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Intra-arterial Mechanical Thrombectomy Stent Retrievers and **Aspiration Devices
in the Treatment of Acute Ischaemic Stroke: A Systematic Review and Meta-
Analysis with Trial Sequential Analysis**

Short title: Thrombectomy with stent retrievers and **aspiration** devices for acute stroke

Darren Flynn, PhD; Richard Francis, PhD; Kristoffer Halvorsrud, PhD; Eduardo Gonzalo-Almorox, MSc; Dawn Craig, MSc; Shannon Robalino, MSc; Peter McMeekin, PhD; Adela Cora MD; Joyce Balami, MD; Gary A. Ford, FRCP; Phil White, MD

Institute of Health and Society, Newcastle University, Newcastle Upon Tyne, UK (DF, DC, KH, SR); Newcastle University Business School, Newcastle University, Newcastle Upon Tyne, UK (EG-A); Institute of Neuroscience (Stroke Research Group), Newcastle University, Newcastle Upon Tyne, UK (RF, PW, AC, GAF); Centre for Evidence Based Medicine, University of Oxford, Oxford, UK (JB); School of Health, Community and Education Studies, Northumbria University, UK (PM); Oxford University Hospitals NHS Trust and Oxford University, UK (GAF)

Correspondence to Phil White, Institute of Neuroscience, Newcastle University 3-4 Claremont Terrace, Newcastle upon Tyne, NE2 4AX, UK. Tel +44 (0)191 208 6238; Fax: +44 (0)191 222 5540; E-mail:phil.white@ncl.ac.uk

ABSTRACT

Purpose: Intra-arterial mechanical thrombectomy (MT) **combined with appropriate patient selection (image-based selection of acute ischaemic stroke patients with large artery occlusion) yields improved clinical outcomes.** We conducted a systematic review and meta-analysis, with trial sequential analysis (TSA) to understand the **benefits, risks and impact of new trials reporting in 2016 on the magnitude/certainty of the estimates for** clinical effectiveness and safety of MT.

Method: Random effects models were conducted of **randomised clinical** trials comparing MT (stent retriever or aspiration devices) with/without adjuvant **intravenous thrombolysis (IVT)** with IVT and other forms of best medical/supportive care in the treatment of acute ischaemic stroke. Study inclusion and risk of bias were assessed independently by two reviewers. Functional independence (mRS 0-2) and mortality at 90 days, including symptomatic intracranial haemorrhage (SICH) rate were extracted. TSA established the strength of the evidence derived from the meta-analyses.

Findings: Eight trials of MT **with a total sample size of 1,841 (916 patients treated with MT and 925 treated without MT)** fulfilled review inclusion criteria. The three most recent trials **more precisely defined the effectiveness of MT (mRS 0 to 2; OR = 2.07, 95% CI = 1.70 to 2.51 based on data from eight trials versus OR = 2.39, 95% CI = 1.88 to 3.04 based on data from five trials).** Meta-analyses showed **no effect on mortality (OR = 0.81, 95% CI = 0.61 to 1.07) or SICH (OR = 1.22, 95% CI = 0.80**

to 1.85) as found in analysis of first five trials. TSA indicated that the information size requirement was fulfilled to conclude the evidence for MT is robust.

Discussion: The impact of three recent trials on effectiveness and safety of MT was a more **precise** pooled effect size for functional independence. TSA demonstrated sufficient evidence for effectiveness and safety of MT.

Conclusion: No further trials of MT versus **no MT** are indicated **to establish clinical effectiveness**. Uncertainty remains as to whether MT reduces mortality or increases risk of SICH.

INTRODUCTION

The benefits of intravenous thrombolysis with recombinant tissue plasminogen activator (IV rt-PA) for acute ischaemic stroke are well-known, time dependent (with earlier treatment within the 4.5 hour treatment window associated with better functional outcomes) and encapsulated by the aphorism ‘Time is Brain’¹⁻³.

Despite the efficacy of intravenous thrombolysis (IVT) in reducing post-stroke disability, recanalisation (restoration of blood flow through a blocked artery) occurs in only ~10 to 45% of patients with large artery occlusion (LAO) depending on site/length of occlusion^{4,5}. A number of approaches are currently being explored to increase IVT recanalisation rates, including use of more fibrin selective thrombolytic drugs, ultrasound and adjunctive anticoagulant therapy. None are yet proven.

