100 Patients Randomized - Thank You and Key Reminders as We Move Forward

Dear Investigators and Study Teams,

We are delighted to announce that **the 100th patient has been randomized**. This is **a major milestone reflecting your dedication and teamwork**. Thank you for your continued commitment!

As we celebrate this achievement, **we would also like to highlight several important points to safeguard trial integrity and optimize enrollment**.

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1) Our aim: 100% Consent and 100% Follow-Up

Our clear objective is a 100% consent rate and 100% follow-up rate. Complete datasets are essential for scientific validity. Please ensure:

- approaching patients or next of kin during hospitalization to obtain consent for both the trial and further use of data
- Early planning of follow-up visits or calls with some extra days to respect the visit window
- Clear documentation of consent
- Immediate action if consent or follow-up appears at risk

Every patient counts.

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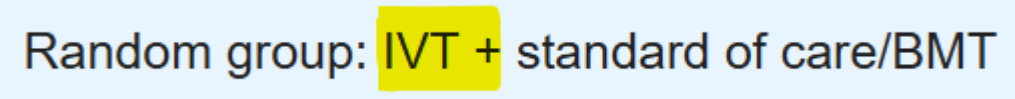
2) Avoid Treatment Cross-Overs

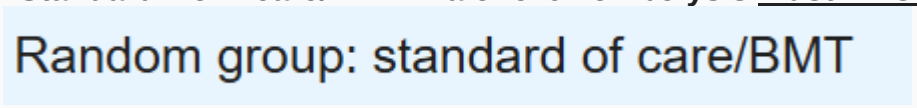
Please familiarize yourself with the terminology and workflow in the test database before enrolling patients. Please instruct teams to practice randomization in the test environment.

Be particularly attentive to:

- **"IVT + standard of care/BMT"**: **thrombolysis must be administered as soon as possible.**



- **"Standard of care/BMT" alone**: **thrombolysis <u>must NOT</u> be administered.**



Strictly avoid any unintended cross-over. Allocation must be adhered to. If you are unsure or cannot find the information: once randomized, **you can also check the allocated group at the top in the middle of the browser**:

<u>We removed the yellow box (if randomized to thrombolysis)</u>, since in some sites it did appear to cause confusion. It is now replaced it by a text alerting you to carefully look at the group allocation:

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3) No Randomization During Transfer

Randomization must only occur after:

- Admission is formally confirmed
- The patient is physically present at your hospital

In Switzerland Tele-Randomization can occur at affiliated stroke units if the patient is transferred after that. In all other countries, do not randomize during transfer. We work on the possibility to allow tele-randomization for affiliated stroke units also in other European countries.

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4) Inclusion of Stroke Mimics

Some mimics are inevitable and acceptable. However, please prioritize enrollment of patients with:

- Clear clinical stroke diagnosis
- A disabling neurological deficit

If the final diagnosis was a stroke mimic, please document this in the stroke etiology dropdown menu.

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5) Endovascular Therapy

Patients eligible for endovascular therapy can and should be enrolled. EVT patients will be capped at 20% of the total study population. However:

- The decision for or against EVT should be completely independent of the randomization (IVT or not)

6) Young Patients

Please remember to also enroll young patients. They are highly relevant for generalizability and should not be treated outside the trial.

7) Coagulation Parameters

Coagulation parameters are not required for DO-IT. There are no upper or lower thresholds defined by the protocol.

However:

- If assessed, please enter INR, TT, aPTT, and specific coagulation assays into the database and indicate whether the blood draw took place before or after IVT administration
- If rapid specific assays are available within 30 minutes and there is reasonable doubt regarding last DOAC intake, investigators may wait for results. In this case, only randomize if DOAC levels are detectable.

8) Co-Enrollment

Co-enrollment is allowed under the following conditions:

Allowed:

- Secondary prevention trials
- Observational studies

Not allowed:

- Hyperacute stroke trials including all thrombolysis trials

If in doubt, please clarify with us before co-enrolling.

9) Communication Within the Study Team

Regular communication within your study team and with emergency department staff, neurologists, and neuroradiology is essential.

Internal meetings help prevent:

- Missed enrollment opportunities
- Protocol deviations
- Randomization errors

Reaching 100 randomized patients is an impressive achievement. Maintaining rigor

while continuing recruitment is even more important. Thank you for your attention to detail and your continued dedication to the success of DO-IT!

Reach out to us with any questions, concerns of hurdles - we are happy to help you!

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Thank you for your continued commitment and collaboration. Le'ts keep the momentum going in the DO-IT trial!

Recruit. Care. Cure. DO-IT!

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