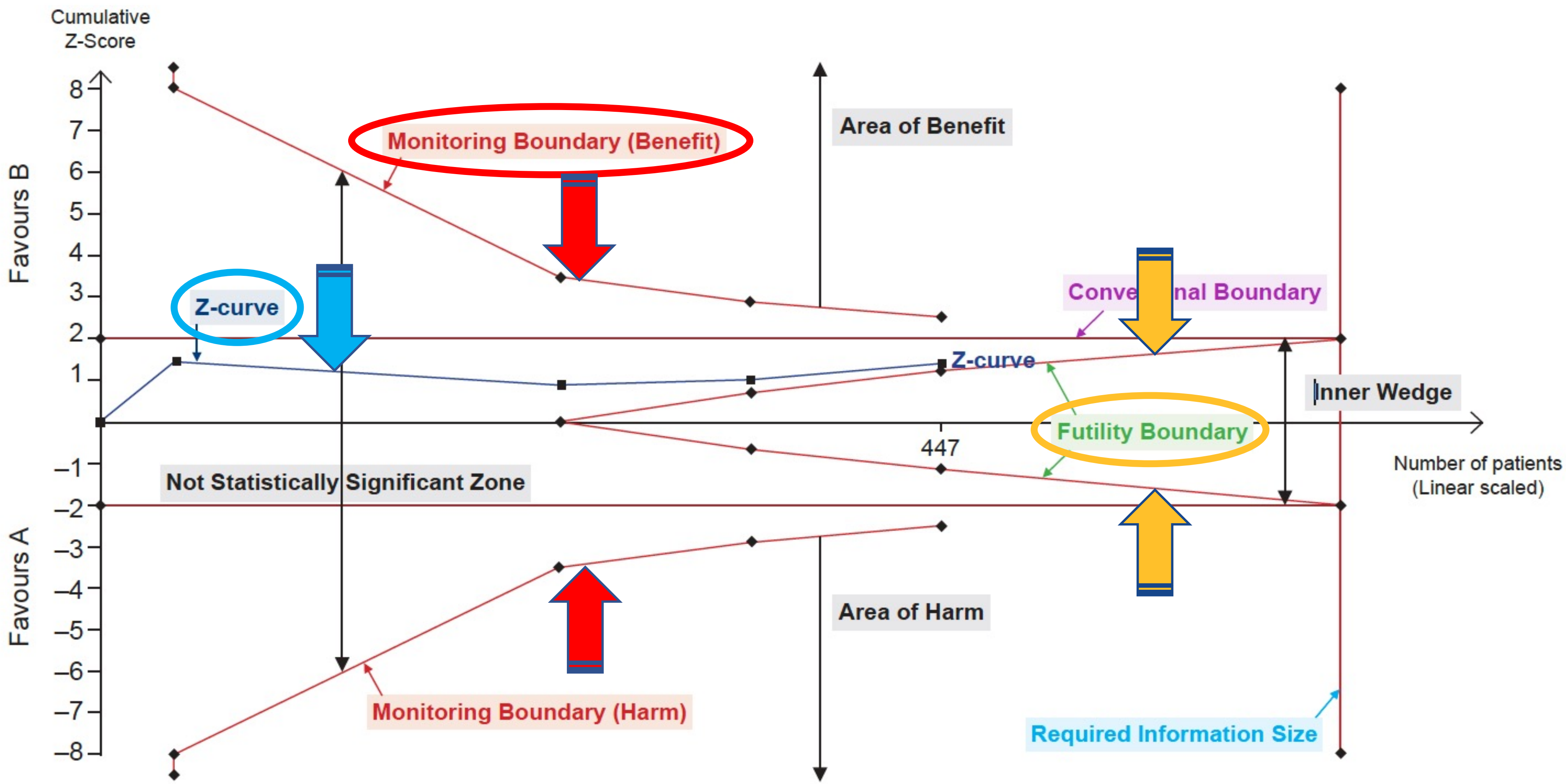
The cumulative Z curve that crosses this dashed line is considered significant effect (corresponding to $p < 0.05$) in conventional meta-analysis (unadjusted significant test).

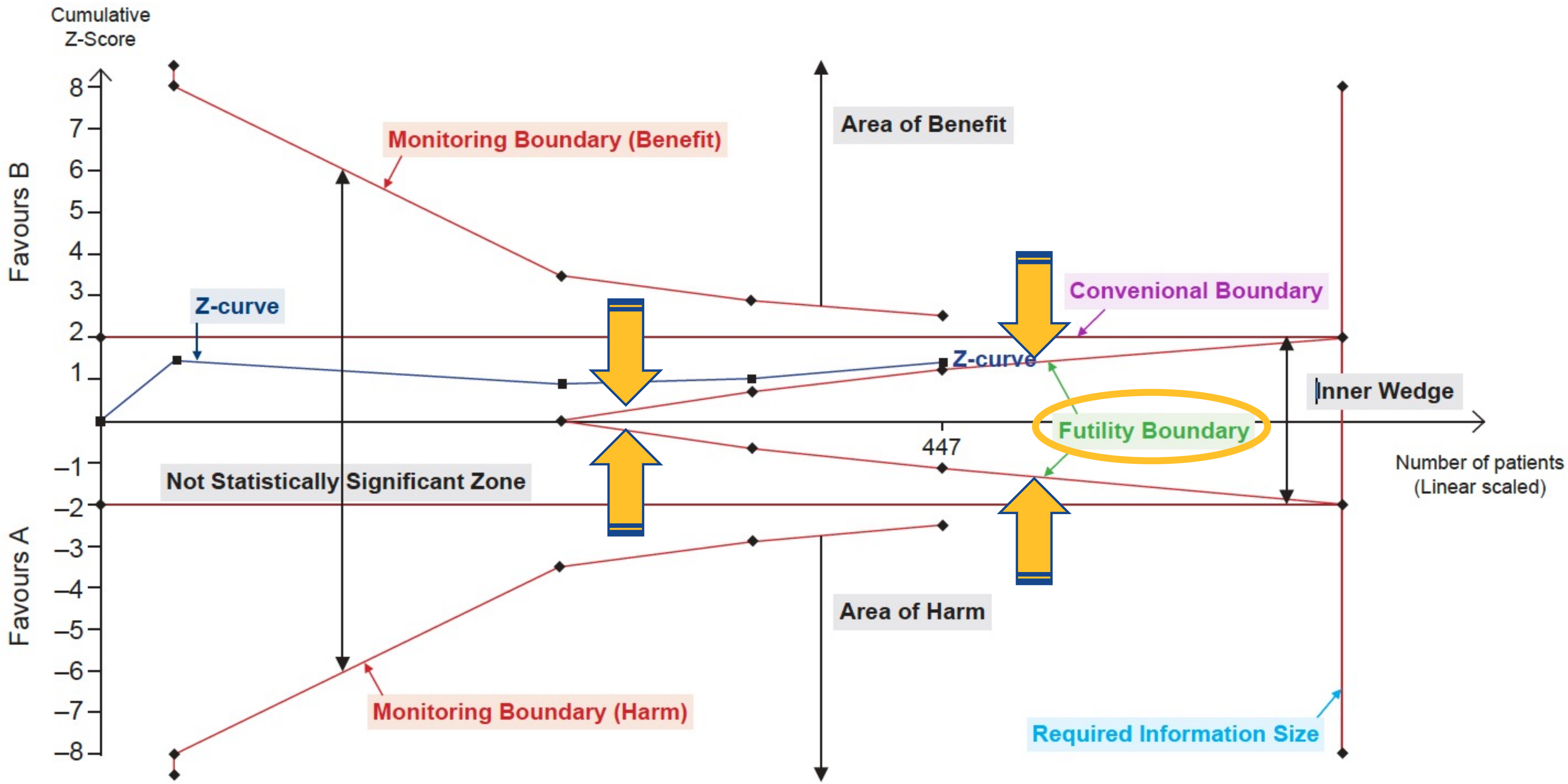



## Required information size:

- The number of participants and events necessary to detect or reject an a priori assumed intervention effect in a meta-analysis
- The calculation is performed considering the variability (heterogeneity variance) between the estimates of the intervention effects of the included trials.