There is overwhelming evidence that MT achieves significantly higher recanalisation rates than IV rt-PA for LAO⁶ and better clinical outcomes with a 13 to 31% absolute increase in patients recovering from acute stroke to be independent in activities of daily living. MT is not associated with an increased risk of symptomatic intracranial haemorrhage (SICH) or mortality^{7,8}.

Meta-analyses of randomised controlled trials (RCTs) have since been published⁹⁻¹¹, each of which has taken a slightly different approach to inclusion criteria; all of which find that MT is an effective treatment with reduced disability rates. The most robust of these is likely to be the individual patient meta-analysis, based on data from 1,287 patients (634 MT and 653 standard care). The results suggest that MT led to significantly reduced disability at 90 days compared with controls (adjusted OR = 2.49, 95% CI = 1.76 to 3.53)¹¹.

The evidence base to define the safety and effectiveness of MT for selected acute ischaemic stroke patients has grown recently, with THERAPY¹², THRACE¹³ and PISTE¹⁴ RCTs all reporting in 2016. An updated evidence synthesis is therefore warranted to understand the impact of these new trials on our understanding of the clinical effectiveness and safety of MT; in particular with stent retrievers and aspiration devices.

Meta-analyses of RCTs increase the power and precision of the estimated intervention effects. However, RCTs of MT over time have evaluated a range of devices and the population considered eligible for treatment has changed. There is therefore a need to ensure that only those RCTs that reflect the current practice to be considered. Trial sequential analysis (TSA) corresponds to group sequential analysis of a single trial and

can be applied to meta-analysis to evaluate the robustness of the evidence. TSA necessitates the use of an information size to evaluate the strength of the evidence. There is a need to inform/estimate that pre-specified intervention effect, in the same manner as a power calculation in a clinical trial. TSA can help to quantify whether meta-analyses are presenting the best available and/or sufficient evidence.

Therefore we conducted a systematic review with meta-analysis alongside TSA, that aimed to update the evidence-base for MT, and evaluate the **benefits, risks and** impact of three recent trials on the **magnitude/uncertainty of the estimate for** clinical effectiveness and safety of MT in the treatment of acute ischaemic stroke.

METHODS

The review adhered to a published protocol¹⁵ and the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement¹⁶.

Randomised clinical trials that included a minimum of 10 adult patients (aged ≥ 18) presenting with acute ischaemic stroke receiving MT (stent retrievers and aspiration devices) with or without adjuvant IVT or standard medical care were eligible for

inclusion in the review. Where applicable, data on comparator interventions (IVT and other forms of best medical or supportive care) of studies evaluating MT were extracted.

Eligible studies had to include at least one of the following outcomes assessed at ≥ 90 days follow-up: modified Rankin Scale (mRS)¹⁷, Oxford Handicap Scale (OHS)¹⁸, National Institute of Health Stroke Scale (NIHSS)¹⁹ or Barthel ADL Index²⁰. Data on secondary outcomes were extracted from eligible studies: length of stay/time in acute care; recanalisation (Treatment in Cerebral Infarction [TICI] score²¹ as a reference measure that can be mapped onto analogous measures such as the Thrombolysis in Myocardial Ischemia [TIMI] score²²) and EQ-5D²³ (or analogous measures of health-related quality of life). Safety of MT was summarised as a function of 90-day mortality, and SICH within 7-days (as per the SITS-MOST definition ‘NIHSS scores worsening ≥ 4 within 24 hours and an intracerebral haemorrhage type PH2’²⁴).

