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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Goyal M, Menon BK, van Zwam WH, et al, for the HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; published online Feb 18. http://dx.doi.org/10.1016/S0140-6736(16)00163-X.

ENDOVASCULAR THROMBECTOMY FOR LARGE VESSEL ISCHAEMIC STROKE: A META-ANALYSIS OF INDIVIDUAL PATIENT DATA FROM FIVE RANDOMISED TRIALS. THE HIGHLY EFFECTIVE REPERFUSION EVALUATED IN MULTIPLE ENDOVASCULAR STROKE TRIALS (HERMES) COLLABORATION.

Supplementary Material

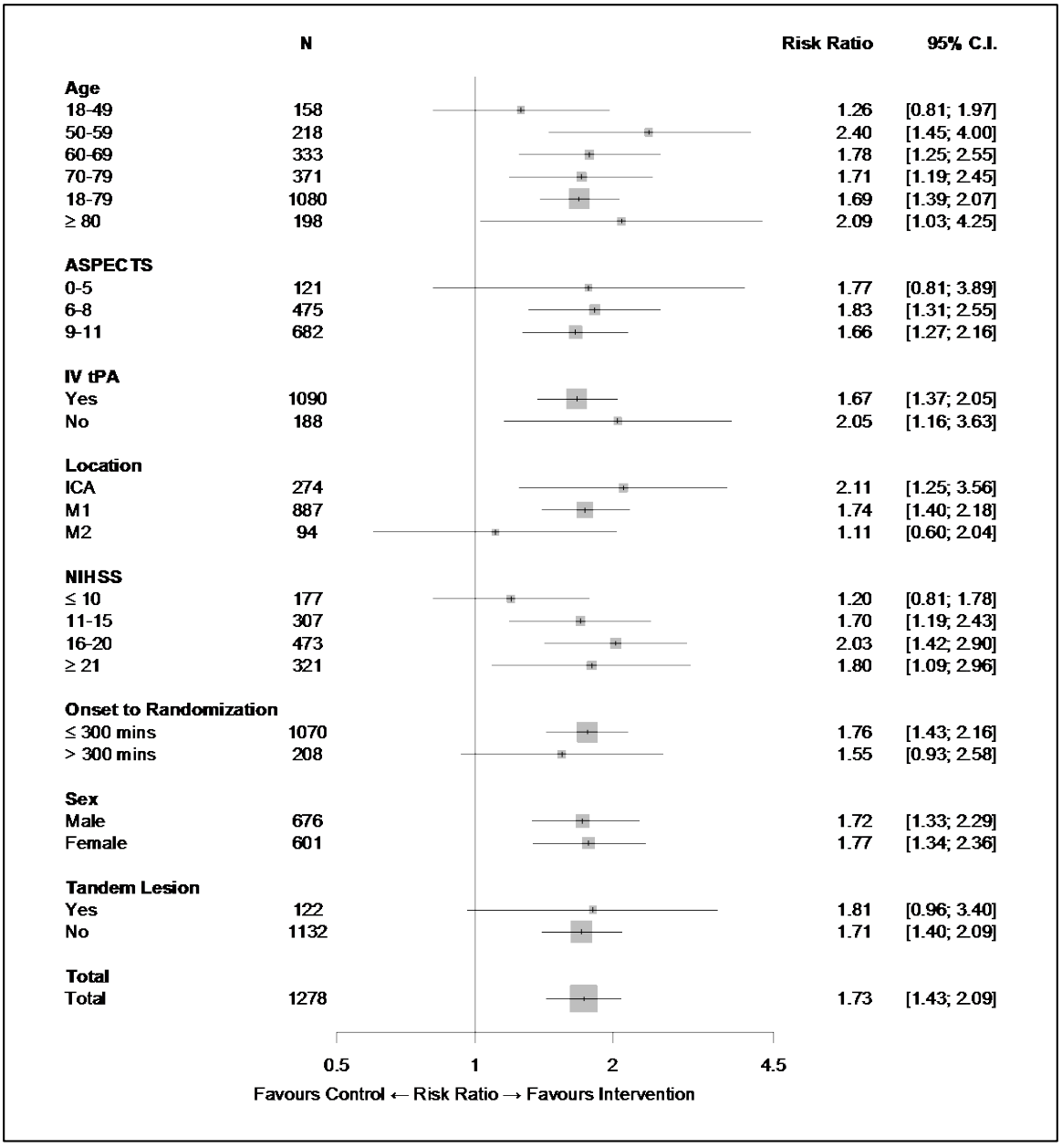
Supplementary Table 1: Qualitative assessment of between trial differences in population, sampling frame and operational definitions of Interventional and Control Groups.

	MR CLEAN	ESCAPE	EXTEND IA	SWIFT PRIME	REVASCAT
Population					
Continent	Europe	North America, Europe, East Asia	Australia/New Zealand	North America and Europe	Europe
Country	Netherlands	Multiple	Two	Multiple	Spain
Sampling Frame					
Imaging Criteria					
Modality	NCCT/CTA	NCCT/CTA *CTP optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA *CTP optional
Occlusion Site	ICA M1 M2	ICA M1	ICA M1 M2	ICA M1	ICA M1
Core	N/A	ASPECTS 6-10 Good Collaterals	CTP mismatch and ischemic core <70mL	CTP or DWI (1st 72 pts), thereafter CT or MR ASPECTS 6-10	ASPECTS 6-10
Clinical Criteria					
Age (years)	≥18	≥18	≥18	18-85 (later amended to 18-80)	18-80 (later amended to allow 81-85 if ASPECTS>8)
Baseline Stroke Severity	N/A	NIHSS >=6	N/A	NIHSS	NIHSS >=6
Time to randomization	6 hours	12 hours	6 hours	6 hours	8 hours
Definition of SICH	Any ICH and ≥4 point increase NIHSS	Any ICH judged to cause ≥2 point increase NIHSS	PH2/SAH + ≥4 point increase NIHSS	Any PH/SAH/IVH + ≥4 point increase NIHSS	PH2 + ≥4 point increase NIHSS
Control Group					
	Standard care	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients	Standard care
Intervention Group					
Wait for response to IV alteplase	No	No	No	No	Yes
Pre-specified time metrics	No	Yes	No	Yes	Yes
Type of Devices	Any	Any	Solitaire	Solitaire	Solitaire