Anesth Pain Med 2021;16:138-150
Transfusion 2016;56;2918–2922

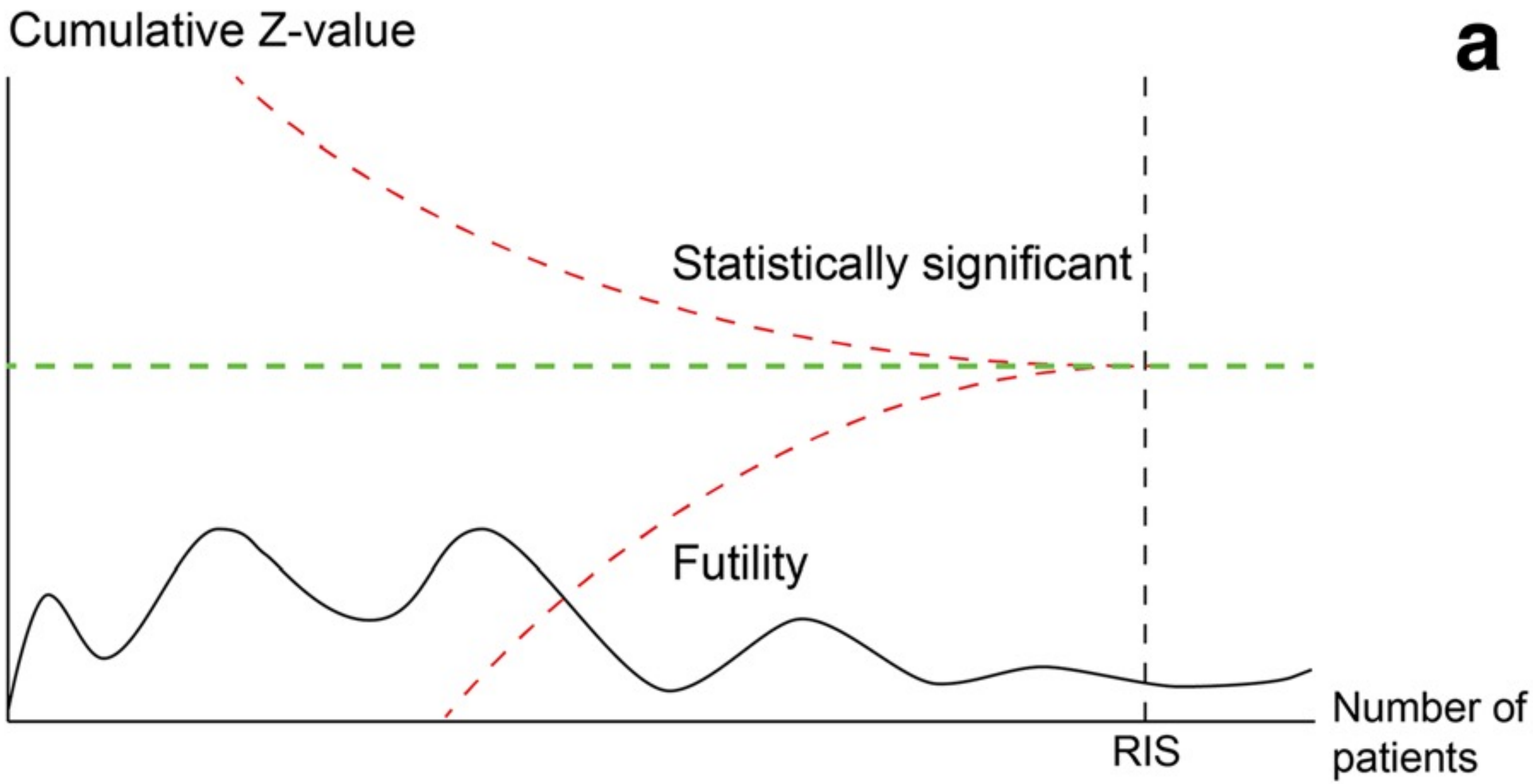

Cumulative Z-Score
Favours B
Favours A
8
7
6
5
4
3
2
1
–1
–2
–3
–4
–5
–6
–7
–8
Monitoring Boundary (Benefit)
Area of Benefit
Z-curve
Conventional Boundary
Z-curve
Inner Wedge
Futility Boundary
447
Number of patients
(Linear scaled)
Not Statistically Significant Zone
Area of Harm
Monitoring Boundary (Harm)
Required Information Size



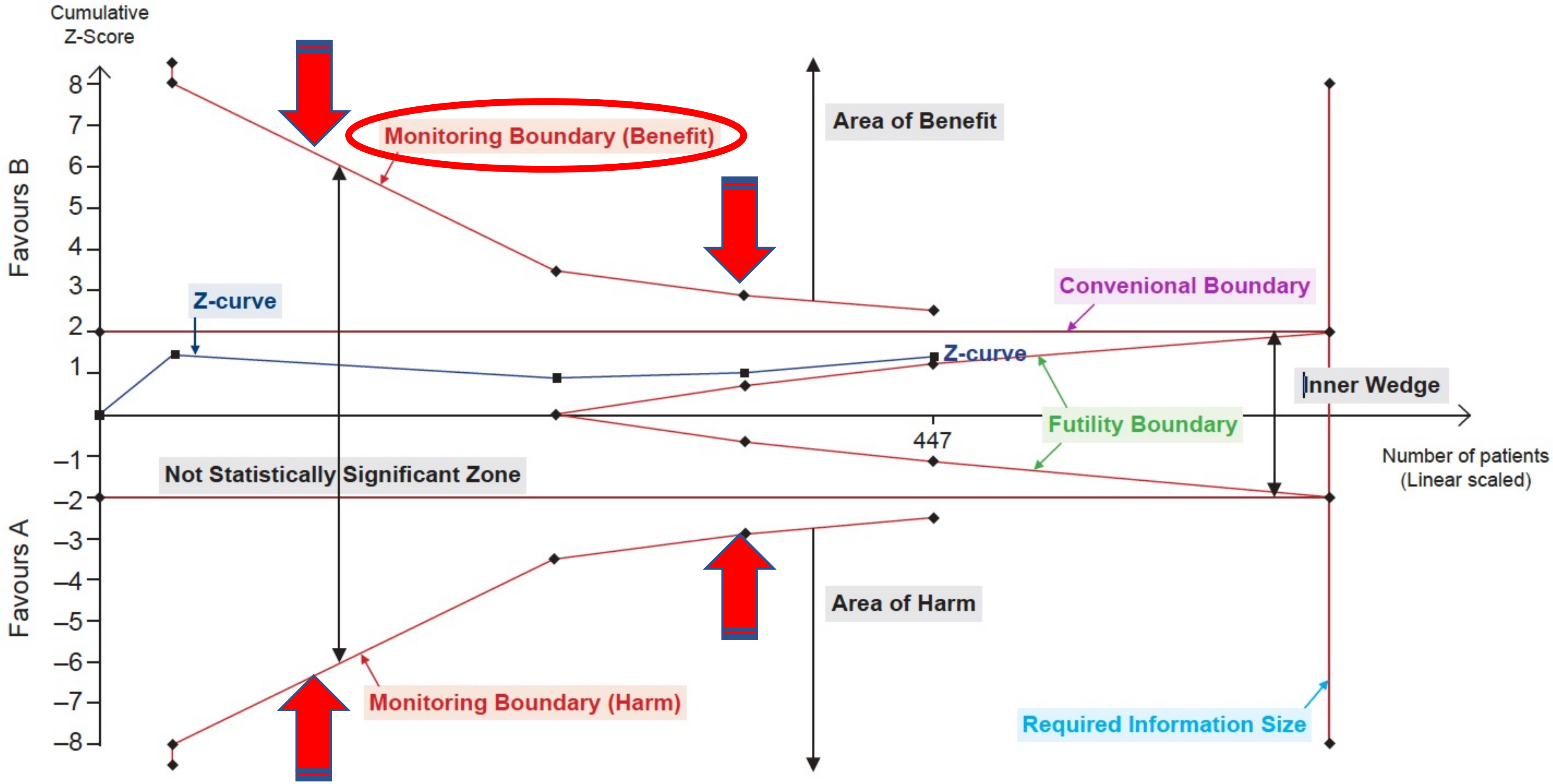

# Futility boundaries:

indicating that it will be unlikely to reach a statistical significant P < 0.05, even if we proceed to include trials randomizing patients until the required information size of 2040 is reached.

