RACECAT STUDY

A Trial Comparing Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory

STATISTICAL ANALYSIS PLAN

Prepared by: Sponsor:

BioClever

FUNDACIÓ ICTUS

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Signatures

RACECAT: A Trial Comparing TRAnsfer to the Closest Local Stroke Center vs. Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory.

The undersigned hereby approve the statistical analysis as described in this Statistical Analysis Plan (SAP) version 2.0.

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<tr>
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<tr>
<td>Neus Cerdà</td>
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<tr>
<td>Senior Statistician</td>
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<td>BioClever</td>
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<td>Dr. Marc Ribó</td>
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<td>Dra. Natalia Pérez de la Ossa</td>
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<td>Co-Principal Investigator</td>
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<td>Dra. Sònia Abilleira</td>
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# 1. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>EEI</td>
<td>Special Interest Event (Event d’Especial Interès)</td>
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<tr>
<td>EMS</td>
<td>Emergency Medical Services</td>
</tr>
<tr>
<td>EPA</td>
<td>Estudio Post-Autorización</td>
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<tr>
<td>EVT</td>
<td>Endovascular Treatment</td>
</tr>
<tr>
<td>EVT-SC</td>
<td>Endovascular Stroke Center</td>
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<tr>
<td>HLT</td>
<td>Highest Level Term</td>
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<tr>
<td>ICA</td>
<td>Intracranial Internal Carotid Artery</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>LLT</td>
<td>Lowest Level Term</td>
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<tr>
<td>Local-SC</td>
<td>Local Stroke Center</td>
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<tr>
<td>LVO</td>
<td>Large Vessel Occlusion</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
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<tr>
<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PP</td>
<td>Per-Protocol</td>
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<tr>
<td>PT</td>
<td>Preferred Term</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SE</td>
<td>Standard Error</td>
</tr>
<tr>
<td>SITREM</td>
<td>Sistema Integral de Tratamiento de EMergencias</td>
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<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>TICAT</td>
<td>TeleIctus-CATalunya registry</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
2. Introduction

2.1 Background and rationale

This statistical analysis plan contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the protocol of the RACECAT study. It includes detailed procedures for executing the main statistical analysis of the primary variable as well as a description of the main secondary objective.

2.2 Objectives

2.2.1 Primary objective

According to the RACECAT Protocol Version 1.0 April 23, 2016, point 2.2, the primary objective of this study is to evaluate if direct transfer of acute ischemic stroke patients with clinically suspected large vessel occlusion (LVO; established by a RACE scale score >4) to an endovascular stroke center (EVT-SC), by passing local stroke center (Local-SC), compared to transfer to the closest Local-SC, offers a better clinical outcome across the entire disability spectrum of the modified Rankin Scale (mRS) at 3 months. This analysis will only include the “enrichment” population, that is, patients with initial diagnostic of ischemic stroke or transient ischemic attack (visit 2, after initial neuroimaging at first stroke center).

2.2.2 Secondary objective

The secondary objective is to evaluate the safety (see 5.10) of the direct transfer to a EVT-SC in all recruited patients and specifically in hemorrhagic stroke patients.

3 Overall study design

3.1 Study design

This is a multicenter, cluster randomized, controlled, usual care conditions, open, blinded-endpoint trial of acute stroke patients with suspected acute LVO identified by emergency medical services (EMS) at first assistance on the field and validated by a stroke Neurologist by teleconsultation, in which two strategies will be compared: transfer to the closest Local-SC vs. direct transfer to an EVT-SC. Subjects will be followed up to 90 days post-randomization.

The trial design has been labeled no-EPA study.
3.2 Randomization

Clusters will be allocated to a specific intervention according to a pre-established temporal sequence. All subjects within the clusters will be allocated to the same intervention.

Allocation will account for 3 strata: time band (two groups of 12 hours), territory (metropolitan versus provincial area) and week day (working versus weekend day). The block sizes will not be disclosed, to ensure concealment.

Cluster randomization by 12 hours periods instead of days or weeks has been established with the aim to ensure that EMS technicians and stroke teams are unaware of the transfer allocation before the patient arrival.

Two possible transfer strategies will be assigned:

- **LOCAL-SC**: Transfer to closest local stroke center as done by the current stroke code protocol.
- **EVT-SC**: Directly transferred to an endovascular stroke center by passing the closest Local-SC.

3.3 Sample Size consideration

The main analysis is a common OR over the first 5 cut-points along the modified Rankin Scale (mRS) (shift analysis) at 90 days analyzed by Ordinal Logistic Regression. So, the two worst mRS values (5 and 6) are treated as equal in the analyses.

The proportion of ischemic stroke patients treated with EVT was estimated to be 30-38% for the EVT-SC group and 12% in the Local-SC, based on the 2015 rate in the area covered directly by an EVT-SC and areas using a drip-and-ship model. For the intervention arm, the rate of good outcomes (mRS≤2) at 90 days was estimated to be around 40-44%, and for the control arm was estimated to be 35-38%, both based on relevant literature. These estimates yield an expected difference of 0.06 in the proportion of good outcome (mRS ≤2). Translating this difference in the proportion for just a single cut-point to a common cumulative OR throughout the mRS scale, results in a required sample size of 1316 ischemic patients assuming one-sided Type I and Type II error probabilities of 0.025 and 0.20, respectively. The total sample size, including non-ischemic patients that will not compute for the final efficacy analysis, is 1754.
3.4 Changes from protocol

At the beginning of the study, the randomization APP failed to follow the previously prepared assignment lists. It was corrected and the interested parties were informed (see Appendix E).

For this reason, a new secondary sensitivity analysis will be included with an analysis of post hoc re-re-randomization, to provide evidence of adequate randomization (see Appendix G).

3.5 Statistical interim analyses and stopping guidance

Two formal efficacy interim analyses will be performed on the primary endpoint when approximately 40% and 70% of patients have completed the 90 days follow-up. The report will be sent to the independent DSMB. The DSMB will have unblinded access to all data and will advise the steering committee. The steering committee will decide on the continuation of the trial and will report to the central ethics committee. The sequential approach based on the Triangular Design is used: the trial will be ended if stopping boundaries (efficacy or futility) are reached. After a search (ref: Whitehead J, 2011, Group sequential trials revisited: Simple implementation using SAS; Statistical Methods in Medical Research 20(6) 635–656) a triangular test is specified with values $a = 1.7048$ and $v_1 = 42.2291$.