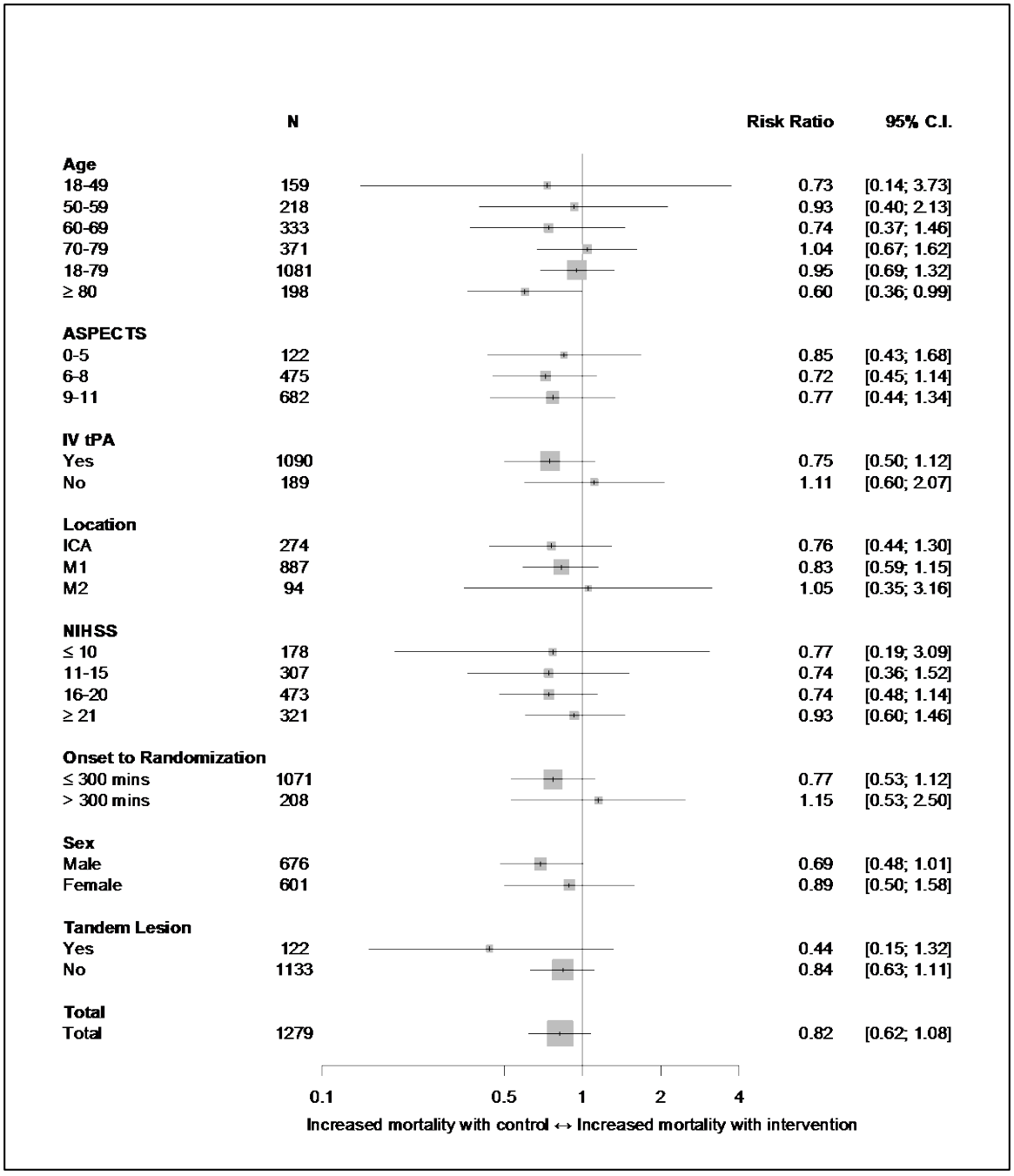
NCCT – Non contrast CT, CTA – CT angiography, CTP – CT Perfusion, MRI –Magnetic Resonance Imaging, ICA –Internal Carotid Artery, MCA – Middle Cerebral Artery ASPECTS - Alberta Stroke Program Early CT Score, PH – Parenchymal Hemorrhage, SAH – Subarachnoid hemorrhage, IVH – Intra-ventricular Hemorrhage, NIHSS – National Institute of Health Stroke Scale, IV - intravenous