Search strategy

A search strategy was designed with assistance from an experienced information scientist (SR) using a combination of MeSH/thesaurus terms and keywords. The following bibliographic databases were searched up to mid-February 2015: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, SCOPUS, and Web of Science. Additionally several trials registries were searched: ClinicalTrials.gov,

International Standard Randomised Controlled Trial Number Register and the Chinese Clinical Trial Registry. **Where published protocols for ongoing randomised trials were identified by the search strategy (to mid-Feb 2015), these were included if published by end of 2016 to ensure that the evidence presented in the review is complete and up-to-date.**

An example search strategy for MEDLINE can be found in **Appendix 1**. As our focus was on MT with stent retriever **devices** and **current generation** aspirational devices, studies published prior to January 2009 were excluded. No restrictions were placed on country of origin. Included studies had to involve humans, and had to have a title and abstract in English. Where available, a search filter for controlled trials²⁵ was used or adapted as appropriate. Hand searching of reference lists and citation searching of studies that fulfilled the eligibility criteria were undertaken. References lists of directly relevant reviews identified by the search strategy were also hand-searched.

Study selection

In stage 1, two reviewers (RF and EGA) independently assessed the titles and abstracts retrieved via the search strategy for eligibility. In stage 2, studies retained at stage 1 were independently assessed for eligibility by PW, RF and AC using a study selection

form (Appendix 2). Disagreements were resolved via discussion or via a third reviewer (PW or AC) adjudicating on inclusion of a study.

Data extraction and risk of bias assessment

A structured data extraction form, with selected items from the template for intervention description and replication [TIDIER] checklist²⁶ was used to capture information on the study population, intervention(s), comparator(s) and outcomes (Appendix 3). Data extraction was undertaken by one reviewer (PW) with fidelity of data extraction checked by a second reviewer (RF and KH) with disagreements resolved via discussion. The methodological quality assessment framework for RCTs developed by the Cochrane Collaboration²⁷ was used independently by two reviewers (RF and DF) to assess the risk of bias within studies (low, medium and high). Where applicable, corresponding study authors were contacted to request missing data.

Data Synthesis

Data on clinical outcomes were synthesised using meta-analytic techniques where sufficient data for calculation of effect sizes existed for each outcome of interest (unadjusted odds ratios and corresponding 95% confidence intervals). To allow for differences between/within studies, random effects models were utilised. Risk of small study bias across studies was established with funnel plots. **Seven out of eight trials**

were stopped early (truncated, two of them only modestly so) due to a pre-specified efficacy stopping point being reached (3 trials), loss of equipoise (3 trials) and in one trial due to efficacy (although a pre-specified stopping point not reached). There has been some debate in the literature around the inclusion of truncated and non-truncated trials in a meta-analysis. Historically, the standard approach has been to incorporate truncated RCTs without any special consideration, however fears that early stopping may be an important source of bias has led to further investigation. A comprehensive investigation of the issues has concluded that early stopping of clinical trials is not a substantive source of bias in meta-analyses and recommend that all studies (truncated and non-truncated) be included²⁸.

Trial Sequential Analysis

A TSA was used to establish the optimal size within our meta-analysis (maintaining Type I error of 0.05 / 5%) after accounting for heterogeneity (diversity) between trials. The TSA was conducted using TSA software version 0.9.5.5 Beta²⁹. An estimated optimal information size requirement was calculated using conventional parameters (power = 0.80, Type II error = 0.20; Type I error = 0.05). Based on a previous TSA of thrombectomy trials³⁰ the following assumptions were made in the current TSA: a threshold of 30% relative risk increase for functional independence (mRS 0 to 2); 30% relative risk reduction for both all-cause mortality and SICH; and control event rates of

pooled control arm rates from the eight trials (30.4%, 17.5% and 4.7%) for functional independence (mRS 0 to 2), mortality and SICH respectively. Trial data were entered into the TSA in order of publication date.

TSA enables the estimation of information size with adjusted threshold for statistical significance – sequential monitoring boundaries³⁰. If the cumulative z-statistical curve crosses the sequential monitoring boundaries, then it can be inferred that future trials would not alter the conclusions about the outcome, and a sufficient level of evidence has been accumulated³⁰. When the z-curve crosses over into the futility area, it can be inferred that any differences between the comparators would be unlikely to change in future trials of MT³⁰.

FINDINGS

Out of 4,993 records identified by the search strategy, eight **randomised clinical** trials were assessed to be eligible for inclusion in the meta-analyses (Figure 1). The eight trials had a combined sample size of **1,841** (916 patients treated with MT **and 925 treated without MT**). However, the N in the treatment group across the trials for the different outcomes was variable. We also identified discrepancies in numbers of cases reported in individual published trials compared with the numbers of cases reported in previous meta-analyses (Appendix 4).