In case the DSMB stops the study for safety or external reasons (such as evidence from other trials), the efficacy analysis will be performed in a classical way, without adjusting the alpha for (impossible) further looks.

4 Analysis Sets

Two populations will be defined for main efficacy analysis; and two for the safety analysis.

4.1 Efficacy Populations

4.1.1 Modified ITT (Enrichment Population)

Reference:

The main analysis will be based on the modified ITT (enrichment population), that is, only in patients with an initial diagnosis of ischemic stroke after the first neuroimaging study (at visit 2) including both ischemic stroke and transient ischemic attack.
All patients allocated to a transfer will be included in this population, regardless of whether they fulfilled all the inclusion criteria or whether they received the assigned transfer. The groups for this population will be defined according to the allocation intervention.

If informed consent is denied the patient’s information will not be used in further efficacy analysis.

If informed consent (to employ further collected information) is not available, the patient's information will only include the mandatory data collected in the CICAT database, and these patients will be included in the main analysis taking into account that the missing data will be treated as specified in section 5.5.1.

4.1.2 Per Protocol Population (PP)

The sensitivity PP population will include patients with ischemic initial diagnostic who have been assigned to an intervention excluding major protocol deviations. Major protocol deviations include the following criteria:

- Missing informed consent
- Crossed over. Patients who modify their assigned group (EVT-SC / Local-SC) due to reasons different to neurological deterioration or severe medical complication during the transfer.

Intervention group will be defined according to initial allocation. Patients who changed the assigned destination route due to medical complications during their transfer, won't be excluded from PP population, as specified in the protocol.

The major protocol deviations will be described in the Anagram management report provided before analysis start:

If the PP population differs from the main enrichment population by 5% or less, the analysis on the PP population will not be performed.

4.2 Safety population

Safety variables will be analyzed in 2 populations: 1) all recruited patients; and 2) hemorrhagic stroke patients. Analyses will be performed using the allocated intervention.
For both populations, the vital status of those patients who have denied informed consent will be included.

5 Statistical methods

5.1 General principles

All data processing, summarization and analyses will be performed using SAS® version 9.4 or higher.

Unless otherwise noted, all variables will be summarized as follows:

- Categorical data will be described by the number and percentage of patients in each category. Missing observations will be tabulated as a separate category. The calculation of proportions will not include the missing category in the denominator.
- Continuous data will be described by the number of missing and non-missing observations; as well as the mean, standard deviation (SD), median, 25th and 75th percentiles (Q1 and Q3, respectively) and the extreme values (minimum and maximum) for the non-missing observations.

5.2 Presentation of data

All summary statistics should be printed out to one more decimal place than the raw value, except for minimum and maximum values that will be printed with the same decimal precision as the raw values. The number of patients will be presented as a whole number. P-values will be given with 3 decimals (or as <0.001 when appropriate).

All fractional numeric values will be printed with a zero to the left of the decimal point (e.g. 0.15, 0.2 etc.).

Percentage values will be printed with one digit to the right of the decimal point (e.g., 63.2%, 15.4% etc.). Less-than-signs “<0.1” will be printed when values are >0.0%

Zero will be used to indicate zero counts in frequency tabulations.
5.3 Labels and names for study visits

The labels to be used in the analysis datasets, tables, listings and figures for the different study visits are defined below.

<table>
<thead>
<tr>
<th>Visit label</th>
<th>Visit name</th>
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<tbody>
<tr>
<td>0</td>
<td>Visit 0. Enrolment</td>
</tr>
<tr>
<td>1</td>
<td>Visit 1. Allocation and intervention</td>
</tr>
<tr>
<td>2</td>
<td>Visit 2. Follow-up: Acute phase</td>
</tr>
<tr>
<td>3</td>
<td>Visit 3. Follow-up: 24 hours</td>
</tr>
<tr>
<td>4</td>
<td>Visit 4. Follow-up: 5 days or discharge</td>
</tr>
<tr>
<td>5</td>
<td>Visit 5. Follow-up: 90 days</td>
</tr>
</tbody>
</table>

5.4 Definitions

Times:

- Time from symptom onset to EMS attention:

  *Data/hora assistència SEM (SITREM) – Data/hora inici símptomes/LTSW*

- Time from symptom onset to randomization:

  *Data/hora aleatorització – Data/hora inici símptomes/LTSW*

- Time from EMS attendance to arrival at center of intervention assigned:

  *Data/hora arribada hospital receptor - Data/hora aleatorització*

- Theoretical time from EMS attendance to Local-SC and to EVT-Center (see Appendix F)
Final diagnostic: Ischemic / hemorrhagic / TIA / mimic:

<table>
<thead>
<tr>
<th>Initial diagnostic</th>
<th>Visit 5d</th>
<th>Final diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isquèmic</td>
<td>Etiologia isquèmic (≠mimic)</td>
<td>Isquèmic</td>
</tr>
<tr>
<td></td>
<td>Etiologia isquèmic (=mimic)</td>
<td>Mimic</td>
</tr>
<tr>
<td>AIT</td>
<td>Etiologia isquèmic (≠mimic)</td>
<td>AIT</td>
</tr>
<tr>
<td></td>
<td>Etiologia isquèmic (=mimic)</td>
<td>Mimic</td>
</tr>
<tr>
<td>HIC</td>
<td>Etiologia hemorràgies</td>
<td>Hemorràgia</td>
</tr>
<tr>
<td>HSA</td>
<td>Camps etiologia buit</td>
<td>Hemorràgia</td>
</tr>
<tr>
<td>Mimic</td>
<td>Camps etiologia buit</td>
<td>Hemorràgia</td>
</tr>
<tr>
<td>Subdural/hemorràgia extraaxial</td>
<td>Camps etiologia buit</td>
<td>Hemorràgia</td>
</tr>
<tr>
<td>Altres</td>
<td>Camps etiologia buit</td>
<td>Mimic</td>
</tr>
</tbody>
</table>

LVO occlusion:

<table>
<thead>
<tr>
<th>Site of occlusion</th>
<th>Visit 2: Acute phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial internal carotid artery</td>
<td>ACI extracranial</td>
</tr>
<tr>
<td>Terminal internal carotid artery</td>
<td>ACI-T</td>
</tr>
<tr>
<td>Tandem</td>
<td>ACI extracranial and ACM M1 or ACM M2</td>
</tr>
<tr>
<td>Middle cerebral artery proximal segment</td>
<td>ACM M1</td>
</tr>
<tr>
<td>Middle cerebral artery proximal segment</td>
<td>ACM M2</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>ACA</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>ACP</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>AB</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>AV</td>
</tr>
</tbody>
</table>

Eligibility for iv tPA:

- Patients eligible for iv tPA vs non iv tPA eligible when attended by EMS

*El pacient és candidat a tPA iv (TICAT)=SI*
Treatment - times:

- Time from symptom onset to iv tPA (patients who received TIV or TIV + TEV): \textit{Data/hora ivtPA} - \\
\textit{Data/hora inici simptomes} (o \textit{LTSW})

- Time from symptom onset to endovascular treatment (patients who received EVT*): \textit{Data/hora punció femoral*} - \textit{Data/hora inici simptomes} (o \textit{LTSW})

*Endovascular treatment: see point 12. Appendix D.

Dramatic early favorable response:

NIHSS at 24H < 3 or NIHSS at 24H – NIHSS score baseline ≥ 8 points

Clinical deterioration at 24 hours:

NIHSS score at 24 H - NIHSS score baseline >= 4 points or exitus in visit 24H

5.5 Imputation for missing values

5.5.1 Missing informed consent:

If informed consent is denied, the patient’s information will not be used in further efficacy analysis. However, vital status of these patients will be included in the safety analysis.

For patients with missing informed consent: accordingly to the protocol, only mandatory variables included in the CICAT (governmental-registry) but not variables added specifically for the RACECAT trial, will be used in patients with no informed consent (RACECAT code, date and time of onset, date and time of inclusion, study group assigned, hospital that offers first attention, date and time of first hospital arrival, initial diagnostic, reperfusion treatment (intravenous or/and endovascular), and mRS at day 5. These data are not monitored.

5.5.2 Missing efficacy data

In case of missing mRS scale value at 90 days, due to missing informed consent or to loss of follow-up, vital status at 90 days will be obtained by usgin the governmental registry where the
CICAT is included. For alive patients, last observation of mRS scale value (visit 5d) will be carried forward (LOCF). Patients in whom the vital status is unknown will be scored as 6.

5.5.3 Missing dates

When the date of birth is not completely known, the following will be imputed:

- If month and year are available, day 15th will be imputed
- If only year is available, June 30th will be imputed

Completely missing dates or missing years will not be imputed. No imputation of any other dates will be performed.

5.5.4 Other parameters

No other imputation for missing or partially missing data will be performed.

5.6 Statistical Analyses

Throughout the analyses the significance level will be 5% two-sided, corresponding to the 2.5% one-sided, except for the main analysis of 2.5% one-sided specified in the protocol.

There are two interim analysis planned, when 40% and 75% of patients have completed the 90 days follow-up.

Those analyses also include safety: the description of mortality at 90 days and clinical deterioration during transfer and at 24h, the principal analysis of efficacy (mRS at 90 days) and the description of baseline characteristics.

5.7 Demographics and baseline characteristics

Descriptive statistics will be shown for demographics and baseline characteristics, such as age, gender, medical history, variables related to the current stroke and time metrics.
5.8 Analyses of main objective. Efficacy

The primary endpoint is defined as a favorable outcome at 90 days after ischemic stroke onset. It is measured by the 0 to 5 scale distribution of the modified Rankin Scale (mRS) score evaluated through a structured telephone interview by a central assessor who will be masked to patients’ group assignment.

The primary analysis will be a between-group comparison of the distribution of the mRS (with values 5, severe disability, and 6, death, collapsed) using an ordinal logistic regression to estimate the common OR (shift analysis). The primary analysis for this study will be conducted using the “as allocation” paradigm. See point 5.5.1 about missing value imputation.

The primary analysis will test, with a one-sided alpha of 0.025, that the cumulative ordinal odds ratio (OR) equals 1 against the alternative hypothesis that treated patients have better evolution:

\[ H_0: \text{OR} = 1 \]
\[ H_A: \text{OR} = 1.35 \]

The primary analysis will be adjusted by stratification factors (time band, territory and week day) as well as RACE and age.

The effect of direct transfer to an EVT-SC as compared to transfer to the closest Local-SC will be measured by estimating the cumulative odds ratio (cOR) corresponding to the EVT-SC effect and its 95% confidence interval by means of the model coefficient and the corresponding Standard Error (SE) derived from the ordinal logistic regression model.

Complementary main analyses

The underlying shift assumption of a common OR throughout all possible mRS cut-points will be visually analyzed by both a comparative barplot of the cumulative proportions and a Forest plot of the classical OR estimates for each possible cut-point.

To look at consistency, main analysis will be repeated (i) without adjusting, and (ii) for the sensitivity population.

5.9 Secondary efficacy analyses

- To explore whether time to stroke center plays any role on the consistency of the intervention effect
The possible effect of time to stroke center will be evaluated in ordinal logistic regression model by testing the interaction term of time by randomized intervention for significance. Adjusted by stratification factors (time band, territory and week day) as well as age and RACE (Appendix H).

Time will be considered in three different ways: (i) difference in theoretical times to EVT-SC and Local-SC; (ii) theoretical time to EVT-SC and (iii) Symptom onset to EMS + theoretical time to EVT-SC.

The same analysis will be performed for 3 different populations: 1) Enrichment population; 2) Hemorrhagic stroke patients and 3) All patients.

- Distribution of the modified Rankin Scale score at 90 days (shift analysis, same analysis than the main analysis) in the following populations: All patients / hemorrhagic / mimics

This analysis will be adjusted by stratification factors (time band, territory and week day) as well as RACE and age

- Subgroups: The main analysis for the enrichment population, will also be repeated for all the following subgroups. Forest plot will be used to show the odds ratio with their confidence interval 95%. This analysis will be adjusted by stratification factors (time band, territory and week day) as well as RACE and age
  - Age <80 // ≥ 80
  - Gender male // female
  - Eligible for iv t-PA // non iv t-PA eligible when attended by EMS
  - Treatment with iv tPA // no treatment with iv tPA at the first hospital admission
  - Confirmed prior mRS 0-2 // mRS >2 evaluated at hospital arrival
  - Patients with values RACE scale 5-7 // RACE 8-9

- Proportion of patients receiving iv tPA
Description of the proportion of patients receiving IV TPA

- **Proportion of patients receiving EVT**

Description of the proportion of patients receiving EVT

- **Time from symptom onset to IV tPA administration (for patients treated with IV tPA) and to groin puncture (for patients treated with endovascular).**

Description of the time from symptom onset to ivtPA (for TIV and TIV+TEV patients), and time from symptom onset to groin puncture (for TIV+TEV and TEVp patients).