# Trial sequential monitoring boundaries for futility



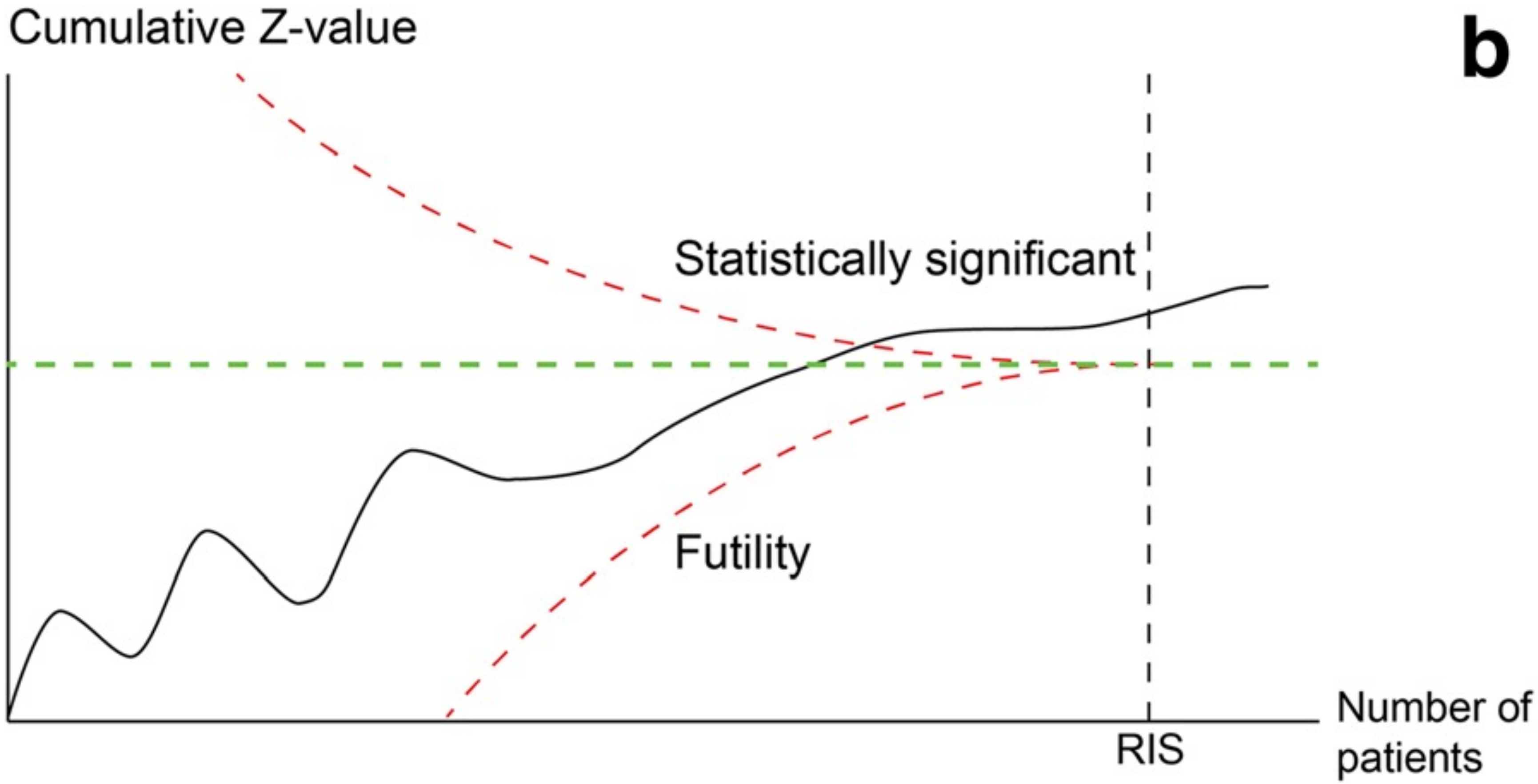

Wetterslev et al. BMC Medical Research Methodology (2017) 17:39




# Monitoring boundaries:

The cumulative Z curve that is greater than the trial sequential boundary is considered a significant effect.

# Trial sequential monitoring boundaries for benefit

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frontiers in Neurology

SYSTEMATIC REVIEW
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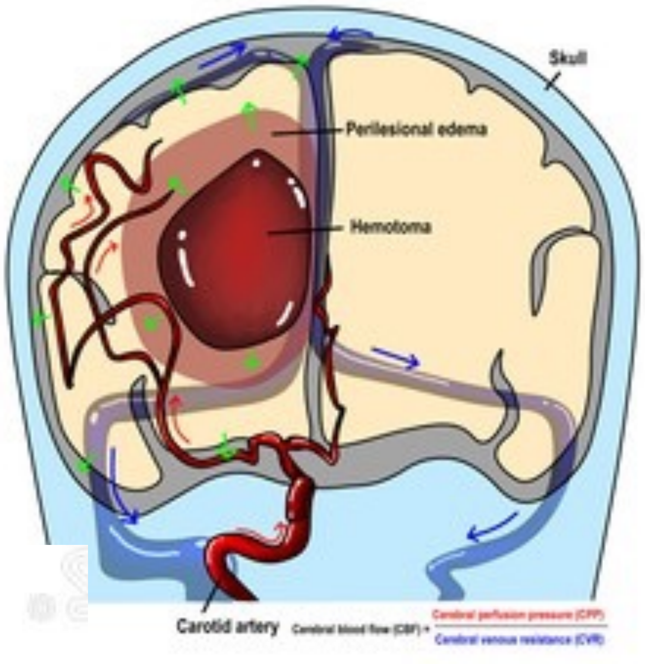
doi: 10.3389/fneur.2020.00426

# Assessment of Evidence Regarding Minimally Invasive Surgery vs. Conservative Treatment on Intracerebral Hemorrhage: A Trial Sequential Analysis of Randomized Controlled Trials

*Xiang Zhou[1†], Li Xie[2†], Yuksel Altinel[3] and Nidan Qiao[1,4,5*]*

# Introduction

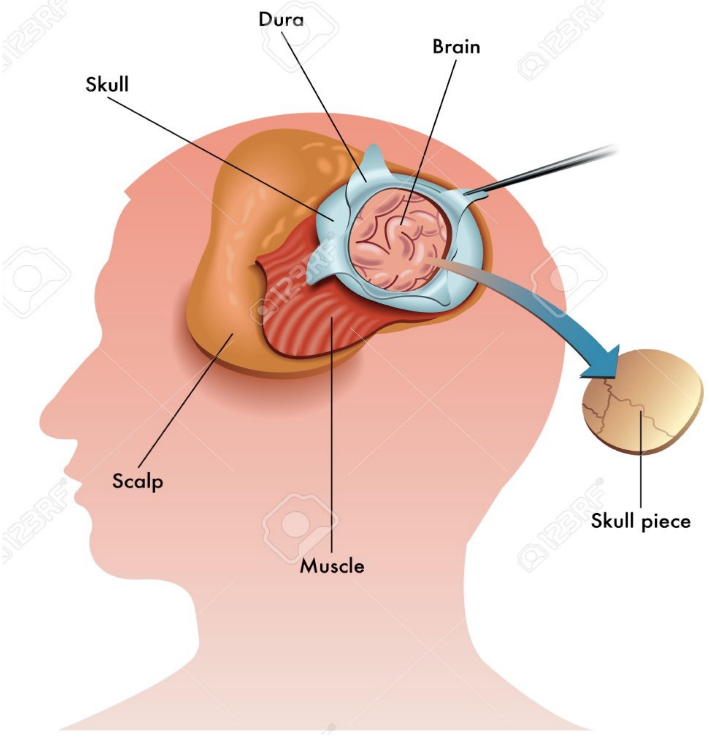
- Stroke contributes 5% to all DALYs loss and 10% to all deaths worldwide
- Hemorrhagic stroke accounts for more DALYs loss than ischemic stroke



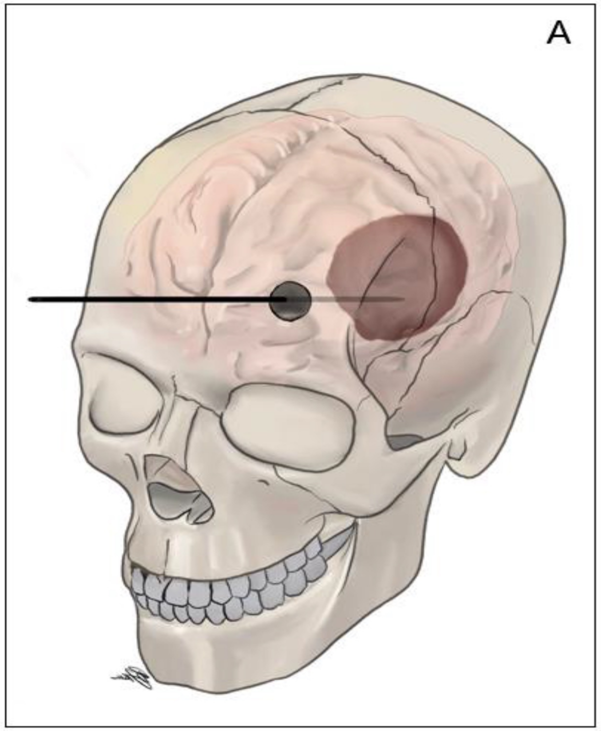



# Introduction

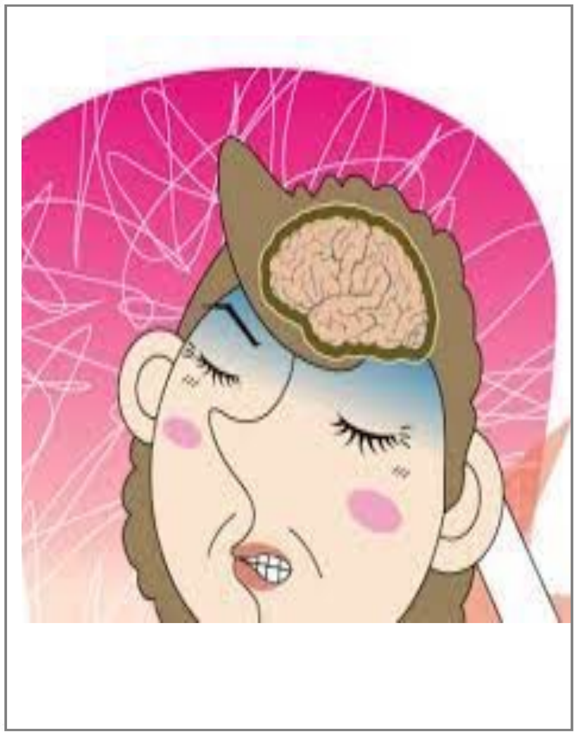
- Several randomized trials failed to prove effectiveness of surgical evacuation of hemorrhage
- More and more patients were treated with these minimally invasive surgeries, but benefit by MIS were controversial