Supplementary Figures

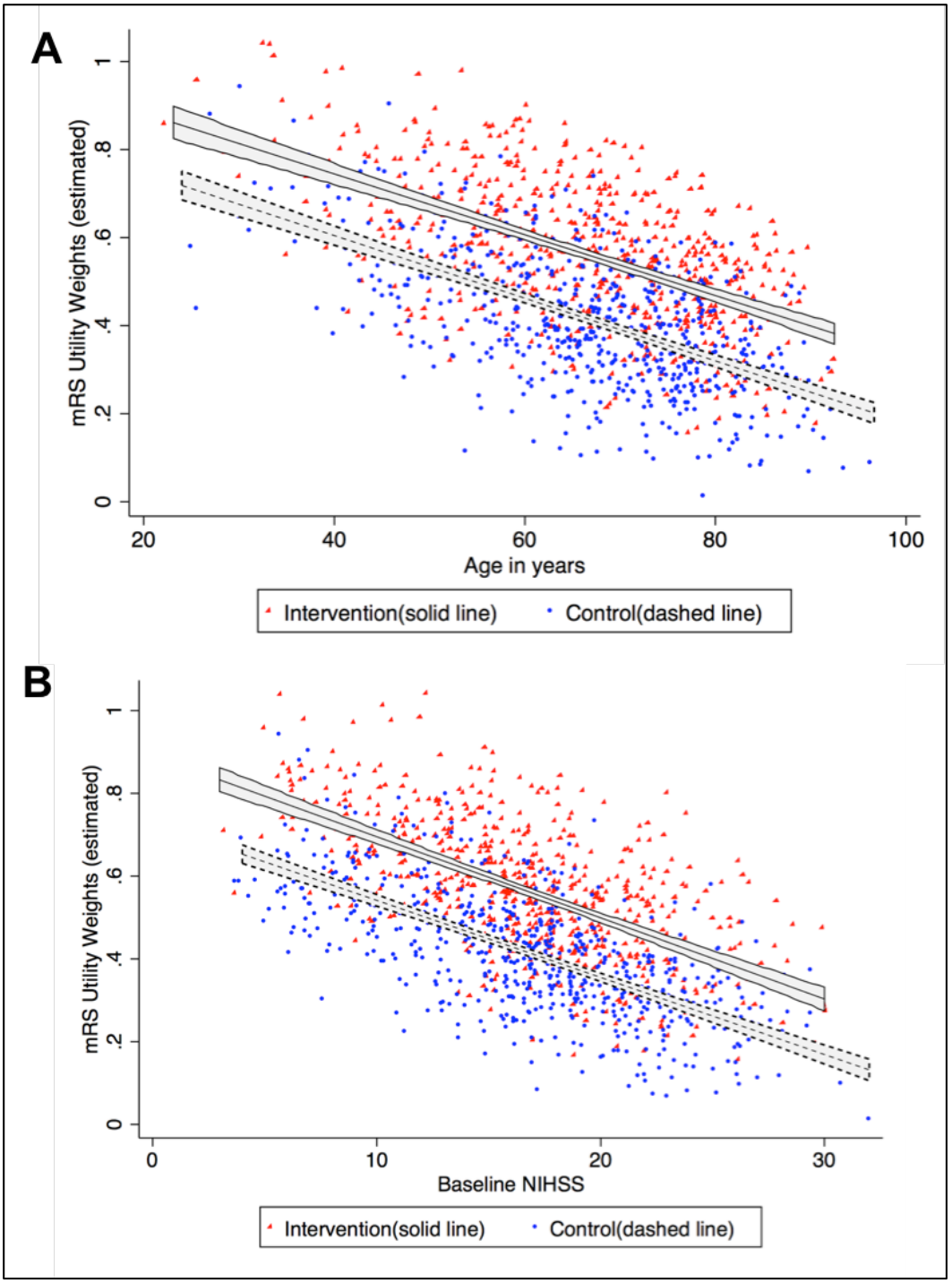
Supplementary Figure 1: Forest plot showing adjusted treatment effect for secondary outcome (mRS 0-2) in pre-specified sub-groups.



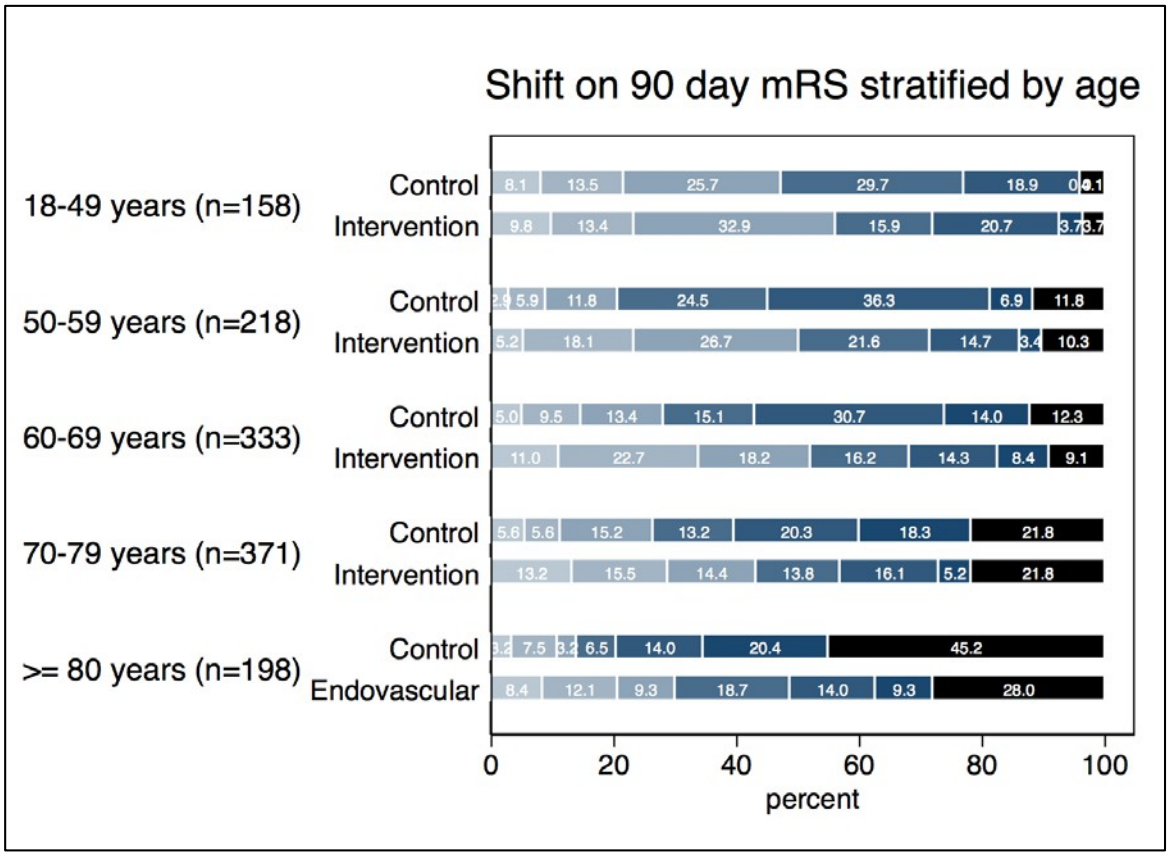
Supplementary Figure 2: Forest plot showing adjusted treatment effect for mortality (within 90 days) in pre-specified sub-groups.