- **Dramatic early favorable response as determined by an NIHSS of 0-2 or NIHSS improvement ≥ 8 points at 24 (-2/+12 hours) hours in patients with ischemic stroke**

Description of the proportion of patients with dramatic early favorable response in patients with ischemic stroke.

- **Analysis of sensitivity re-randomization**

  This analysis will be presented in a separate document from the report and only will be included the patients affected by the mismatch (see Appendix G).

### 5.10 Secondary safety analyses

Safety outcomes will be analyzed by means of the description of patients with EEI and complications for each intervention.

- **Mortality at 90 days in all patients**

  A Kaplan-Meier analysis of mortality will be performed at 90 days by comparing interventions (95% CI in Hazard Ratio)

- **Mortality at 90 days in ICH patients**
A Kaplan-Meier analysis of mortality in ICH patients will be performed at 90 days by comparing interventions (95% CI in Hazard Ratio)

- Clinical deterioration requiring intubation during primary or secondary transfers
  
  Description of the percentage of patients with clinical deterioration requiring intubation during primary or secondary transfers.

- Clinical deterioration (≥4 points on the NIHSS) at 24 hours
  
  Description of the percentage of patients with clinical deterioration at 24 hours

5.11 Subgroups analysis

The principal analysis will be analyzed by different subgroups. These are specified in point 5.9.

6 Coding systems

6.1 Coding of adverse events

Adverse events (lowest level term [LLT]) are assigned to a PT and will be classified by high level term (HLT) and SOC according to the MedDRA thesaurus, version 15.1. Sponsor agreed to use the same MedDRA dictionary version throughout the study.

MedDRA allows terms to be grouped by different SOCs. Where terms are represented in more than one SOC, one SOC will be defined by the dictionary as the primary SOC. Primary SOCs are pre-determined by MedDRA mapping and there is no opportunity to alter this during the coding process. MedDRA documentation outlines the rules employed in the dictionary for allocating primary SOCs.

6.2 Coding of concomitant medication

Not applicable.
7 References

Michael A Proschan *Re-randomization tests for unplanned changes in clinical trials* clinical Trials 2017 Vol 14(5) 425-431


Whitehead J, Branson M. and Todd S., A combined score test for binary and ordinal endpoints from clinical trials; 2010, Statistics in Medicine vol 29 521-532
### Appendix A. Schedule of events

<table>
<thead>
<tr>
<th>Time point</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Follow-up (hospital admission)</th>
<th>Follow-up (90 days +/- 15 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
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<tr>
<td>T1</td>
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<tr>
<td>T1</td>
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<td></td>
<td>T2 (acute phase)</td>
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<td>T2 (acute phase)</td>
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<td>T3 (24 hours)</td>
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<td>T3 (24 hours)</td>
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<td>T4 (5 days or discharge)</td>
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<td>T5</td>
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<td>T5</td>
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</tr>
</tbody>
</table>

**Enrolment:**

- EMS identification: X
- Stroke Neurologist confirmation: X
- Eligibility criteria: X
- Allocation (randomization program by internet used by the Telestroke neurologist): X
- Registry on the TICAT registry (Telestroke neurologist): X
- Notification to the receptor center (Telestroke neurologist): X

**Interventions:**

- Direct transfer to EV-SC: X
- Transfer to the Local-SC: X
- Secondary transfer from Local-SC to CSC (if candidate to EVT): XX
- Return to the Local-SC (if necessary): XX

**Assessments:**

<table>
<thead>
<tr>
<th>Time point</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Intervention</th>
<th>Follow-up (hospital admission)</th>
<th>Follow-up (90 days +/- 15 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
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<td>T2 (acute phase)</td>
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<td>T3 (24 hours)</td>
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<td>T3 (24 hours)</td>
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<td>T4 (5 days or discharge)</td>
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<td>T4 (5 days or discharge)</td>
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<td>T5</td>
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**Version:** 2.0 (JUN 2019)
<table>
<thead>
<tr>
<th>Event/Measurement</th>
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<tr>
<td>IV-tPA eligible when attended by EMS</td>
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<td>Clinical deterioration during transfer</td>
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<td>Prior mRS (at hospital)</td>
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<td>Medical history</td>
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<td>Stroke etiology</td>
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<td>Vital signs</td>
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<tr>
<td>Baseline NIHSS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion therapy (IV-tPA or/and EVT)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Time to reperfusion therapy</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS at 24h (-2/+12h)</td>
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<td>X</td>
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<tr>
<td>Severe adverse events</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>mRS at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Appendix B: List of tables, figures and listings

Study patients
Table 1  Patient disposition – Analysis populations
Table 2 Patient discontinuation – mITT population (Enrichment Population)

Baseline characteristics
Table 3 Demographics and baseline characteristics.

Efficacy
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Table 4.2 Summary of the test statistics and upper (u) and lower (λ) stopping limits – mITT population (Enrichment Population)
Figure 1 State of the sequential plot - mITT population (Enrichment Population)
Table 4.3 Odds ratio for primary endpoint at 90 days - mITT population (Enrichment Population)
Figure 2 Description of the modified Rankin Score at 90 days by intervention - mITT population (Enrichment Population)
Table 4.4 Odds ratio (unadjusted) for primary endpoint at 90 days - mITT population (Enrichment Population)
Table 4.5 mRs at 90 day by intervention group – PP population
Table 4.6 Summary of the test statistics and upper (u) and lower (λ) stopping limits – PP population
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Table 4.7 Odds ratio for primary endpoint at 90 days - PP population
Figure 4 Description of the modified Rankin Score at 90 days by intervention - PP population
Table 4.8 Odds ratio (unadjusted) for primary endpoint at 90 days - PP population
Figure 5.1 Difference in theoretical time to EVT-SC and Local-SC – mITT population (Enrichment population)
Figure 5.2 Theoretical time to EVT-SC – mITT population (Enrichment population)
Figure 5.3 Symptom onset to EMS + theoretical time to EVT-SC – mITT population (Enrichment population)
Figure 5.4 Difference in theoretical time to EVT-SC and Local-SC – Hemorrhagic stroke patients
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Figure 5.7 Difference in theoretical time to EVT-SC and Local-SC – All patients
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Figure 5.9 Symptom onset to EMS + theoretical time to EVT-SC – All patients
Figure 6.1 Distribution adjusted of the modified Rankin Scale score at 90 days – all patients
Figure 6.2 Distribution adjusted of the modified Rankin Scale score at 90 days – hemorrhagic
Figure 6.3 Distribution adjusted of the modified Rankin Scale score at 90 days – mimics
Figure 7 Forest plot for subgroups adjusted by stratifications factors - mITT population (Enrichment population)