The countries of origin of the eight trials were: Australia and New Zealand (EXTEND-IA³¹); Canada, Ireland, South Korea, UK and USA (ESCAPE³²); Spain (REVASCAT³³); Austria, Denmark, France, Germany, Spain, Switzerland, USA (SWIFT PRIME³⁴); The Netherlands (MR CLEAN⁸); Germany and USA (THERAPY¹²); France (THRACE¹³); and UK (PISTE¹⁴).

The device types, imaging modalities and recanalisation rates for patients treated with MT in the eight trials are shown in Table 1. All eight trials were assessed to have a low risk of bias (Table 2).

Synthesis of results

Functional independence

Patients treated with MT compared with those receiving IVT and other forms of best medical or supportive care were more significantly more likely to be functional independent (mRS 0 to 2) at 90-days follow-up (OR = 2.39, 95% CI= 1.88 to 3.04) based on data from five trials (Figure 2). The additional impact of the three recent trials was a slightly decreased pooled effect size, but with increased certainty of the mid-point estimate (OR = 2.07, 95% CI = 1.70 to 2.51).

Mortality

Patients treated with MT compared with those receiving IVT and other forms of best medical or supportive care did not show any effect on mortality at 90-days follow-up (Figure 3). The addition of the three most recent trials did not impact on mortality, but there was increased certainty of the mid-point estimate with a continuing trend towards reduced mortality.

SICH

Patients treated with MT compared with those receiving IVT and other forms of best medical or supportive care (Figure 4) did not show any statistically significant increased likelihood of SICH within 7 days based on data from 5 trials. Data from the PISTE trial were not estimable in this meta-analysis, as there were no events recorded of SICH within 7 days for either the treatment or the control group. Inclusion of the remaining two recent trials did not impact on probability of SICH.

Findings of the Trial Sequential Analysis (TSA)

A series of TSA were undertaken using data from eight **randomised clinical** trials.

Functional independence TSA

The adjusted 95% CI for the TSA was 1.55 to 2.76 (heterogeneity = 0%). The adjusted information size estimate was $N = 724$. **Figure S1 (Appendix 5)** shows that the cumulative z-statistic curve crossed the sequential monitoring boundary for benefit of MT. The TSA demonstrates robust evidence for a 30% relative benefit for MT compared with IVT for mRS 0 to 2.

Mortality TSA

The TSA analysis **(Figure S2, Appendix 5)** shows that the cumulative z-statistic curve failed to cross the traditional boundaries for statistical significance; despite surpassing the diversity adjusted information size requirement ($N=1,803$), suggesting a lack of robust evidence to demonstrate a 30% relative risk reduction for MT over IVT. The TSA results suggest that future trials of MT are unlikely to demonstrate a significant effect on mortality as the adjusted 95% CI was 0.57 to 1.13.

SICH TSA

The TSA-adjusted 95% CI was 0.53 to 2.78 (diversity = 0). The diversity adjusted information size was estimated to be $N = 6,057$; this number was not reached, suggesting that the meta-analysis is underpowered for the SICH outcome. **Figure S3 (Appendix 5)** shows that the cumulative z-statistic curve failed to cross the convention

statistical significance boundary, nor does it cross the boundary for futility, which indicates that future trials may show differences for SICH between MT and IVT.

DISCUSSION

Data from the five MT **randomised clinical** trials reporting in 2015 yielded significantly increased likelihood of functional **independence** (mRS 0 to 2) at 90-days follow-up (OR = 2.39, 95% CI= 1.88 to 3.04). The impact of the increased evidence base for MT (THERAPY¹², THRACE¹³, PISTE¹⁴) was a marginally decreased effect size, but with increased certainty as shown by CIs with a narrower range (mRS 0 to 2; OR = 2.07, 95% CI = 1.70 to 2.51). These findings further confirm the effectiveness of MT, in particular with stent retrievers and aspiration devices. Compared with other meta-analyses of MT in the treatment of acute ischaemic stroke, including the recent Hermes meta-analysis⁹⁻¹¹, our effect size for functional independence is smaller in magnitude.