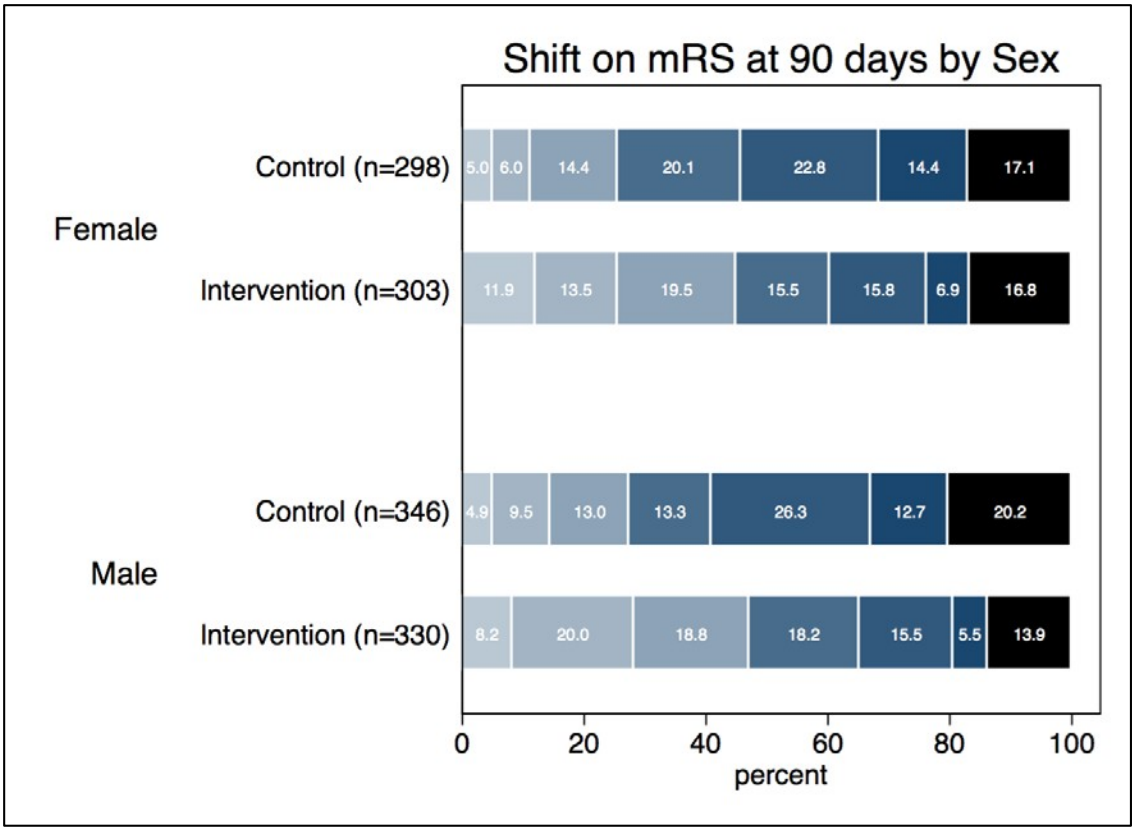
Supplementary Figure 3: Graphs showing utility weighted modified Rankin Scale at 90 days estimated using a mixed methods linear regression vs. age (panel A) and baseline NIHSS (panel B). Data is stratified by intervention vs. control group. Models adjust for co-variates (age, sex, baseline stroke severity, site of occlusion, IV tPA (yes/no), ASPECTS score, and time from onset to randomization).



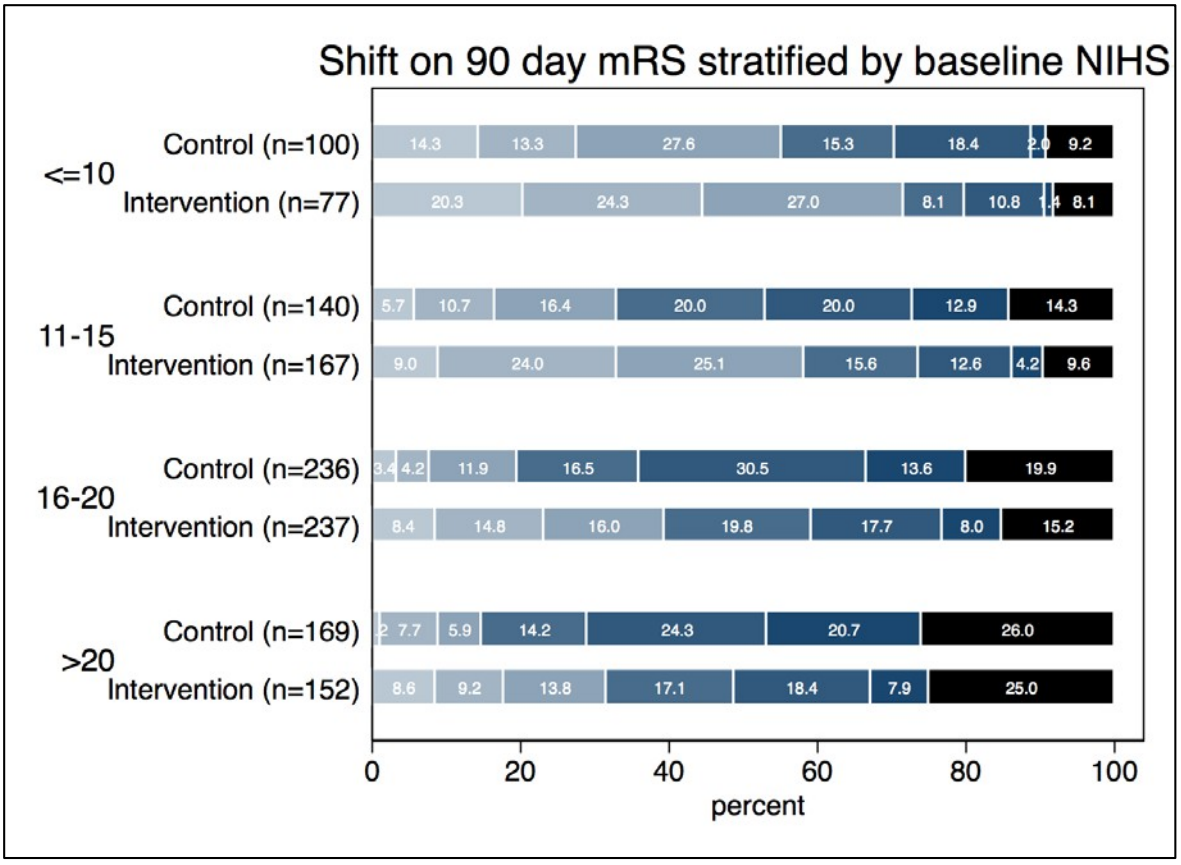
Supplementary Figure 4: Distribution of mRS at 90 days in the intervention and control groups according to age. (p = 0.07 for interaction).