Table 5 Dramatic early favourable response as determined by an NIHSS of 0-2 or NIHSS improvement ≥ 8 points at 24 hours (-2/+12 hours) hours in patients with ischemic stroke

Safety

Table 6 Mortality at 90 days in all patients and ICH patients

Figure 7 Kaplan-Meier analysis of mortality at 90 days in all patients by intervention

Figure 8 Kaplan-Meier analysis of mortality at 90 days in ICH patients by intervention

Table 7 Clinical deterioration at 24 hours

Table 8 Patient with clinical deterioration who requiring intubation during primary or secondary transfer

Table 9 Description of EEI- All patients

Table 10 Description of adverse events - All patients
Appendix C: Program in SAS® for main analysis

```
proc sort data=stat.mrs90_varppal; by cod_pac; run;
proc sort data=stat.random; by cod_pac; run;
proc sort data=stat.population; by cod_pac; run;
data unio; merge stat.mrs90_varppal stat.random stat.population; by cod_pac; run;

data unio; set unio;
   if interv_assign=2 then trt=1; *EVT-SC;
   if interv_assign=1 then trt=0; *Local-SC;
   con = 1-trt; * Local-SC;
   zero = 0;
   if mrs = 6 then mrs = 5;
run;

* Logistic regression;
proc logistic data = unio ;
   class dia area torn;
   model mrs = dia area torn /tech = fisher gconv = 1E-12;
   output out = resfit predprobs = cumulative;
run;

proc sort data=unio ; by cod_pac; run;
proc sort data=resfit ; by cod_pac; run;
data cov;
   merge unio resfit;
   by cod_pac;
   array cpa(7) zero cp_0 cp_1 cp_2 cp_3 cp_4 cp_5;
   array bettera(6);
   array worsea(6);
   array ppa(6);
   do u = 1 to 6;
      bettera(u) = cpa(u);
      worsea(u) = 1 - cpa(u+1);
      ppa(u) = cpa(u+1) - cpa(u);
   end;
   drop cp_0 cp_1 cp_2 cp_3 cp_4 cp_5 ;
run;
proc datasets;
   delete resfit;
run;quit;

/* From all of the results computed, the test statistics Z and V are computed */
data zv;
   set cov;
   array bettera(6);
   array worsea(6);
   array ppa(6);
   array ya(6);
   array zpart(6);
```

array vpart(6,6);
do u = 1 to 6;
    ya(u) = (mrs - (u-1));
    zpart(u) = trt*(ya(u) - ppa(u))*(worsea(u) - bettera(u));
end;
do u = 1 to 6;
do v = 1 to 6;
    ppuv = (u = v)*ppa(u);
    vpart(u,v) = (worsea(u) - bettera(u))*(worsea(v) - bettera(v))*ppuv;
end;
end;
zq = 0;
do u = 1 to 6;
    zq = zq + zpart(u);
end;
vq = 0;
do u = 1 to 6;
do v = 1 to 6;
    vq = vq + vpart(u,v);
end;
end;
zsum = sum(zsum, zq, 0);
vsum = sum(vsum, vq, 0);
retain zsum vsum 0;
ne = sum(ne, trt, 0);
nc = sum(nc, con, 0);
retain ne nc 0;
n = ne + nc;
zfinal = zsum;
vfinal = (ne*nc)*vsum/(n*n);
run;

/* The test statistics Z* and V* are derived and printed out */
data summary;
    set zv;
    if _n_ < 701 then delete;
    zdash = zfinal;
    vdash = vfinal;
    theta = zdash/vdash;
    sd = sqrt(1/vdash);
    test = zdash/sqrt(vdash);
pvalue = 2*(1 - probnorm(test));
    low = theta - 1.96*sd;
    up = theta + 1.96*sd;
    or=exp(theta);
    orlow=exp(low);
    orup=exp(up);
    keep n zdash vdash theta sd test pvalue or orlow orup;
run;

proc print data = summary; run;
proc print data = summary;
    var n zdash vdash;
    title 'Table 1. Summary of the test statistics and upper and lower stopping limits (enrichment population)';
    run;

data output_ia1;
    set summary;
    keep n zdash vdash;
run;

data output_ia1_aj; set output_ia1; statistics='1'; run;

proc datasets library=work; delete summary zv cov; q uit; run;

data dadeszv; set Output_ia1_aj /*Output_ia2_aj Output_ia3_aj*/; run;

data dadeszv; set dadeszv;
    if n=701 then i=(701/701);
    if n=1228 then i=(1228/701);
    if n=1754 then i=(1754/701);
    rename zdash=z vdash=v;
run;

proc datasets library=work; delete plot; q uit; run;

data plot; set dadeszv;
    v1_triang = 42.154;
    a_triang = 1.7047;
    v_triang = i*v1_triang;
    lb_triang = (-a_triang*(1 - i/2.5021398))*(sqrt(v_triang)/sqrt(i));
    ub_triang = a_triang*(1 + i/2.5021398))*(sqrt(v_triang)/sqrt(i));
run;

goptions reset = all;
axis1 length = 25 minor - none w - 1 order = (-10 to 30 by 5);
axis2 length = 75 minor - none w - 1 order = (30 to 120 by 5);
symbol1 value = dot c - red interpol = join;
symbol2 value = dot c - red interpol = join;
symbol3 value = squarefilled c - blue interpol = join;
symbol4 value = squarefilled c - blue interpol = join;
symbol5 value = squarefilled c - blue interpol = join;
symbol6 value = squarefilled c - blue interpol = join;

proc gplot data = plot;
    plot lb_triang*v_triang ub_triang*v_triang z*v
    /vaxis = axis1 haxis = axis2 overlay;
run; q uit;

proc datasets library=work; delete Output_ia4_aj dadeszv plot; q uit; run;
Appendix D: Syntax to obtain the received endovascular treatments

