STATISTICAL ANALYSIS PLAN

TWO-YEAR FOLLOW-UP OF THE MR CLEAN-LATE TRIAL

Section 1: Administrative Information

Title	Two-Year Outcomes after Collateral-Based Selection for Endovascular Treatment of Acute Ischaemic Stroke in the Late Window: Follow-Up of the MR CLEAN-LATE Trial
Trial registration	NL58246.078.17, ISRCTN19922220, Registered on 11 December 2017
Protocol ID	MEC-2017-367
SAP version and date	1.0, November 2023
Protocol version	1.8, June 2021
SAP revision	None
Roles & responsibility	**Coordinating PhD students:** Florentina M.E. Pinckaers & Ilse Huijberts **Statistical advisor:** Sander M.J. van Kuijk **Chief Investigators/Principal Investigators:** Prof. dr. Robert J. van Oostenbrugge, MUMC+ Prof. dr. Wim H. van Zwam, MUMC+ Signature & date: 24-11-2023

Section 2: Introduction

Background and rationale:

The MR CLEAN-LATE showed that EVT in the late window (6-24h after onset or last seen well) was safe and effective for acute ischemic stroke (AIS) in patients with collateral flow on CT angiography (1). This follow-up of the MR CLEAN-LATE trial reports clinical outcomes two years after randomization.

Objectives:

The primary objective of this extended follow-up of the MR CLEAN-LATE is to assess the two-year post-stroke functional outcome of EVT with best medical treatment compared to best medical treatment alone in patients with AIS, caused by an intracranial large vessel occlusion of the anterior circulation and at least some collateral flow, who can be treated between 6 and 24 hours (LATE-EVT) after symptom onset or last seen well.

Secondary objectives are to assess the effect of EVT versus best medical treatment on all-cause mortality, quality of life (EQ-5D-5L), major vascular events, and the ability to perform daily living activities (Barthel index) at two years post-stroke.

Status of the extended follow-up procedure and timing of analysis:

Currently, 485 out of the 502 patients have been contacted for follow-up at the two-year post-stroke time point. The final patient will be contacted at the end of January 2024. Data cleaning will be performed within 2 weeks, after which the database will be locked. Statistical analyses will be performed by the study-coordinators and results will be confirmed by a statistician. We aim to submit the manuscript for publication in April 2024.

Section 3: Study Methods

Trial design:

The MR CLEAN-LATE (ISRCTN19922220) was a multicenter phase III clinical trial with randomized treatment allocation, open-label treatment, and blinded endpoint evaluation (PROBE design). The study protocol has been previously published (2). Patients were included in the trial between February 2018 and January 2022.

Extended follow-up procedure:

The long-term follow-up procedures were added to the trial protocol in May 2021. From then on, patients or their representatives were also contacted by telephone at one year (± 3 months) and two years (- 3 months, + 6 months) after randomization for a renewed assessment of functional outcome and our secondary outcome measures. A trained researcher, blinded for treatment allocation, conducted the extended follow-up telephone interview using standardized forms. If patients declined consent for the two-year follow-up interview, if patients were unreachable, or if the two-year follow-up point had passed, the Dutch Death Certificate Register was consulted to assess the vital status.

Section 4: Study Population

In- and exclusion criteria:

All 502 patients included in the MR CLEAN-LATE trial will be included in the present study.

Outcomes:

Primary outcome:

- Score on the modified Rankin Scale (mRS) at two-years post-stroke (- 3 months, + 6 months).

Secondary outcomes:

- Dichotomized mRS of 0-1 vs 2-6 at two-years post-stroke (- 3 months, + 6 months).
- Dichotomized mRS of 0-2 vs 3-6 at two-years post-stroke (- 3 months, + 6 months).
- Dichotomized mRS of 0-3 vs 4-6 at two-years post-stroke (- 3 months, + 6 months).
- All-cause mortality.
- Score on the EQ-5D-5L at two-years post-stroke (- 3 months, + 6 months).
- Score on the Barthel index at two-years post-stroke (- 3 months, + 6 months).
- Major vascular events between 90 days and two-years post-stroke (i.e., stroke, major cardiac events, peripheral arterial disease, and thrombo-embolic events).