Craniotomy




Minimally invasive surgery



Conservative treatment

# Introduction

**TABLE 2 |** Summary of previous published meta-amylases on the similar topic.

| References | Treatment | Control | Included studies | Primary outcomes | Limits | Conclusion |
|---|---|---|---|---|---|---|
| Zhou et al. (9) | MIS | Conservative treatment or craniotomy | RCT | Death or dependence | The selection of MIS in Zuccarello Mendelow studies was biased; mixture control | MIS better |
| Akhigbe et al. (8) | MIS | Conservative treatment | RCT | Mortality | The selection of MIS in Zuccarello study was biased; only include five studies | Inconclusive |
| Yao et al. (7) | Endoscope | Stereotactic evacuation, conservative treatment or craniotomy | RCT + non-RCT | Mortality | Biased due to non-randomized studies; mixture control | Endoscope better |
| Xia et al. (6) | MIS | Craniotomy | RCT + non-RCT | Mortality | Biased due to non-randomized studies | MIS better |
| Tang et al. (5) | MIS | Conservative treatment or craniotomy | RCT + non-RCT | Death or dependence | Only include Eastern Asian patients; biased due to non-randomized studies; mixture control | MIS better |
| Scaggiante et al. (10) | MIS | Conservative treatment or craniotomy | RCT | Death or dependence | The selection of MIS in Zuccarello studies was biased; mixture control | MIS better |

*MIS, Minimal invasive surgery; RCT, randomized control trial.*

**Previous SR and MA of MIS**

- potential confounding and bias
- different outcome measurements and control group selections

# MISTIE-III

THE LANCET

ARTICLES | VOLUME 393, ISSUE 10175, P1021-1032, MARCH 09, 2019

Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial

Prof Daniel F Hanley, MD * • Richard E Thompson, PhD * • Michael Rosenblum, PhD • Gayane Yenokyan, PhD * • Karen Lane, CMA * • Nichol McBee, MPH * • et al. Show all authors • Show footnotes

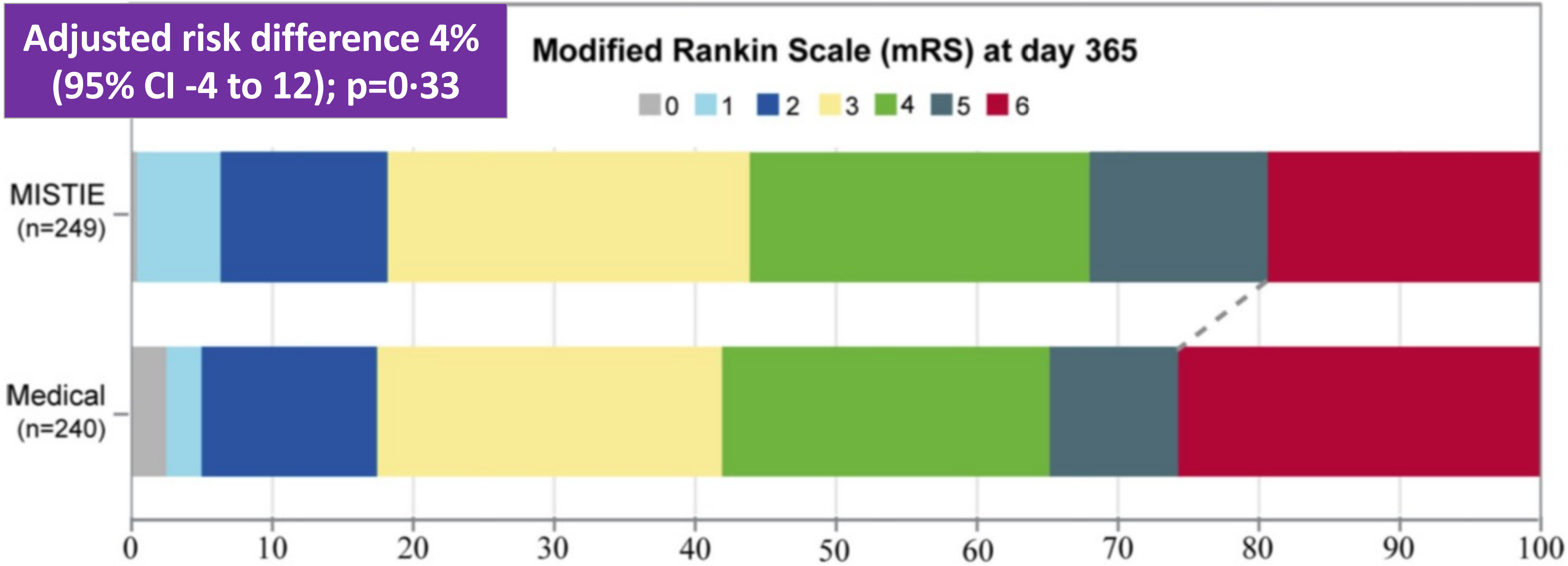
| | |
|---|---|
| **P** | **Patients with intracerebral hemorrhage** |
| **I** | **Minimally invasive catheter evacuation followed by thrombolysis (MISTIE)** |
| **C** | **Standard medical care** |
| **O** | **Good functional outcome (mRS 0-3) at 365 days** |

Lancet. 2019 Mar 9;393(10175):1021-1032.

# MISTIE-III

| | |
|---|---|
| **P** | **Patients with intracerebral hemorrhage** |
| **I** | **Minimally invasive catheter evacuation followed by thrombolysis (MISTIE)** |
| **C** | **Standard medical care** |
| **O** | **Good functional outcome (mRS 0-3) at 1 year** |

**Adjusted risk difference 4% (95% CI -4 to 12); p=0·33**

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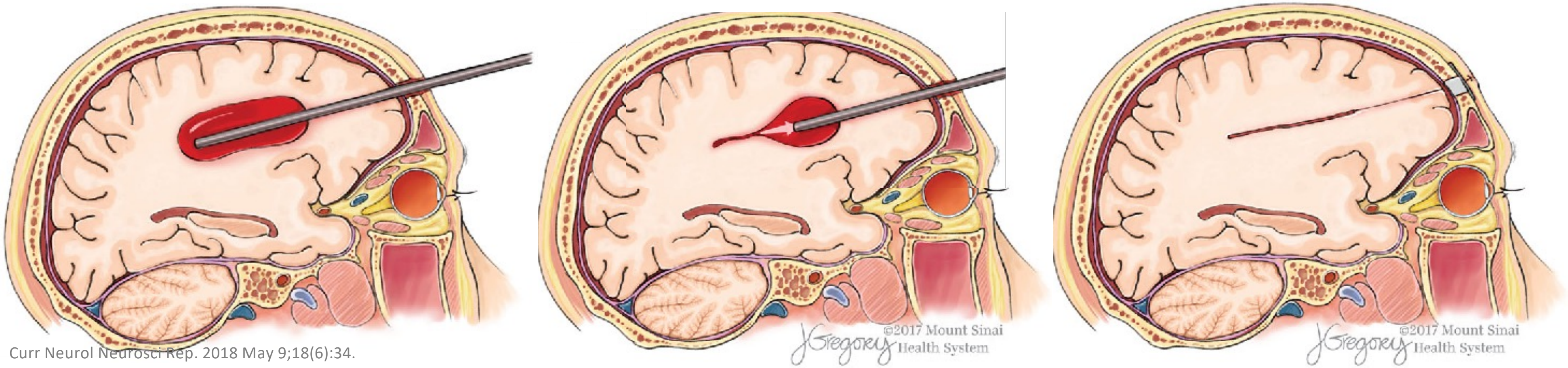



Curr Neurol Neurosci Rep. 2018 May 9;18(6):34.

# Assessment of Evidence Regarding Minimally Invasive Surgery vs. Conservative Treatment on Intracerebral Hemorrhage: A Trial Sequential Analysis of Randomized Controlled Trials