\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{Modalitat 1}]='Desestimat'='Aillades',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{Modalitat 1}]='Només arterio dx'='Aillades',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{NIHSS pre-arteriografia}]='X'='Aillades',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV+TEV' \text{ and } [\text{Modalitat 1}]='Només arterio dx'='Aillades',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='Cap' \text{ and } [\text{Modalitat 1}]='Desestimat'='Desestimat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV+TEV'='Rescat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{Modalitat 1}]='Farmacològica'='Rescat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{Modalitat 1}]='Mecànica'='Rescat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TIV' \text{ and } [\text{Modalitat 1}]='Ambdues'='Rescat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TEVp' \text{ and } [\text{Modalitat 1}]='Només arterio dx'='Desestimat',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='TEVp'='Primari',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='Cap' \text{ and } [\text{Modalitat 1}]='Farmacològica'='Primari',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='Cap' \text{ and } [\text{Modalitat 1}]='Mecànica'='Primari',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='Cap' \text{ and } [\text{Modalitat 1}]='Ambdues'='Primari',
\]
\[
\text{if}([\text{Tractaments de reperfusió administrats}]='Cap' \text{ and } [\text{Modalitat 1}]='Només arterio dx'='Arterio DX'
\]
Appendix E: Documentation on the information and the measures established in the mismatch detected in the randomization APP

The RACECAT trial was labelled as a ‘cluster trial’ in the sense that randomization was designed to be performed at the cluster instead of at the patient level, according to a pre-established temporal sequence. Following the protocol, the Emergency Medical Services contact a stroke neurologist whenever an eligible patient is identified, and the stroke neurologist uses an App that assigns the transfer group to each patient accordingly with the pre-established temporal sequence. One company was responsible for generating the randomization code (Bioclever) and another one (Doonamis) for implementing it on the app.

During the course of the trial, after 350 patients included, we detected a mismatch between randomization and allocation. The company that parameterised the allocation sequence did not follow the randomization code provided by Bioclever. Patients were allocated following a random sequence that changes the routing group for every following patient, instead of respecting the cluster groups.

After consulting with statisticians advisors, we can affirm that:

- On the Racecat trial, intra-class correlation between patients of the same cluster was assumed to be 0, and clusters were defined in such a way that almost all clusters are expected to have no repeated patients. Only 11.8% of the patients included in the trial were not allocated to the corresponding cluster, as expected by randomization.

- Despite the deviation between the randomization list and the allocation program, patients were allocated following a pre-established, masked and unpredictable sequence, independently of any patient characteristic.

- For patients allocated in these conditions, route groups are well balanced in all the strata (location, time of day and working day/public holiday). The deviation can neither pervert baseline group balance nor introduce bias.

- This deviation does not alter the final results and reliability of trial results is not affected.

- Patients still receive one of the two treatments specified on the protocol, and this deviation does not have further implications about human subject protection.

In consequence, the Principal Investigators decided to:

- Correct the error and re-program the App as soon as possible. The assignation list programmed on the App was corrected on 20th December 2017.

- Define patient population with the words ‘as allocated’ instead of ‘as randomized’, according to CONSORT 2010 E&E BMJ guidelines.
- Informing the DSMB so that they can support the decisions taken

- Informing Ethics Committees and authorities in the next annual report

With the purpose of informing you, we are at your disposal for further information.

Principal Investigators of the RACECAT trial
Marc Ribó, Sònia Abilleira and Natalia Pérez de la Ossa
Barcelona, December 20th 2017
Appendix F: Documentation on the information about the software to calculate the theoretical time to EVT-SC or Local-SC

[see attached document]
Appendix G: Sensitivity analysis: program in SAS® post hoc pre-randomization analysis

* BD with patients with a mismatch between randomization and allocation;

```sas
* Generate a sensitivity analysis by program in SAS® post hoc pre-randomization analysis;

data aleat; set stat.random; keep cod_pac interv_assign dia area torn; run;

data mrs90d; set stat.Mrs90_varppal; run;

proc sort data=aleat; by cod_pac; run;
proc sort data=mrs90d; by cod_pac; run;

data newdata; merge aleat mrs90d; by cod_pac; run;

* Generates "rep" samples with random assignment of the intervention (two groups);
%macro assign(bd,grup,rep);
  %do i= 1 %to &rep;
    %let x=%sysfunc (ranuni(15));
    %let llavor=%sysevalf (&x*100000, integer);
    %put &llavor;
    proc surveyselect data=&bd out=RandomGroups_&i noprint
      groups=&grup
      seed=&llavor;
    run;
    data RandomGroups_&i; set RandomGroups_&i;
      Replicate = &i;
      run; quit;
  %end;
%mend;

* Execute program;
%assign(bd=newdata, grup=2, rep=1000);

proc freq data=RandomGroups; tables replicate GroupID; run;

data RandomGroups; set RandomGroups;
  if groupid = 1 then intervention = 0;
  if groupid = 2 then intervention = 1;
run;
ods listing close;

* To obtain p-value for all samples replicate;
ods output ParameterEstimates=ParEst;
proc logistic data=RandomGroups;
  class mrs intervention (param-ref) dia (param-ref) area (param-ref) torn(param-ref) /
  ref=first;
```

model mrs= intervention dia area torn / expb;
by Replicate;
oddsratio intervention;
output out-outall p=predict l=lower u=upper;
run;

proc print data=parest;
var replicate variable Estimate StdErr WaldChiSq ProbChiSq ExpEst;
where Variable = 'intervention';
run;

data parest; set parest; keep replicate variable Estimate StdErr WaldChiSq ProbChiSq ExpEst;
where Variable = 'intervention';
proc sort; by ProbChiSq; run;