Section 5: Statistical Analysis

Analyses will be performed based on the intention-to-treat principle. All regression analyses will be conducted after imputation of missing data. Effect estimates will be presented with their 95% confidence intervals. If continuous outcome measures exhibit a non-normal distribution, log transformation will be employed to address this issue. If log transformation fails to address normality concerns, categorizing the variable will serve as an alternative approach.

Missing data:

The extent of and reason, if known, for missing data will be reported. Missing data will be handled with multiple imputation. The number of imputations will be set to the percentage of incomplete records. Predictive mean matching will be used to draw imputations for incomplete continuous variables. EQ-5D-5L health utility and Barthel index will be valued as "0" for those who died during follow-up.

Analysis of treatment effect on the primary outcome measure:

The mRS-score at two years post-stroke will be compared between the EVT- and the control arm using ordinal logistic regression. The effect estimate will be presented as an adjusted

common odds ratio representing the shift towards better functional outcome. The estimates will be adjusted for the same prognostic variables as in the MR CLEAN-LATE: age, pre-stroke mRS-score, time from onset or last seen well to randomization, baseline NIHSS score, collateral grade, unwitnessed stroke onset. Adjusted and unadjusted effect estimates will be reported with corresponding 95% confidence intervals.

In conformity with the MR CLEAN-LATE trial analysis plan, the effect of the intervention on the modified Rankin Scale will be analysed separately for the following subgroups:

- Age: age under 68, age between 68 and 77 and age above 77
- Sex: male or female
- Systolic blood pressure: 98-142, 143-165 or 166-250mmHg
- Baseline NIHSS score of 1-6, 7-14 or 15-39
- Time from onset or last seen well to randomization: 5.8-9.8, 9.8-14 or 14-28h
- Time from onset or first symptoms to randomization: 0.8-2.8, 2.8-5.0 or 5.1-22h
- Diabetes mellitus: yes versus no
- Atrial fibrillation: yes versus no
- Tandem lesion: yes versus no
- Occlusion location: ICA, ICA-T, M1, M2/3
- ASPECTS: 0-4, 5-7, 8-10
- Collateral flow: Grade 0, 1, 2 or 3
- Witnessed stroke onset: yes versus no
- Intravenous thrombolysis: yes versus no

In the interest of statistical power, for subgroups that are based on a continuous variable, the continuous variable will be used in the statistical analysis of the interaction with treatment (e.g. the whole range of age instead of the categorized variable). Statistical significance is defined as $p<0.05$.

Analysis of treatment effect on the secondary outcome measures:

- Dichotomized mRS-scores: logistic regression models will be used to estimate odds ratios.
- All-cause mortality: a Cox regression model will be used to estimate the hazard ratio. A Kaplan-Meier plot will be presented.
- EQ-5D-5L: the EQ-5D-5L score will be converted into a utility. A linear regression model will be used to estimate the between-group difference.
- Barthel index: a linear regression model will be used to estimate the between group difference.
- Major vascular events between 90 days and 2 years: all events during this period will be reported. The event rate per allocation will be calculated based on person-years at risk. The between-group difference will be presented as a relative risk reduction.

Secondary outcome analyses will be performed with the same adjustments as detailed for the primary outcome analysis. Adjusted and unadjusted effect estimates will be reported with corresponding 95% confidence intervals.

Sensitivity analysis:

We will conduct the following sensitivity analyses for the primary and secondary outcome measures:

1. As-treated analysis. Patients will be categorised as "treated" upon undergoing groin puncture for endovascular treatment (EVT).
2. Analysis solely including patients with observed functional outcome at two years post-stroke.

References

1. Olthuis SGH, Pirson FAV, Pinckaers FME, Hinsenveld WH, Nieboer D, Ceulemans A, et al. Endovascular treatment versus no endovascular treatment after 6-24 h in patients with ischaemic stroke and collateral flow on CT angiography (MR CLEAN-LATE) in the netherlands: A multicentre, open-label, blinded-endpoint, randomised, controlled, phase 3 trial. Lancet. 2023;401(10385):1371–80.

2. Pirson F, Hinsenveld WH, Goldhoorn RB, Staals J, Ridder IR de, Zwam WH van, et al. MR CLEAN-LATE, a multicenter randomized clinical trial of endovascular treatment of acute ischemic stroke in the netherlands for late arrivals: Study protocol for a randomized controlled trial. Trials. 2021;22(1):160.