
HoBiT

Rationale

- **Perfusion of ischemic brain may remain impaired** in almost 80% of the patients achieving successful recanalization, and hypoperfusion is associated with worse outcomes [1].

- **Head of bed (HoB)** positioning at 0 degrees in the setting of an acute intracranial vessel occlusion is associated with **improved cerebral blood flow** [2].

- Existing data from randomized clinical trials further supports the **safety (HeadPoST) [3] and potential efficacy (ZODIAC) [4] of HoB at 0-degrees.**

1. Rubiera M, et al. Stroke 2020.
2. Wojner-Alexandrov AW, et al. Neurology. 2005.
3. Anderson CS, et al. N Engl J Med 2017
4. Alexandrov AW, et al. JAMA Neurol 2025

Inclusion criteria

1. **Age 18 years** or older on the date of randomization

2. **EVT for LVO in the anterior circulation**, according to current guidelines and local standards of clinical care. The definition of LVO may include the ICA, and/ or M1-MCA, and/ or the proximal M2 segment of the MCA.

3. Capable of giving signed **informed consent** either independently, or by a LAR, or via a deferred consent process approved by the relevant ethics committee.

Exclusion criteria

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1. **Mechanical ventilatory support** for acute medical condition prior to procedure (i.e. required for reasons other than procedure).

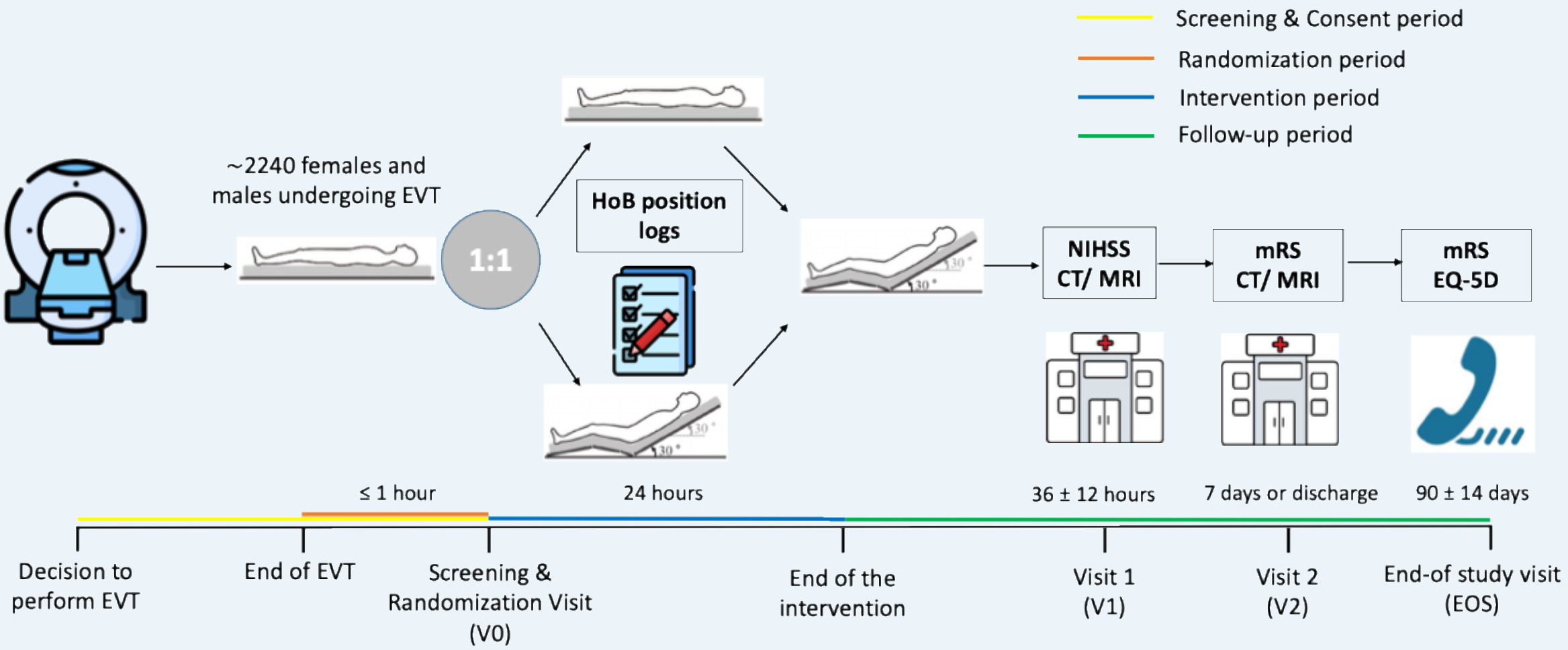
2. **Symptomatic congestive heart failure, chronic obstructive pulmonary disease**, or any other medical condition that would make either HoB position inappropriate for patient care in the judgement of the investigator.

3. Any condition, such as but not limited to, **agitation/ delirium or severe nausea/ vomiting**, that, in the view of the investigator, is expected to significantly impede maintaining the assigned HoB position.

4. Any condition with **life expectancy of less than 3 months**.

5. **Inability to randomize within 1 hour** from the end of the EVT.