Our pooled effect size for functional independence derived from the 5 RCTs published in 2015 differed to previous meta-analyses, including meta-analysis conducted by the Hermes collaboration¹¹. This can be explained by discrepancies in primary dichotomous study data (Appendix 4) and calculating unadjusted (as opposed to adjusted) odds ratios. RCTs often adjust their analyses for prognostic factors which are thought to influence

outcomes (e.g age, severity). Trials published in 2015 used both unadjusted and adjusted pooled effect sizes, and it is worth noting that the latter are unlikely to have been adjusted using the same variables. There is no consensus about whether, or how to pool adjusted and unadjusted findings, although it is regarded best practice to avoid this approach. The simplest option to avoid heterogeneity due to the differences in adjustment with each RCT is to report unadjusted pooled effects, as we have done here.

Consistent with previous meta-analyses of MT in the treatment of stroke¹¹, we identified no impact on previous estimates of safety (i.e. no increased risk of mortality and SICH at 90 days and 7-days respectively). Although our meta-analyses showed a trend that MT may lead to a decreased risk of mortality this effect was not statistically significant. In the case of SICH, the divergent definitions and low event rates across the eight trials may have confounded the overall effect for this outcome. A trial sequential analysis confirmed that the meta-analyses fulfilled the information size requirement to satisfy the criterion for ‘sufficient evidence’ on the effectiveness, but not all safety outcomes for MT. The information requirement was met for mortality at 90 **days**; however uncertainty remains as to whether MT is associated with increased risk of SICH. **The robustness of efficacy data for MT would likely prohibit further randomised clinical trials of MT versus no MT. Further data on mortality and SICH could**

reliably be obtained from on-going or planned trials of MT versus MT plus intravenous thrombolysis.

Questions remain around how best to image/triage emergent LAO stroke and optimal MT device types, including technical questions such as use of stentriever or aspiration, including issues around use of different modes of anaesthesia³⁵ which are currently being addressed in on-going trials^{36,37}. Efficacy of either MT or IVT for Wake up Stroke (wUS) / stroke of unknown time onset (SUTO) is also unclear.

Our findings make a strong case that no further trials to evaluate the effectiveness of MT versus **no MT** are warranted. Our meta-analyses included patients from different healthcare systems, patient characteristics and a range of devices which shows the generalisability of effectiveness and safety of MT (with uncertainty around SICH). This assertion is strengthened by our use of full systematic review methodology (including considerations of non-English language literature) and a supplementary trial sequential analysis to establish the robustness of the effect sizes with reference to a specified information size. We also included substantially more patient numbers treated with modern MT compared with previous meta-analyses.

There is uncertainty regarding generalisability of published trials to populations of non-European ancestry (and countries where there may be marked differences in concomitant healthcare systems); however, given the compelling evidence for the efficacy of MT, it is unlikely that further randomised clinical trials of MT versus no MT will be undertaken. Therefore, registry data in other populations will be important to confirm that outcomes and safety in different populations and healthcare systems are consistent with existing trial data.

Subgroups in many categories are still small especially if the query is broken down by any categorisation of trials e.g. advanced imaging selection/all IVT control or timing of MT since onset from symptoms. Furthermore, we did not have access to individual patient data (IPD). However, the IPD meta-analysis undertaken by the Hermes collaboration¹¹ has already reported on patient-level evidence favouring treatment with MT (patients aged ≥ 80 years, patients randomised > 300 min after symptom onset, and patients not eligible for IVT). An updated meta-analysis of individual patient is planned³⁸, and this will add further evidence in terms of sub-groups with differential effectiveness and safety of MT.

Given the robustness and generalisability of the evidence base for MT, there is a pressing need to invest in acute stroke care services to support delivery of this complex

high technology service to all eligible patients. In the UK, few centres provide 24/7 MT and there is large variability between services in MT pathways and delivery³⁹. A recent study has also shown that 10% of all stroke admissions in the UK could benefit from MT⁴⁰. **Economic analyses of MT indicate substantial gains in quality adjusted life years and cost-savings^{41,42}, with one analysis reporting larger gains for younger patients⁴². Costs or cost effectiveness of MT** to inform service re-design is currently the subject of much research in the UK and **elsewhere⁴³**.