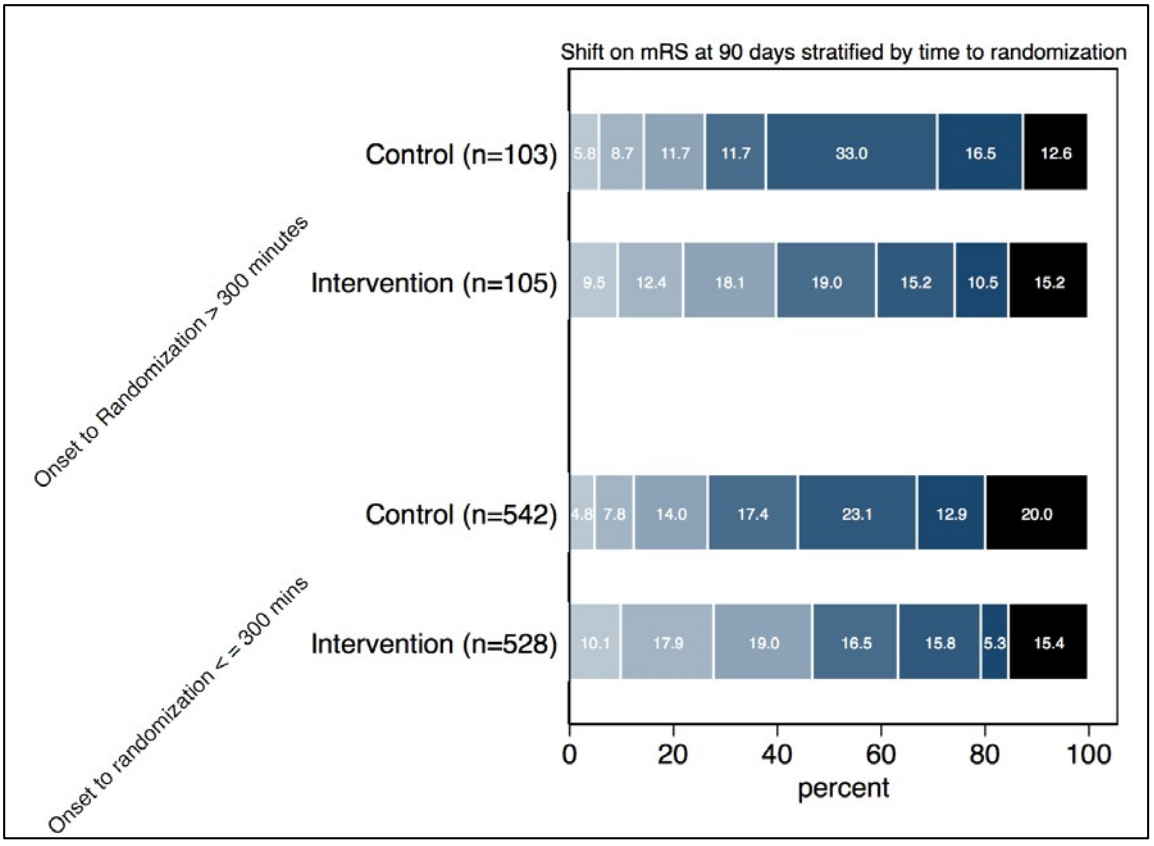
Supplementary Figure 5: Distribution of mRS at 90 days in the intervention and control groups according to sex. (p = 0.36 for interaction).