Trial schema



Schedule of activities

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Procedure	Screening[a]	Randomization[a]	Intervention	Visit 1	Visit 2	EOS visit
Timelines	Decision to perform EVT – ≤ 1 hour from the end of the EVT[b]	0	0 – 24 hours	36±12 hours	7 days, or hospital discharge if first	90±14 days
Type of visit	Hospital	Hospital	Hospital	Hospital	Hospital	Virtual
Informed consent	X					
Demographics	X					
Medical history/ medications	X					
Eligibility criteria	X					
Vital signs[c]	X	X	X	X		
NIHSS	X	X		X		
Intervention Adherence			X			
CT/CTP or MRI/MRP (clinical)[d]	X			X	X	
mRS					X	X
EQ-5D-5L						X
Adverse events				X	X	
TCD (sub-study)			X			

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HEALTH THROUGH KNOWLEDGE

a Screening visit can be the same as the randomization visit, if all eligibility criteria are met.
b Defined as the time at which all endovascular devices are removed and vascular sheath closure is completed.
c Including blood pressure and heart rate.
d Collection of any studies performed prior to randomization, within 24+/-12 hours or 5-7 days from randomization as per clinical care.

Endpoints

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Primary outcome:

Functional disability at 90±14 days from randomization - modified Rankin Scale (mRS) score (ordinal analysis). Rankin Focused Assessment Ambulation (RFA-A) will be used.

Secondary outcomes:

1. Absolute difference in the NIHSS scores between randomization and 36±12 hours.
2. ENI (absolute decrease of the NIHSS score by 4 points or more at 36±12 hours from randomization)
3. Functional impairment at day 7 from randomization or discharge, assessed with the mRS score.
4. Functional independence at day 7 from randomization or discharge if happens first (mRS 0-2).
5. Functional independence at 90±14 days from randomization (mRS 0-2).
6. Quality of life at 90±14 days from randomization, assessed with the EQ-5D-5L.
7. Adherence to the assigned HoB position for 24 hours from randomization.
8. Total time spent in the assigned HoB position in the first 24 hours from randomization.
9. Infarct volume on the brain imaging (CT/ MRI) within 24 +/- 12 hours from randomization.
10. Infarct volume on the brain imaging (CT/ MRI) performed within 5-7 days from randomization.

Endpoints – safety

- Early neurological deterioration (absolute increase of NIHSS score by 4 points or more within 36 hours from randomization)
- SICH within the first 36 hours from randomization.
- Hospital acquired pneumonia within 7 days from randomization.
- Hemicraniectomy for malignant cerebral edema within 7 days from randomization.
- All-cause mortality within 7 days from randomization.
- All-cause mortality within 90±14 days from randomization.

Sample size calculation

HoBIT

- We assume a distribution of the mRS in the control arm (HoB at 30-degrees) at 90±14 days as per the EVT treatment arm of pivotal EVT trials [1], an allocation ratio of 1:1 between the two arms of the trial and that HoB at 0-degrees will improve the mRS scores at 90±14 days by a **common OR of 1.3**.

- Assuming that 46% of participants allocated to HoB 30-degrees achieve functional independence (mRS 0-2) at 90 days, improvement of 90-day mRS scores by a common OR of 1.3 with HoB positioning at 0-degrees would correspond to an absolute 6.6% increase in the odds of functional independence at 90±14 days and a number needed to treat **(NNT) of 16**.

- With an estimated cross-over rate of 13% for the HoB at 0-degrees group and 6% for the HoB at 30-degrees group, as seen in the HeadPoST trial and an expected loss to follow-up of 5% at 90±14 days [2], we would need to enroll **1,120 participants in each group (<u>total 2,240</u>)** to achieve a power of 80% with a two-sided alpha of 5% using an ordinal logistic regression model. We anticipate lower cross-over rates in HoBIT given that we are recruiting patients with severe stroke syndromes who are less likely to mobilize early.

- Participants will be recruited from approximately 48 clinical sites in Asia, Australia, Europe and N. America.

1. Goyal M, et al. Lancet
2. Anderson CS, et al. N Engl J Med 2017

TCD substudy – only for TICI 2b or higher

	R-EICA	L-EICA
Peak systolic velocity (cm/s)	☐☐☐	☐☐☐
End diastolic velocity (cm/s)	☐☐☐	☐☐☐
Mean Flow Velocity (cm/s)	☐☐☐	☐☐☐
Pulsatility index	☐☐.☐☐	☐☐.☐☐
	R-MCA	**L-MCA**
Presence of temporal window?	☐ No ☐ Yes	☐ No ☐ Yes
Insonation Depth (mm)	☐☐	☐☐
Peak systolic velocity (cm/s)	☐☐☐	☐☐☐
End diastolic velocity (cm/s)	☐☐☐	☐☐☐
Mean Flow Velocity (cm/s)	☐☐☐	☐☐☐
Pulsatility index	☐☐.☐☐	☐☐.☐☐
Presence of focal stenosis	☐ No ☐ Yes	☐ No ☐ Yes
Insonation Depth of focal stenosis	☐☐	☐☐
Total quality of the study	☐ Good ☐ Moderate ☐ Poor	

- **Primary Endpoint:** Detect absolute differences in mean flow velocity and pulsatility index for the recanalized vessel.

- **Mean flow velocity (MFV) – Pulsatility index (PI):** Measured in bilateral middle cerebral arteries (MCAs) on the TCD examination performed within 24 hours from randomization. Those indices will be compared between the two groups (HoB at 0-degrees vs. HoB at 30-degrees or higher) in both the affected MCAs (side of LVO treated with EVT) and contralateral MCAs. Guidance on measurements will be provided to a separate TCD substudy manual.

- A sample of **300 participants** undergoing TCD within 24 hours from randomization will provide 90% power (alpha=0.05%) to detect an 8 cm/s absolute increase in the MFV in the MCA of the vessel treated with EVT for participants allocated to a HoB positioning at 0-degrees, when compared to participants allocated to a HoB positioning at 30-degrees or higher.

1. Olavarria VV, et al. Cerebrovasc Dis. 2014.
2. Olavarria VV, et al. Int J Stroke 2018.