*Xiang Zhou [1†], Li Xie [2†], Yuksel Altinel [3] and Nidan Qiao [1,4,5*]*

Front Neurol. 2020 Jun 4;11:426

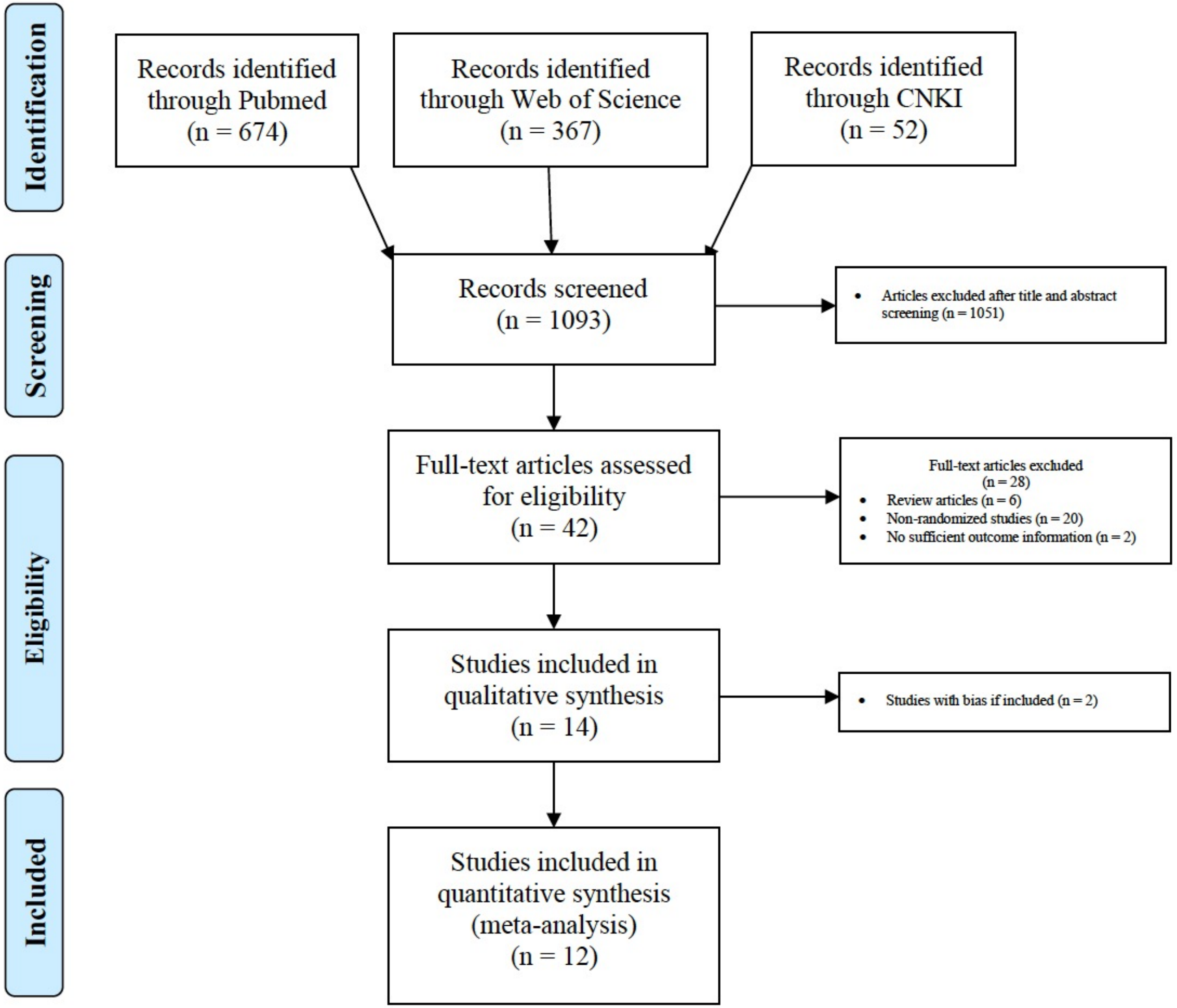
# Objective

To answer the question:

**Do we need more trials to compare MIS vs. conservative treatment in patients with intracerebral hemorrhage?**

# METHODS

# Search Strategy and Selection Criteria

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| | |
|---|---|
| **P** | Patients with intracerebral hemorrhage |
| **I** | Minimally invasive surgery (MIS) |
| **C** | Conservative treatment |
| **O** | Significant neurological debilitation or death |

# METHODS

# Detailed search strategy

| | |
|---|---|
| Pubmed | ("intracerebral hemorrhage" or "intracranial hemorrhage" or "cerebral hemorrhage" or "brain hemorrhage" or "basal ganglia hemorrhage" or "thalamic hemorrhage" or "hemorrhagic stroke" and "hemorrhage" or "hematoma") and ("minimally invasive" or "minimal surgical procedures" or "endoscopy" or "endoscopic" or "stereotaxic" or "stereotactic" or "aspiration" or "keyhole" or "craniopuncture" or "surgery")<br>Filters: **Randomized Controlled Trial** |
| Web of Science/CNKI | TS("intracerebral hemorrhage" or "intracranial hemorrhage" or "cerebral hemorrhage" or "brain hemorrhage" or "basal ganglia hemorrhage" or "thalamic hemorrhage" or "hemorrhagic stroke" and "hemorrhage" or "hematoma")<br>AND<br>TS=("minimally invasive" or "minimal surgical procedures" or "endoscopy" or "endoscopic" or "stereotaxic" or "stereotactic" or "aspiration" or "keyhole" or "craniopuncture" or "surgery") |

**Exclusion criteria:**

- Studies with brain hemorrhage due to traumatic brain injury, tumor, coagulopathy, or vascular disease
- Studies with both craniotomy and MIS, but the decision of craniotomy or MIS was made at the discretion of surgeons
- Nonrandomized studies
- Trials in which outcome information was not available

# METHODS
# Outcomes

**1º outcome:**

proportion of patients with significant neurological debilitation or death (mRS >3 or GOS <4) at the postrandomization follow-up

**2º outcome:**

proportion of patients who died at the postrandomization follow-up

- Regarding crossover in the included trials, we used the intention-to-treat effect.
- We also imputed the loss to follow-up data as the worst outcome.

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# METHODS
## Data Extraction

- X.Z. and L.X. independently screened the literature, selected studies, extracted the relevant information, and assessed the risk of bias with the Cochrane risk of bias tool.
- Any controversies were resolved by consensus and arbitration by the entire review team.

# METHODS
## Data Synthesis and Statistical Methods

- A conventional MA was used to pool risk ratios comparing MIS with conservative treatment
- We initially used random-effects models to aggregate data and the $I^2$ tests to examine heterogeneity
- Subgroup analysis by
  - Different mean ages (<60 or >60 years old)
  - Follow-up period ( ≤ 1 year)
  - Study quality (blind or unblind outcome assessment
  - Publication year (before 2010 or after 2010)
  - Study location (Eastern Asia or Western)
  - Surgical modality (endoscopic surgery or stereotactic evacuation)

# METHODS
# Trial sequential analysis

- We conducted a TSA assuming 5% as an acceptable risk of type I error (α).

**We set several prior to the TSA:**

1) Effect size: 18.8% RRR as a priori (from the conventional MA)
2) Statistical power: 80%
3) Event proportion in the control arm: 67.4% (from the pooled 1$^{o}$ outcome from all the control groups)
4) Amount of heterogeneity: 81.9% as the observed diversity across the included trials

# METHODS
## Sensitivity analyses

1. We used more conservative analyses prior, such as a
    - reduced risk reduction (15 and 10%)
    - increased power (90%)
    - decreased event proportion in the control arm (58%) according to the most recent trial
2. We repeated the analysis only in trials with high quality (blind outcome assessment).
3. We further assumed the result of the ongoing RCT (NCT02880878) to be futile to discern the impact on the analysis.

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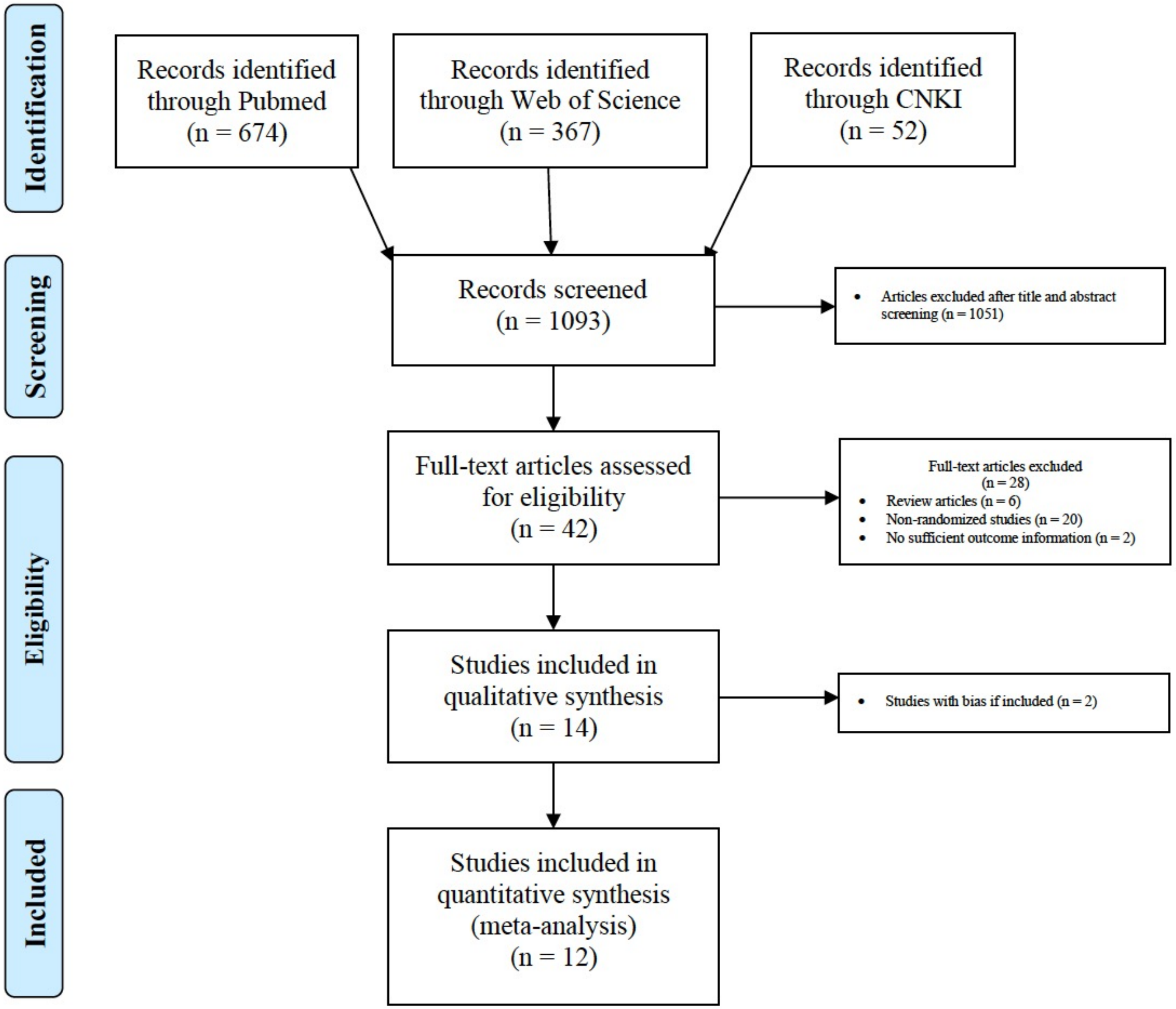
# METHODS

Statistical analyses were performed with RStudio version 1.0.143 (Boston, MA) for the conventional meta-analysis and Trial Sequential Analysis software 0.9 (Copenhagen Trials Unit, Copenhagen, Denmark) for the TSA.