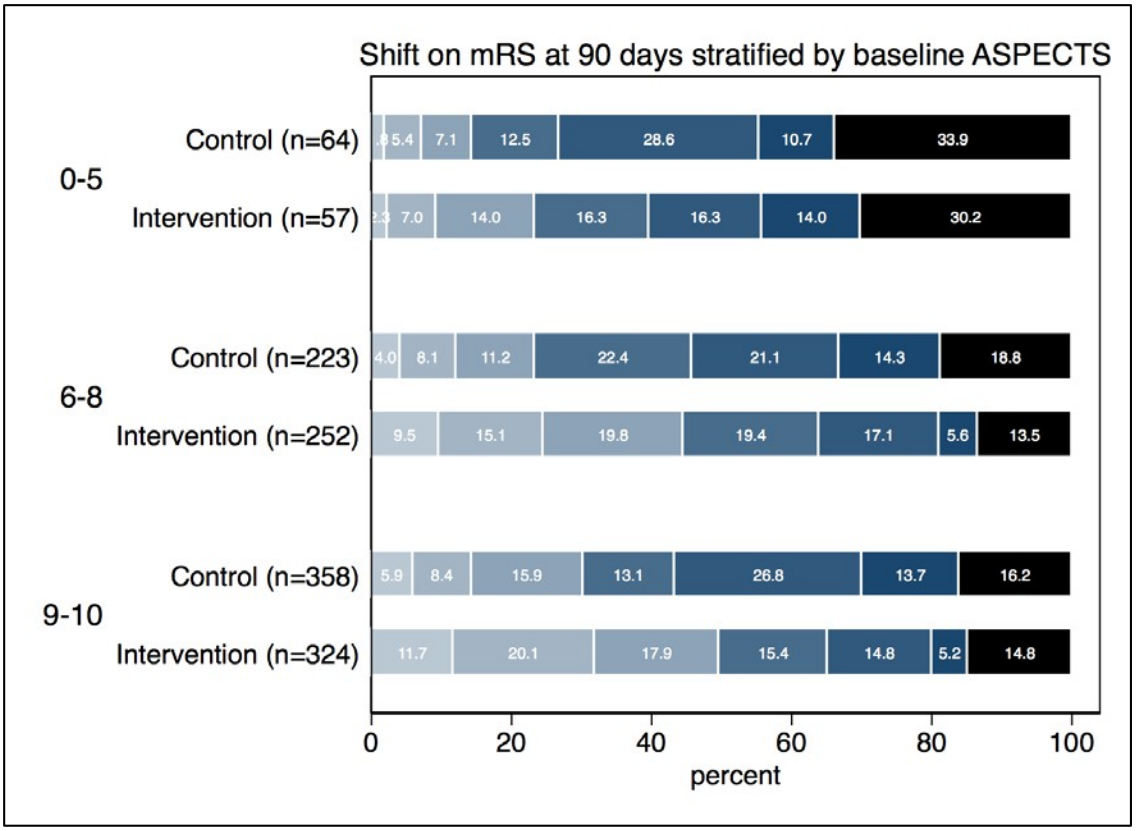
Supplementary Figure 6: Distribution of mRS at 90 days in the intervention and control groups according to baseline stroke severity measured by NIHSS. (p = 0.47 for interaction).



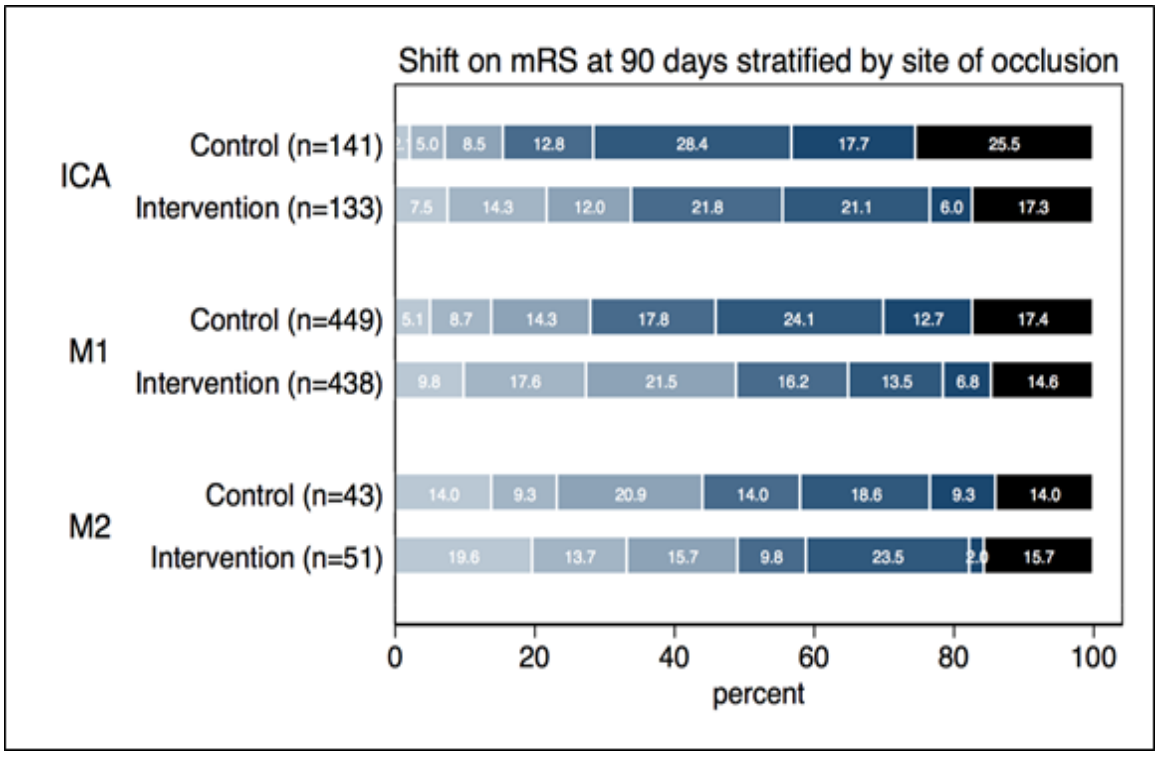
Supplementary Figure 7: Distribution of mRS at 90 days in the intervention and control groups according to time from stroke symptom onset to randomization. (p = 0.13 for interaction).