* To obtain p-value for real intervention in sample;
ods output ParameterEstimates=ParEstreal;
proc logistic data=newdata;
class mrs interv_assign (param-ref) dia (param-ref) area (param-ref) torn(param-ref)/
ref=first;
model mrs= interv_assign / expb;
oddsratio interv_assign;
output out-results p=predict l=lower u=upper;
run;
Appendix H. Program in R for one secondary efficacy analysis: “To explore whether time to stroke center plays any role on the consistency of the intervention effect”

```r
### Initialization
# Remove data
rm(list=ls())

### Parameters
palette.mrs <- rev(heat.colors(7))

### Read data
setwd('...')                                  # Set the working directory
d <- read.table('...',header=TRUE,sep=';')
d$tto <- as.factor(d$tto-1)                   # Change treatment levels from 1-2 to 0-1
d$mrs <- factor(d$mrs,ordered = TRUE)         # Convert mrs to ordered factor
summary(d)                                    # Summary of the data

### Ordinal response
# Descriptive plots
windows(12,8)                                  # Open a new window
par(mfrow=c(1,2),las=1,font.axis=4,font.lab=2) # Set graphical parameters

### Plot 1: Ordinal mRS depending on treatment
t <- table(d$mrs,d$tto)                        # table mrs x treatment
barplot(t,col=palette.mrs)                    # barplot mrsxtreatment
par(xpd=NA)                                    # legend
legend(1.2,350,paste('mRS -',0:6),col=palette.mrs, 
       yjust=0,ncol=4,xjust=0.5,pch=15,bty='n',pt.cex = 1.2)
par(xpd=FALSE)

# Lines for the union of the two plots
y0 <- cumsum(t[,0])
y1 <- cumsum(t[,1])
segments(rep(1.2,7),y0,rep(1.4,7),y1,lty=2,lwd=2)

### Plot 2: Ordinal mRS depending on distance
plot(mrs~x,d,col=palette.mrs,pch=19,cex=1.1,xlab='Distance',ylab='mRS',main='mRS according to distance')
```

# Plots based on the model
#-- Run logistic regression model
model <- polr(mrs ~ tto*x, data=d)  
# Fit the model
summary(model)  
# Output of the model

### Create a temporary dataframes of hypothetical values
dist.data <- expand.grid(x = seq(min(d$x), max(d$x), 0.5), tto=as.factor(0:1))  
# All combinations of distance and treatment
dist.data1 <- data.frame(x = seq(min(d$x), max(d$x), 0.5))  
# All combinations of distance

### Predict the fitted values given the model and hypothetical data
predicted.data <- as.data.frame(predict(model, newdata = dist.data, type="probs", se=TRUE))

### Combine the hypothetical data and predicted values
new.data <- cbind(dist.data, predicted.data)

### Calculate cumulative probabilities
for(i in 0:6){
  if(i!=0) new.data[,paste0('cum',i)] <- rowSums(new.data[,3:(3+i)])
  if(i==0) new.data[, 'cum0'] <- new.data[,3]
}

### Covert to long format
new.data2 <- reshape::melt.data.frame(new.data, id.vars=1:2, measure.vars = 10:16, variable_name='mrs')

### Create auxilar variable ymin for plotting shade regions
new.data2 <- as.data.table(new.data2)
N <- nrow(new.data2)
for(i in 1:N){
  if(i %% 100==0) cat('Iteration:',i,'of',N,'\n')
  mrs_aux <- paste0('cum',as.numeric(substr(new.data2$mrs[i],4,4))-1)
  new.data2$ymin[i] <- ifelse(new.data2$mrs[i]=='cum0',0,new.data2$tto==new.data2$tto[i] &
                          x==new.data2$x[i] &
                          mrs==mrs_aux,value)
}
new.data2$mrs <- factor(substr(new.data2$mrs,4,4))

### Point Treatment OR's
b_tto <- as.numeric(coef(model)[1])  
# Beta for treatment
b_int <- as.numeric(coef(model)[3])  
# Beta for interaction
dist.data1$OR <- exp(-b_tto - b_int*dist.data1$x)  
# Point OR for the treatment effect according to diatance (Remark: Sign of betas should be changed)

### Confidence intervals for OR's
smodel <- summary(model)  
# Summary of the model
vmodel <- vcov(model)  
# Variance Covariance matrix of coefficients
dist.data1$se <- sqrt(vmodel[1,1]) +
  dist.data1$x^2 * vmodel[3,3] +
  dist.data1*x * vmodel[3,1]  
# V[b_tto + b_int] =
V(b_tto) + V[b_int] + Cov(b_tto,b_int) --> SE[] =sqrt()
dist.data1$ymin <- exp(-b_tto - b_int*dist.data1$x - 2*dist.data1$se)  
# Lower limit
dist.data1$ymax <- exp(-b_tto - b_int*dist.data1$x + 2*dist.data1$se)  
# Upper limit

### Plot
# Cumulative mRS in control arm
p1 <- ggplot(new.data2[tto==0]) + # geom_point() + aes(x=x, y=value, colour=tto) + geom_ribbon(aes(x=x, ymin=ymin, ymax=value, fill=mrs), alpha=1, colour='black') + labs(x="Distance", y="Cumulative probabilities for mRS category") + scale_fill_manual(values = palette.mrs, guide = guide_legend()) + scale_y_continuous(limits = c(0,1)) + labs(title="mRS for Control group") + theme(legend.position="bottom")

# Cumulative mRS in treated arm
p2 <- ggplot(new.data2[tto==1]) + # geom_point() + aes(x=x, y=value, colour=tto) + geom_ribbon(aes(x=x, ymin=ymin, ymax=value, fill=mrs), alpha=1, colour='black') + labs(x="Distance", y="Cumulative probabilities for mRS category") + scale_fill_manual(values = palette.mrs, guide = guide_legend()) + scale_y_continuous(limits = c(0,1)) + labs(title="mRS for Treated group") + theme(legend.position="bottom")

# OR according to Distance
p3 <- ggplot(dist.data1, aes(x=x, y=OR)) + geom_line(size=1.1) + geom_ribbon(aes(ymin=ymin, ymax=ymax), alpha=0.5) + labs(x="Distance", y="Treatment OR") + scale_colour_manual(values = c("red", "blue", "green")) + scale_y_log10(limits=c(0.1,10)) + labs(title="Odds ratio according to distance") + geom_hline(yintercept = 1, col=1)

# Plot three figures together
windows(18,8)
grid.arrange(p1, p2, p3, nrow=1)

############################################################
# Plots based on Non-parametric estimations
############################################################
## Controls
##---------------------------------------------------
## Calculate estimated probabilities for Controls
d0 <- d[d$tto==0,] # Select control patients
d0 <- d0[order(d0$x),] # Sort by distance
d0$mrs_num <- as.numeric(d0$mrs) - 1 # mrs to numeric
PLX0 <- matrix(NA, ncol=7, nrow=350) # Matrix to store the results