# RESULTS

# PRISMA flow chart

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# Characteristics of included studies

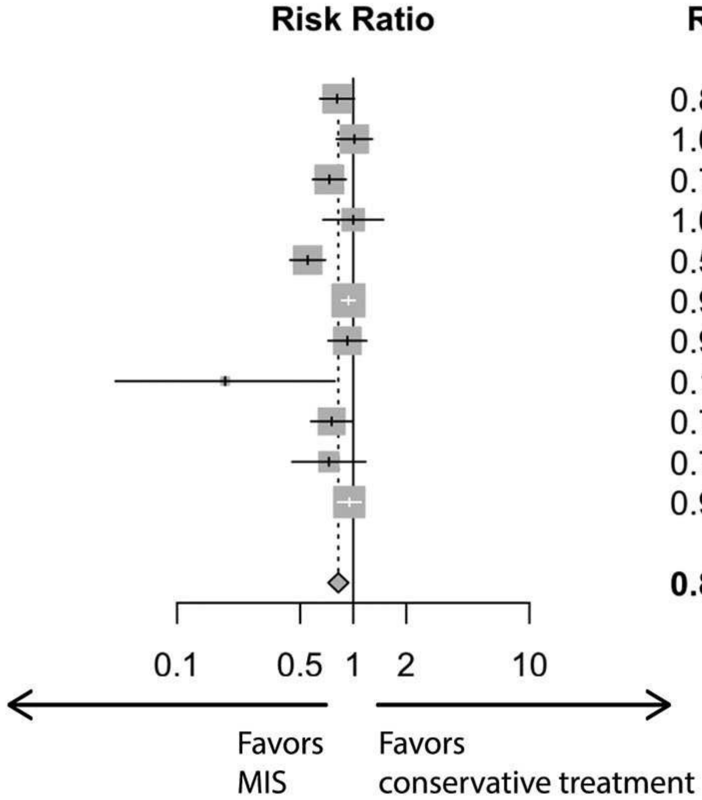
| Year | Author | Location | Treatment/control (Male: Female) | Age | Treatment | Outcome | Results |
|---|---|---|---|---|---|---|---|
| 1989 | Auer | Graz, Australia | 50(28:22)/50(33:17) | 46.1 | Endoscope | 6 months mRS | Futile |
| 2003 | Teernstra | Maastricht, Netherland | 36(19:17)/34(21:13) | 68.0 | Stereotactic evacuation + urokinase | 6 months mRS | Futile |
| 2004 | Hattori | Tokyo, Japan | 121(71:50)/121(77:44) | 60.5 | Stereotactic evacuation | 12 months ADL | Superior |
| 2008 | Luo | Guangzhou, China | 36(21:15)/39(23:16) | 55.3 | Stereotactic evacuation + urokinase | 6 months ADL | Superior |
| 2008 | Miller | Los Angeles, USA | 6(6:0)/4(3:1) | 59.0 | Endoscope | 3 months mRS | Futile |
| 2009 | Kim | Masan, Korea | 204(257:47)/183(132:51) | 65.8 | Stereotactic evacuation | 6 months mRS | Superior |
| 2009 | Wang | Beijing, China | 195(114:81)/182(122:60) | 56.7 | Stereotactic evacuation + urokinase | 14 days mRS | Superior |
| 2010 | Wei | Sichuan, China | 36(19:17)/39(22:17) | 57.0 | Stereotactic evacuation | 3 months GOS | Superior |
| 2011 | Wang | Tianjin, China | 32(18:14)/30(16:14) | 46.0 | stereotactic evacuation + urokinase | 6 months ADL | Superior |
| 2016 | Hanley | Multicenter | 54(35:19)/42(28:14) | 60.9 | Stereotactic evacuation + urokinase | 12 months mRS | Futile |
| 2016 | Vespa | Multicenter | 14(9:5)/42(28:14) | 61.0 | Endoscope | 12 months mRS | Futile |
| 2019 | Hanley | Multicenter | 250(159:91)/249(146:103) | 62.0 | Stereotactic evacuation + alteplase | 12 months mRS | Futile |

mRS: modified Rankins Score; ADL: Activities of Daily Living; GOS: Glasgow outcome scale

# Conventional meta-analysis

| Study | Experimental Events | Experimental Total | Control Events | Control Total | RR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|
| Auer 1989 | 34 | 50 | 42 | 50 | 0.81 | [0.65; 1.01] | 10.5% |
| Teernstra 2003 | 29 | 36 | 27 | 34 | 1.01 | [0.80; 1.28] | 10.3% |
| Hattori 2004 | 60 | 121 | 82 | 121 | 0.73 | [0.59; 0.91] | 10.7% |
| Miller 2008 | 6 | 6 | 4 | 4 | 1.00 | [0.67; 1.48] | 6.4% |
| Kim 2009 | 67 | 204 | 109 | 183 | 0.55 | [0.44; 0.69] | 10.4% |
| Wang 2009 | 159 | 195 | 158 | 182 | 0.94 | [0.86; 1.03] | 14.2% |
| Wei 2010 | 25 | 33 | 27 | 33 | 0.93 | [0.72; 1.19] | 9.8% |
| Wang 2011 | 2 | 32 | 10 | 30 | 0.19 | [0.04; 0.79] | 0.8% |
| Hanley 2016 | 32 | 54 | 33 | 42 | 0.75 | [0.57; 0.99] | 9.2% |
| Vespa 2016 | 8 | 14 | 33 | 42 | 0.73 | [0.45; 1.18] | 5.1% |
| Hanley 2019 | 138 | 249 | 140 | 240 | 0.95 | [0.81; 1.11] | 12.6% |
| **Random effects model** | | **994** | | **961** | **0.82** | **[0.72; 0.94]** | **100.0%** |

Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.0301$, $p < 0.01$

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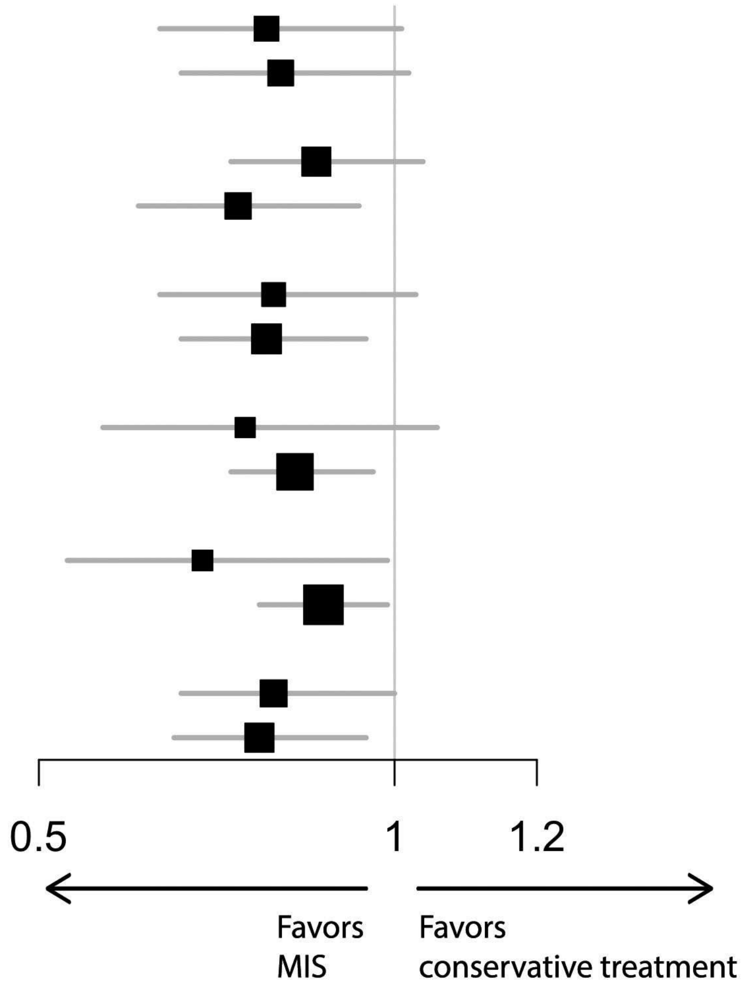
# Subgroup analysis in conventional MA

| | Sample size | Risk ratio [95% CI] |
|---|---|---|
| Publication year | | |
| before or at 2010 | 1186 | 0.82[0.67-1.01] |
| after 2010 | 769 | 0.84[0.70-1.02] |
| Mean age | | |
| less than or euqal to 60 | 605 | 0.89[0.77-1.04] |
| more than 60 | 1340 | 0.78[0.64-0.95] |
| Follow-up | | |
| 3 or 6 months | 1072 | 0.83[0.67-1.03] |
| 12 months | 883 | 0.82[0.70-0.96] |
| Outcome assessment | | |
| Unblind | 695 | 0.79[0.59-1.06] |
| Blind | 1260 | 0.86[0.77-0.97] |
| Study location | | |
| Eastern Asia | 1134 | 0.73[0.54-0.99] |
| Western | 821 | 0.90[0.81-0.99] |
| Surgical modality | | |
| Endoscope | 166 | 0.83[0.70-1.00] |
| Stereotactic evacuation | 1789 | 0.81[0.69-0.96] |