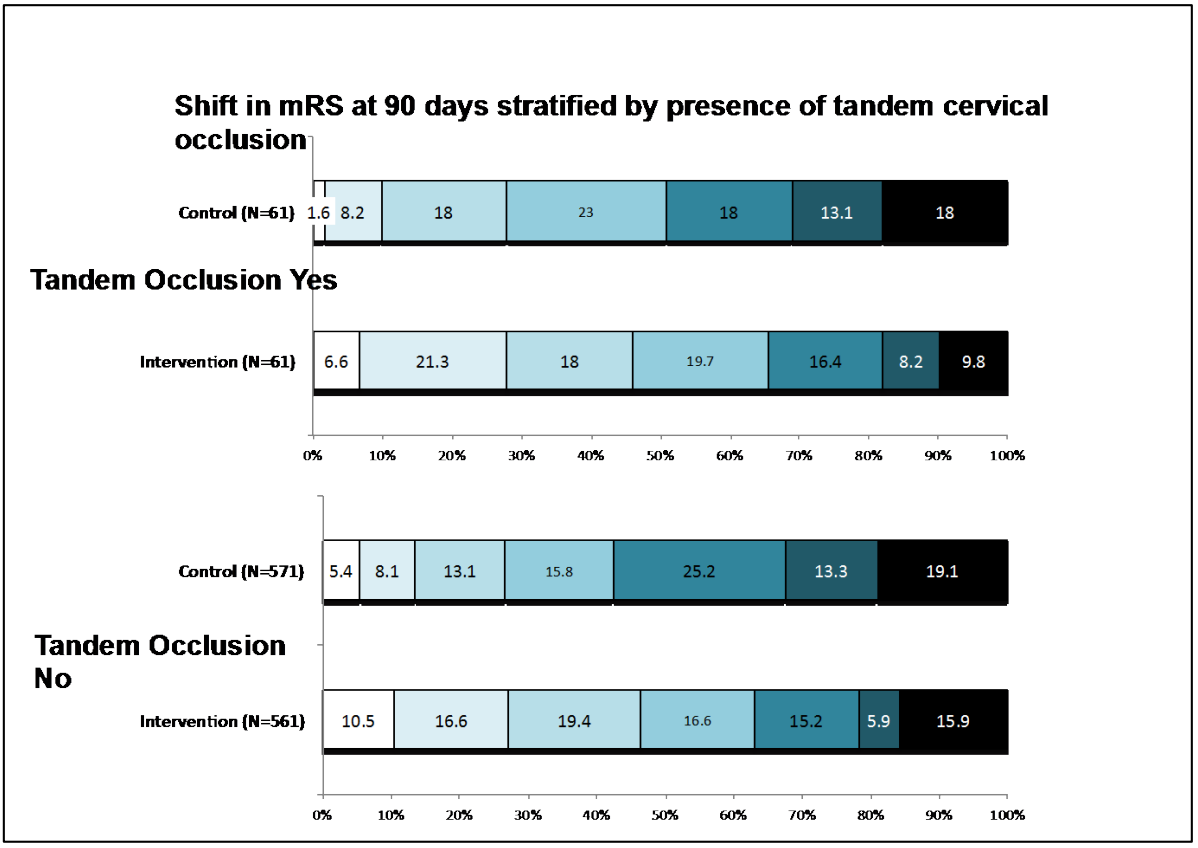
Supplementary Figure 8: Distribution of mRS at 90 days in the intervention and control groups according to baseline non-contrast CT ASPECTS. (p = 0.49 for interaction).



Supplementary Figure 9: Distribution of mRS at 90 days in the intervention and control groups according to site of baseline artery occlusion. (p = 0.35 for interaction).



Supplementary Figure 10: Distribution of mRS at 90 days in the intervention and control groups according to presence or absence of tandem occlusion. (p = 0.49 for interaction).



HERMES STATISTICAL ANALYSIS PLAN FOR THE META-ANALYSIS OF INDIVIDUAL PATIENT DATA FROM FIVE RANDOMISED TRIALS OBJECTIVES, DESIGN AND METHODOLOGY

I. Objectives

The HERMES consortium seeks to combine patient level data available from clinical trials that used second-generation mechanical devices (primarily stent retrievers) to test if additional mechanical thrombectomy (intervention group) is better than standard care (control group) in patients with acute ischemic stroke. These trials used imaging criteria to sample from the population. This sample is broadly defined as patients with anterior circulation ischemic stroke and proximal thrombi. Outcome was ascertained at 3 months from onset by means of an ordinal scale, the modified Rankin Scale (mRS; an ordinal scale).

The trials differ with respect to many aspects. These are outlined below and will be described in supplementary Table 1:

1) Definition of the population: The trials enrolled patients from 3 different continents and therefore from different health care systems. These ranged from highly centralized large hub and spoke models to smaller more distributed networks. Differences in systems of health care ranged from socialized systems to private payment models. Differences potentially exist in baseline demographics and health indicators of the population including life expectancy, lifestyle, prevalence of cardiovascular risk etc.
2) Definition of the sampling frame: The trials differ in the definition of the sampling frame. Variability exists on imaging criteria used to define the broad sample as well as clinical criteria (including time to presentation) used to further define the sample.
3) Definition of the control group: Two trials defined the control group as patients receiving Intravenous tissue plasminogen activator (tPA). The remaining three trials defined the control group as patients receiving currently acceptable standard care. This was defined in the trial protocols of the respective trials.
4) Definition of the Intervention group: Specific differences in defining the intervention group that are not captured in point 1 above include assessment of response to IV tPA, pre-specified time targets to groin puncture and reperfusion and type of devices used.

PRIMARY ANALYSES

The pooled analysis will primarily try to answer the following question:

Do patients with acute ischemic stroke and proximal anterior circulation occlusions benefit from additional mechanical thrombectomy compared with standard care (which includes iv t-PA in eligible patients)?

For the primary analyses, we propose the following

1. Use mixed methods ordinal logistic regression with "trial" and “trial*treatment” as random effects variables and the mRS at 90 days as outcome with scores 5 and 6 collapsed into a single category for analysis purposes.
2. Analyses will be unadjusted and adjusted.
3. The adjusted analysis will adjust for 7 pre-specified co-variates: age, sex, baseline stroke severity, site of occlusion, IV alteplase (yes/no), ASPECTS score, and time to randomization.

Time to randomization is dichotomized at 300 minutes. This cut-point is chosen as it likely corresponds to a stroke onset to arterial access time of 6 hours or 360 minutes; a time point currently suggested by guidelines as a threshold to determine eligibility for endovascular treatment.