# Estimated probabilities for each category of the mRS according to distance
for(i in 0:6){
  daux <- d0
  daux$mrs_num <- ifelse(daux$mrs_num==i,1,0)
  plx <- predict(loess(daux$mrs_num ~ daux$x, span=2), se=T) # smoothness with SE (not used)
  PLX0[,i+1] <- pmin(pmax(0,plx$fit),1)
}
###-- Arrange controls: with the smoothness it is possible that the sum of the probabilities are not exactly 1

```r
PLX0_CUM <- as.data.frame(cbind(daux$x,t(apply(PLX0,1,cumsum)))) # rep(0,nrow(daux)),
colnames(PLX0_CUM) <- c('x',0:6)
dd0 <- as.data.table(reshape::melt.data.frame(PLX0_CUM,id.vars=1,measure.vars = 2:8,variable_name='mrs'))
for(i in 1:nrow(dd0)){
  if(i %% 100==0) print(i)
  mrs_aux <- as.character(as.numeric(as.character(dd0$mrs[i]))-1)
  dd0$ymin[i] <- ifelse(dd0$mrs[i]=='0',0,dd0[x==dd0$x[i] & mrs==mrs_aux,value])
}
dd0$mrs <- as.factor(dd0$mrs)   # mRS category
dd0$ymin <- pmin(dd0$ymin,1)    # Cumulative probability for the previous category (auxiliar variable to create the plot)
dd0$value <- pmin(dd0$value,1)  # Cumulative probability for each category
```

### Treateds ---------------------------------------------------

###-- Calculate estimated probabilities for Treateds

```r
d1 <- d[d$tto==1,]                 # Select treated patients
d1 <- d1[order(d1$x),]             # Sort by distance
d1$mrs_num <- as.numeric(d1$mrs)-1 # mrs to numeric
PLX1 <- matrix(NA,ncol=7,nrow=350) # Matrix to strore the results
for(i in 0:6){
daux <- d1
  daux$mrs_num <- ifelse(daux$mrs_num==i,1,0)
  plx <- predict(loess(daux$mrs_num ~ daux$x, span=2), s=T)  # smoothness with SE (not used)
  PLX1[,i+1] <- pmin(pmax(0,plx$fit),1)
}
```

###-- Arrange treated: with the smoothness it is possible that the sum of the probabilities are not exactly 1

```r
PLX1_CUM <- as.data.frame(cbind(daux$x,t(apply(PLX1,1,cumsum)))) # rep(0,nrow(daux)),
colnames(PLX1_CUM) <- c('x',0:6)
dd1 <- as.data.table(reshape::melt.data.frame(PLX1_CUM,id.vars=1,measure.vars = 2:8,variable_name='mrs'))
for(i in 1:nrow(dd1)){
  if(i %% 100==0) print(i)
  mrs_aux <- as.character(as.numeric(as.character(dd1$mrs[i]))-1)
  dd1$ymin[i] <- ifelse(dd1$mrs[i]=='0',0,dd1[x==dd1$x[i] & mrs==mrs_aux,value])
}
```

```
dd1$mrs <- as.factor(dd1$mrs)   # mRS category
dd1$ymin <- pmin(dd1$ymin,1)    # Cumulative probability for the previous category (auxiliar variable to create the plot)
dd1$value <- pmin(dd1$value,1)  # Cumulative probability for each category
```

p4 <- ggplot(dd0) +
  geom_ribbon aes(x=x, ymin=ymin, ymax=value, fill=mrs), alpha=1,colour='black') +
  labs(x="Distance", y="Cumulative probabilities for mRS category") +
  scale_fill_manual(values = palette.mrs,guide = guide_legend()) +
  scale_y_continuous(limits = c(0,1)) +
```
## Plot 2----------------------
### Aggregate
\[
\text{d2} <- \text{as.data.table}(d)  \\
\text{d2$x2} <- \text{factor(cut(d2$x,br=c(0,seq(20,160,15),205),include.lowest = TRUE)))}  \\
\text{d2$x3} <- \text{sapply(lapply(strsplit(gsub('[\[/\]\],''\[\]'','',
\text{each interval} \rightarrow \text{mean}  \\
\text{gsub('[\[/\]\],''\[\]'','',
\text{sub('\[',',','',as.character(d2$x2))))},','),as.numeric),mean)}  \\
\text{d3} <- \text{d2[,(n=N),by=(x2,x3,tto,mrs)]}  \\
\text{setkey(d3,x2,tto,mrs)}  \\
\]  

### Calculate smooth OR as the mean of the logs of all cumulative ORs for each distance
\[
x <- y <- c()  \\
\text{for}(i \text{ in } 1: \text{nlevels(d2$x2)}){  \\
\text{daux} <- \text{d3[x2==levels(x2)[i]]}  \\
\text{daux$mrs} <- \text{as.numeric(daux$mrs)-1}  \\
\text{logOR} <- c()  \\
\text{for}(k \text{ in } 1:6){  \\
\text{bad_ctrl} <- \text{sum(daux[tto==0 & mrs>=k,n]) + 0.5}  \\
\text{good_ctrl} <- \text{sum(daux[tto==0 & mrs<k ,n]) + 0.5}  \\
\text{bad_trt} <- \text{sum(daux[tto==1 & mrs>=k,n]) + 0.5}  \\
\text{good_trt} <- \text{sum(daux[tto==1 & mrs<k ,n]) + 0.5}  \\
\text{logOR[k]} <- \text{log(bad_trt*good_ctrl/good_trt/bad_ctrl)}  \\
}  \\
\text{y[i]} <- \text{exp(mean(logOR))}  \\
\text{x[i]} <- \text{unique(daux$x3)}  \\
}  

### data.frame with data for the plot
\[
\text{dd4} <- \text{data.frame(x=x,y=y)}  \\
\text{p6} <- \text{ggplot(dd4,aes(x=x,y=y)) + geom_smooth(col=1,se = FALSE) + geom_hline(yintercept = 1, col=1)}  \\
\text{scale_y_log10(limits = c(0.1,10)) + scale_x_continuous(limits=c(0,200))}  
\]
grid.arrange(p4, p5, p6, nrow=1)