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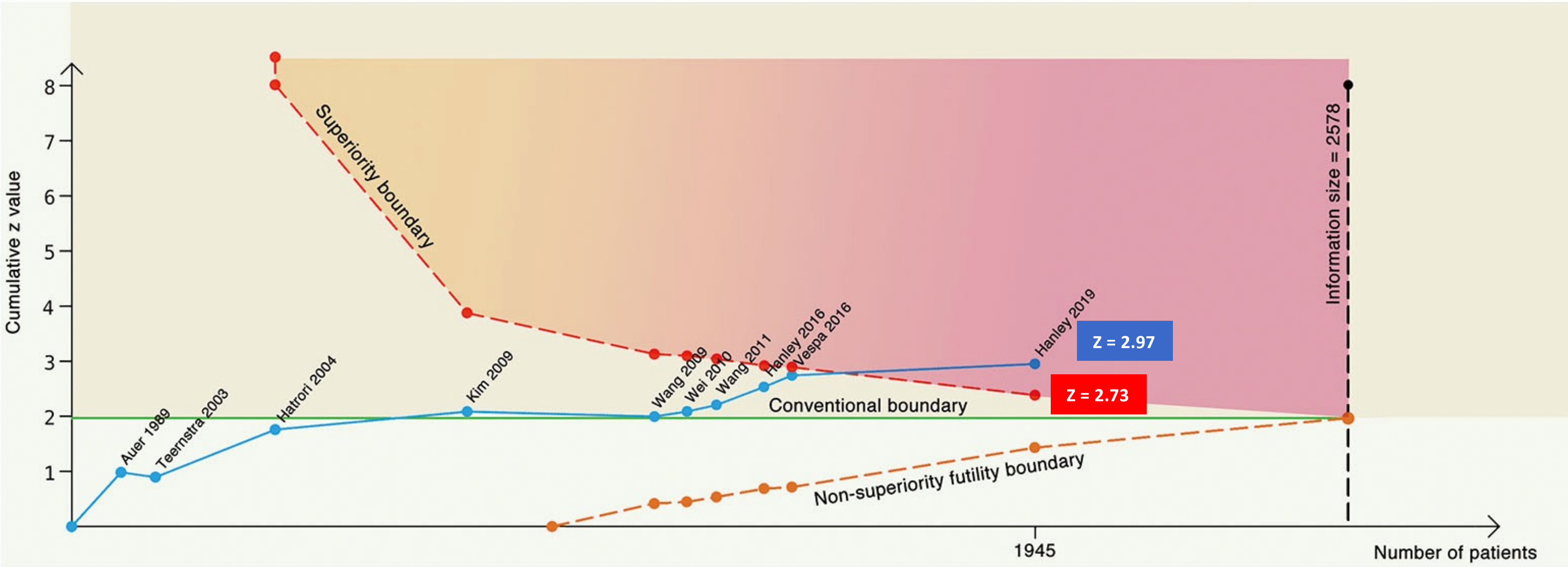
# Trial sequential analysis

## with α = 5%, β = 80% to detect 18.8% RRR

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# TSA on 1º and 2º outcome with different prior

| | Relative risk reduction | Power | Incidence in the control | Heterogeneity (diversity) | Information size | Risk ratio | Boundary | Explanation |
|---|---|---|---|---|---|---|---|---|
| **(A) TRIAL SEQUENTIAL ANALYSIS ON PRIMARY OUTCOME (PROPORTION OF PATIENTS WITH MODIFIED rANKIN SCORE > 3)** | | | | | | | | |
| Conventional meta-analysis with random-effects model | | | | | | 0.82 (0.72–0.94) | | |
| TSA | 18.8 (Estimated) | 80% | 67.4% | 81.9% (Estimated) | 2578, not reached | 0.81 (0.69–0.96) | Superiority crossed | MIS better |
| | 15 | 80% | 67.4% | 81.9% (Estimated) | 3994, not reached | 0.81 (0.66–1.01) | Superiority nearly cross | Inconclusive |
| | 10 | 80% | 67.4% | 81.9% (Estimated) | 8807, not reached | 0.81 (0.65–1.02) | Superiority not crossed | Inconclusive |
| | 18.8 (Estimated) | 90% | 67.4% | 81.9% (Estimated) | 3452, not reached | 0.81 (0.67–0.99) | Superiority crossed | MIS better |
| | 18.8 (Estimated) | 80% | 58.0% (Latest study) | 81.9% (Estimated) | 4885, not reached | 0.81 (0.66–1.00) | Superiority crossed | MIS better |
| **(B) TRIAL SEQUENTIAL ANALYSIS ON SECONDARY OUTCOME (MORTALITY)** | | | | | | | | |
| Conventional meta-analysis with fix-effects model | | | | | | 0.76 (0.64–0.89) | | |
| TSA | 24.3 (Estimated) | 80% | 25.3% | 0.0% (Estimated) | 1435, reached | 0.76 (0.63–0.90) | Superiority crossed | MIS better |
| | 20 | 80% | 25.3% | 0.0% (Estimated) | 2157, not reached | 0.76 (0.63–0.91) | Superiority crossed | MIS better |
| | 15 | 80% | 25.3% | 0.0% (Estimated) | 3898, not reached | 0.76 (0.61–0.94) | Superiority crossed | MIS better |
| | 10 | 80% | 25.3% | 0.0% (Estimated) | 8956, not reached | 0.76 (0.60–0.96) | Superiority crossed | MIS better |
| | 24.3 (Estimated) | 90% | 25.3% | 0.0% (Estimated) | 1921, reached | 0.76 (0.62–0.93) | Superiority crossed | MIS better |
| | 24.3 (Estimated) | 80% | 25.3% | 30.0% | 2050, not reached | 0.76 (0.64–0.90) | Superiority crossed | MIS better |

*MIS, Minimal invasive surgery; TSA, Trial sequential analysis.*

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# TSA on 1º and 2º outcome with different prior

| | Relative risk reduction | Power | Incidence in the control | Heterogeneity (diversity) | Information size | Risk ratio | Boundary | Explanation |
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| **(A) TRIAL SEQUENTIAL ANALYSIS ON PRIMARY OUTCOME (PROPORTION OF PATIENTS WITH MODIFIED rANKIN SCORE > 3)** | | | | | | | | |
| Conventional meta-analysis with random-effects model | | | | | | 0.82 (0.72–0.94) | | |
| TSA | 18.8 (Estimated) | 80% | 67.4% | 81.9% (Estimated) | 2578, not reached | 0.81 (0.69–0.96) | Superiority crossed | MIS better |
| | 15 | 80% | 67.4% | 81.9% (Estimated) | 3994, not reached | 0.81 (0.66–1.01) | Superiority nearly cross | Inconclusive |
| | 10 | 80% | 67.4% | 81.9% (Estimated) | 8807, not reached | 0.81 (0.65–1.02) | Superiority not crossed | Inconclusive |
| | 18.8 (Estimated) | 90% | 67.4% | 81.9% (Estimated) | 3452, not reached | 0.81 (0.67–0.99) | Superiority crossed | MIS better |
| | 18.8 (Estimated) | 80% | 58.0% (Latest study) | 81.9% (Estimated) | 4885, not reached | 0.81 (0.66–1.00) | Superiority crossed | MIS better |
| **(B) TRIAL SEQUENTIAL ANALYSIS ON SECONDARY OUTCOME (MORTALITY)** | | | | | | | | |
| Conventional meta-analysis with fix-effects model | | | | | | 0.76 (0.64–0.89) | | |
| TSA | 24.3 (Estimated) | 80% | 25.3% | 0.0% (Estimated) | 1435, reached | 0.76 (0.63–0.90) | Superiority crossed | MIS better |
| | 20 | 80% | 25.3% | 0.0% (Estimated) | 2157, not reached | 0.76 (0.63–0.91) | Superiority crossed | MIS better |
| | 15 | 80% | 25.3% | 0.0% (Estimated) | 3898, not reached | 0.76 (0.61–0.94) | Superiority crossed | MIS better |
| | 10 | 80% | 25.3% | 0.0% (Estimated) | 8956, not reached | 0.76 (0.60–0.96) | Superiority crossed | MIS better |
| | 24.3 (Estimated) | 90% | 25.3% | 0.0% (Estimated) | 1921, reached | 0.76 (0.62–0.93) | Superiority crossed | MIS better |
| | 24.3 (Estimated) | 80% | 25.3% | 30.0% | 2050, not reached | 0.76 (0.64–0.90) | Superiority crossed | MIS better |