To account for between trial differences, we will mixed-effects modeling for all analyses, with fixed effects for parameters of interest such as treatment assignment. In keeping with these principles, treatment effects for each trial (t_1, t_2, etc.) need not be deterministically equal, but rather are drawn from a common distribution centered on T (the overall effect across trials). This structure is captured by including “trial” and the interaction term “trial*treatment” as random effects variables in all mixed models. (As this interaction term is a structural element of the modeling, it is not tested nor is the term removed regardless of the actual variability observed between trials.) We will report the overall treatment effect T and all other effects using this model, which ensures that between-trial variance is incorporating in estimating all parameters, their standard errors and associated confidence intervals. The overall treatment effect will also reported as number needed to treat (NNT) by calculating the geometric mean of the values derived by the algorithmic joint outcome table method and the permutation test on the final mRS distribution.

SECONDARY ANALYSES

We will report the following secondary outcomes in the intervention and control arm where applicable. We will also perform pre-specified secondary analyses on these variables. Please see Table 3 for details of reporting.

Efficacy:

1) Functional independence (mRS 0-2) at 90 days (%)
2) Excellent functional outcome (mRS 0-1) at 90 days (%)
3) Stroke severity as measured using the National Institute of Health Stroke Scale (NIHSS) at 24 hours post stroke onset
4) NIHSS 0-2 at 24 hours post stroke onset (%)
5) Major early neurological recovery at 24h, defined as a reduction in National Institutes of Health Stroke Scale (NIHSS) from baseline of at least 8 points or reaching 0-1 (%)
6) Change in NIHSS from baseline to 24 hours (delta NIHSS)
7) Reperfusion (mTICI 2b/3) (%); only for intervention arm

Safety:

8) Symptomatic ICH (%)
9) Parenchymal hematoma 2 (%)
10) Mortality (%)

These pre-specified secondary analyses will use mixed effects logistic or linear regression as appropriate taking "trial" and “trial*treatment” again as random effects variables. The adjusted analysis will adjust for 7 pre-specified co-variates: age, sex, baseline stroke severity, site of occlusion, IV tPA (yes/no), ASPECTS score, and time to randomization. Wherever possible, for dichotomous outcomes results will be reported as rate ratios.

SUBGROUP ANALYSES

These will look for effect modification of the relationship between treatment and outcome (mRS at 90 days) ascertained in the primary objective by clinically relevant variables. The results will be presented as common odds ratio whenever feasible. Secondarily, we will perform similar analyses for the following secondary outcomes (mRS 0-2 vs. 3-6 at 90 days) and Mortality at 90 days. These results will also be reported as forest plots.

Subgroup analyses will be adjusted. They will include the random effects variables “trial” and “trial*treatment” terms. In addition, the models will include the interaction term “treatment*pre-specified variable.” Note the pre-specified variables are described in detail below and can be continuous or categorical or both. Main effects will be reported if no interaction is seen. If interaction is noted, relevant stratum specific effects will be reported. Subgroup analyses will be on the following variables.

1) Age
    a. Dichotomized at 18-79 vs. 80 and older
    b. More granularly divided as: 18-49, 50-59, 60-69, 70-79, 80 and older
    c. Continuous
2) Sex (Male vs. Female)
3) Baseline Stroke Severity, NIHSS: <10, 11-15, 16-20, >20
   Baseline Stroke Severity, NIHSS: continuous
4) Time from onset to endovascular treatment strategy selection (randomization): 0-300 minutes vs. greater than 300 minutes
5) Baseline ASPECTS as trichotomy – 0-5, 6-8, 9-10.
6) Baseline site of thrombi on vascular imaging (trichotomous: ICA, M1, M2) as adjudicated by core lab
7) Concomitant ipsilateral carotid artery occlusion or carotid artery stenosis (yes vs no))
8) IV alteplase (yes vs. no)

Figures:

1. Forest plot for above subgroup analyses for primary outcome. Forest plots for mRS 0-2 as outcome and mortality as outcome with similar reporting as above will be reported in Appendix.
2. Plot of model estimated mRS on the y-axis and age on the x-axis for treatment and control (along with 95% CI).
3. Plot of model estimated mRS on the y-axis and baseline NIHSS on the x-axis for treatment and control (along with 95% CI).

4. Plot of model estimated utility weighted mRS on the y-axis and age on the x-axis for treatment and control (along with 95% CI).
5. Plot of model estimated utility weighted mRS on the y-axis and baseline NIHSS on the x-axis for treatment and control (along with 95% CI).

Tables:

Table: Baseline characteristics and process measures.
Table: Primary and secondary Efficacy outcomes
Table: Safety outcomes for the pooled data
Table: Qualitative assessment of between trial differences in population.

II. Design and Methodology

The trialists propose a pooled patient level meta-analysis to address the above objectives. The trialists propose the following steps in study design. The final statistical analysis plan will be informed after discussions on the following points with the lead statistician.

1) Identifying *qualitatively* differences in trial protocols (Table 1)
2) Identifying *quantitatively* differences in patient characteristics between trials
3) Address objectives using pre-specified analytical methods. The trialists propose a random effects model while pooling to address potential *between trial* heterogeneity. Note primary analysis will be using a mixed effects model as described in sections above
4) Address secondary objectives as above
5) Address the issue of missing data and the potential for bias in missing-ness by trial design
   Missing data for baseline co-variates will be reported (%). For Table 1 describing baseline characteristics, no imputation will be made. For adjusted primary and secondary analyses, simple imputation using Median/ Mode will be attempted. Missing data on primary outcome (mRS) will be reported. No imputation technique will be used for primary outcome.
6) Address the potential existence of co-variate imbalance between treatment and control arms while pooling data
   Adjusted analysis with pre-specified co-variates as described above will offer a solution to potential existence of co-variate imbalance between treatment and control arms.
7) Address the issue of multiple comparisons and type 1 error rates while performing above tests
8) Address issue of adequate power while performing the above tests
9) Address the issue of bias in the estimated pooled effect when not including past and future trials.