CONCLUSIONS

The expanded evidence base for MT yielded a more **precise** assessment of effectiveness in terms of functional independence (mRS 0 to 2), with no increased risk of mortality or SICH. Uncertainty remains as to whether MT reduces mortality or is associated with increased risk of SICH.

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Table 1. Summary of device type, imaging modality and recanalisation in the eight trials

| Primary author; Study Name | Device Type | Advanced Imaging* | Recanalisation % |
|---|---|--------------------------|--|
| Berkhemer 2015; <i>MR CLEAN</i> ⁸ | Trevo retrievable stents and others | No | MT treatment group = 115/196 (59) |
| Campbell 2015; <i>EXTEND:IA</i> ³¹ | Solitaire FR retrievable stent | CT perfusion imaging | IV rt-PA plus MT = 25/35 (86) |
| Goyal 2015; <i>ESCAPE</i> ³² | Retrievable stents or aspiration | Yes | IV rt-PA plus MT = 113/156 (72) |
| Jovin 2015; <i>REVASCAT</i> ³³ | Solitaire FR | Y (in defined subgroups) | IV rt-PA within 4.5h plus MT = 67/103 (65) |
| Saver 2015; <i>SWIFT PRIME</i> ³⁴ | Solitaire FR or Solitaire 2 | Y (in a majority) | IV-tPA plus MT = 73/83 (88) |
| Mocco 2016; <i>THERAPY</i> ¹² | Penumbra, Solitaire or Trevo | No | IV rt-PA plus MT = 30/43 (70) |
| Bracard 2016; <i>THRACE</i> ¹³ | Merci, Penumbra, Catch, Solitaire | Y (MRI in a majority) | IV rt-PA plus MT = 95/138 (69) |
| Muir 2016; <i>PISTE</i> ¹⁴ | Any CE-marked device approved for MT (stentrievers or aspiration) | No | IV rt-PA plus MT = 26/30 (87) |

*Advanced imaging is taken as use of MRI techniques, Perfusion CT or a systematic combination of CTA collateral scoring and ASPECTS on CT brain (ESCAPE trial)

Table 2. Methodological Quality and Risk of Bias Assessment

| Primary Author; Study Name | Power calculation | Sample size achieved (reason for stopping early) | Attrition (n/%) | Adequate sequence generation | Allocation concealment | Blinding of participants / personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Free of other problems | Overall Risk of Bias |
|--|----------------------|---|--------------------|------------------------------------|---------------------------|--|--------------------------------------|-------------------------------|-----------------------------------|------------------------------|----------------------------|
| Berkhemer 2015; <i>MR CLEAN</i> ⁸ | Yes | Yes | 2/0.4% | Low risk | Low risk | High risk** | Low risk | Low risk | Low risk | Low risk | Low |
| Campbell 2015; <i>EXTEND:IA</i> ³¹ | Yes | No (Efficacy) | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| Goyal 2015; <i>ESCAPE</i> ³² | Yes | No (Efficacy) | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| Jovin 2015; <i>REVASCAT</i> ³³ | Yes | No (Efficacy) | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| Saver 2015; | Yes | No | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |

| | | | | | | | | | | | |
|----------------------------------|-----|------------------------|-----|----------|----------|-------------|----------|-----|----------|----------|-----|
| <i>SWIFT PRIME</i> ³⁴ | | (Efficacy) | | | | | | | | | |
| Mocco 2016; | Yes | No | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| <i>THERAPY</i> ¹² | | (Loss of equipoise) | | | | | | | | | |
| Bracard 2016; | Yes | No | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| <i>THRACE</i> ¹³ | | (Efficacy) | | | | | | | | | |
| Muir 2016; | Yes | No | N/A | Low risk | Low risk | High risk** | Low risk | N/A | Low risk | Low risk | Low |
| <i>PISTE</i> ¹⁴ | | (Loss of equipoise) | | | | | | | | | |

** Not feasible to blind interventionists and was unlikely to have biased outcome in these trials