*MIS, Minimal invasive surgery; TSA, Trial sequential analysis.*

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# TSA on 1º and 2º outcome with different prior

| | Relative risk reduction | Power | Incidence in the control | Heterogeneity (diversity) | Information size | Risk ratio | Boundary | Explanation |
|---|---|---|---|---|---|---|---|---|
| **(A) TRIAL SEQUENTIAL ANALYSIS ON PRIMARY OUTCOME (PROPORTION OF PATIENTS WITH MODIFIED rANKIN SCORE > 3)** | | | | | | | | |
| Conventional meta-analysis with random-effects model | | | | | | 0.82 (0.72–0.94) | | |
| TSA | 18.8 (Estimated) | 80% | 67.4% | 81.9% (Estimated) | 2578, not reached | 0.81 (0.69–0.96) | Superiority crossed | MIS better |
| | 15 | 80% | 67.4% | 81.9% (Estimated) | 3994, not reached | 0.81 (0.66–1.01) | Superiority nearly cross | Inconclusive |
| | 10 | 80% | 67.4% | 81.9% (Estimated) | 8807, not reached | 0.81 (0.65–1.02) | Superiority not crossed | Inconclusive |
| | 18.8 (Estimated) | 90% | 67.4% | 81.9% (Estimated) | 3452, not reached | 0.81 (0.67–0.99) | Superiority crossed | MIS better |
| | 18.8 (Estimated) | 80% | 58.0% (Latest study) | 81.9% (Estimated) | 4885, not reached | 0.81 (0.66–1.00) | Superiority crossed | MIS better |
| **(B) TRIAL SEQUENTIAL ANALYSIS ON SECONDARY OUTCOME (MORTALITY)** | | | | | | | | |
| Conventional meta-analysis with fix-effects model | | | | | | 0.76 (0.64–0.89) | | |
| TSA | 24.3 (Estimated) | 80% | 25.3% | 0.0% (Estimated) | 1435, reached | 0.76 (0.63–0.90) | Superiority crossed | MIS better |
| | 20 | 80% | 25.3% | 0.0% (Estimated) | 2157, not reached | 0.76 (0.63–0.91) | Superiority crossed | MIS better |
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*MIS, Minimal invasive surgery; TSA, Trial sequential analysis.*

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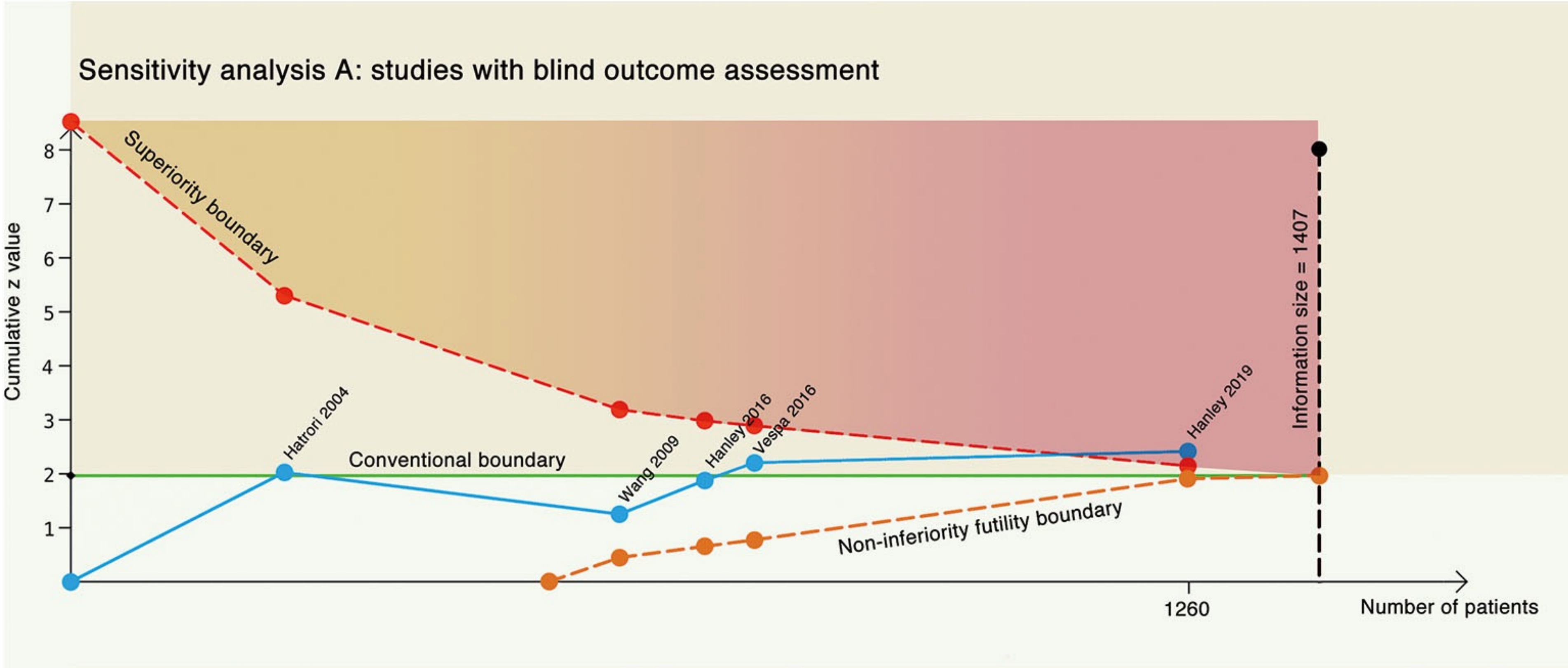
# Sensitivity analysis: Studies with blind outcome assessment

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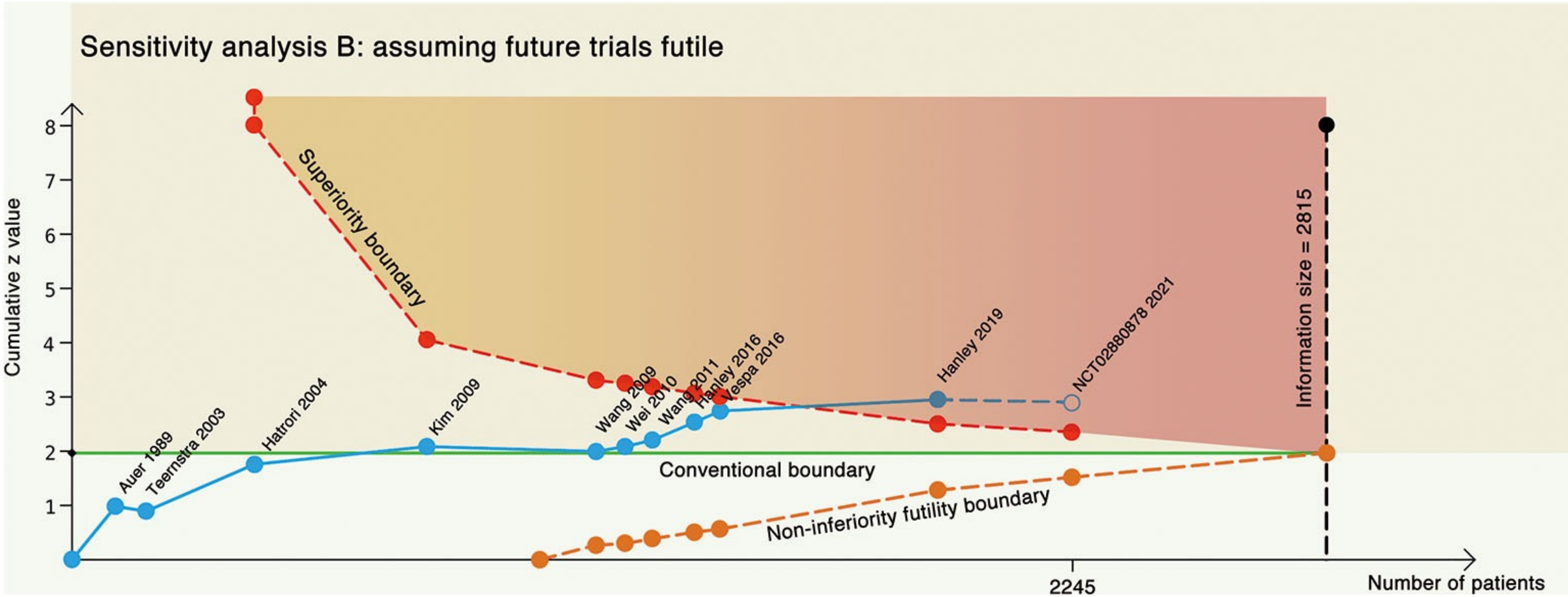
# Sensitivity analysis:
# Assuming future trial futile

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# DISCUSSION

# Discussion

The analysis answered the question of

1. which treatment is better, especially in the circumstances that the latest trial was futile
2. whether we need more trials to compare MIS vs. conservative treatment in patients with intracerebral hemorrhage

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# STUDY CONCLUSION

- Minimally invasive surgery seems to be more effective than conservative treatment
- Sensitivity analyses show that our results were robust
- We answered the question whether we need more trials to save the cost of future unnecessary trials

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# Advantages of TSA

- Avoid premature conclusion when meta-analyses based on traditional hypothesis testing would have falsely identified the effect as significant (12, 15)
- Estimate the sample size of future trials if the current result is inconclusive

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# Limitation of TSA

- Prespecified prior may have a significant impact on the result, which requires many sensitivity analyses to test the robustness

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# CONCLUSION

- TSA can be a powerful tool capable of assessing the conclusiveness of meta-analytical findings
- Updating the MA in a SR each time a new trial is published is a rational decision
- Previous trial results ought to be considered whenever we evaluate the cons and pros of designing new trials, as the evidence on a given intervention may already be sufficient