MR ASAP

Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch

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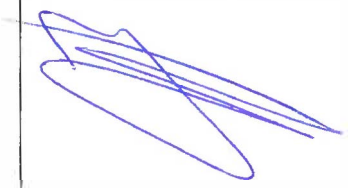
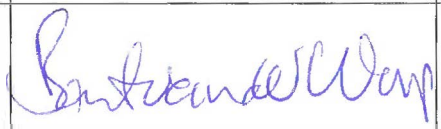
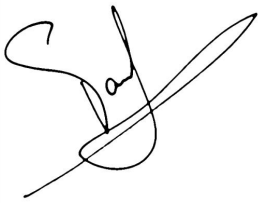
Sponsor: Prof. Dr. J.H. Veldink Manager Research Division of Neuroscience University Medical Center Utrecht		2/3/21
Project leaders: Dr. H. Bart van der Worp University Medical Center Utrecht Dr. Paul J. Nederkoorn Academic Medical Center	 	2/3/2021 2-3-21

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
ACA	**Anterior Cerebral Artery**
ADL	**Activities of Daily Living**
AE	**Adverse Event**
AR	**Adverse Reaction**
ARR	**Absolute risk reduction**
ATACH-2	**Antihypertensive Treatment of Acute Cerebral Hemorrhage II**
ATC	**Anatomical Therapeutic Chemical classification system**
BA	**Basilar Artery**
BI	**Barthel Index**
CA	**Competent Authority**
CATIS	**China Antihypertensive Trial in Acute Ischemic Stroke**
CBF	**Cerebral Blood Flow**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CI	**Confidence Interval**
CONSORT	**Consolidated Standards of Reporting Trials**
CONTRAST	**Collaboration for New Treatments of Acute Stroke**
CN	**Cranial Nerve**
CRF	**Case Report Form**
CRP	**C-Reactive Protein**
CRU	**Clinical Research Unit**
CT	**Computed Tomography**
CTA	**Computed Tomography Angiography**
DALY	**Disability-adjusted life-years**
DSA	**Digital subtraction angiography**
DSMB	**Data Safety Monitoring Board**
eCRF	**Electronic Case Report Form**
ECG	**Electrocardiogram**
ENOS	**Efficacy of Nitric Oxide in Stroke trial**
EU	**European Union**
EuroQol	**European Quality of Life**

EQ-5D-5L	**EuroQol 5-dimensions 5-level**
EudraCT	**European drug regulatory affairs Clinical Trials**
FAST	**Face-Arm-Speech Test**
FAST-MAG	**Field Administration of Stroke Therapy – Magnesium trial**
GCP	**Good Clinical Practice**
GTN	**Glyceryl trinitrate**
IAT	**Intra-arterial Treatment**
IC	**Informed Consent**
ICA	**Internal Carotid Artery**
ICF	**Informed Consent Form**
ICH	**Intracerebral Haemorrhage**
ICH-GCP	**International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
INR	**International Normalized Ratio**
INTERACT-2	**Second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial**
ISF	**Investigator Site File**
IVT	**Intravenous Thrombolysis**
LOC	**Level of Consciousness**
MCA	**Middle Cerebral Artery**
METC	**Medical research ethics committee (REC); in Dutch: Medisch Ethische Toetsings Commissie**
MR ASAP	**Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch**
MRI	**Magnetic Resonance Imaging**
mRS	**Modified Rankin Scale**
NIHSS	**National Institutes of Health Stroke Scale**
NFU	**The Netherlands Federation of University Medical Centres (in Dutch: Nederlandse Federatie van Universitair Medische Centra)**
NO	**Nitric Oxide**
OR	**Odds Ratio**
PCA	**Posterior Cerebral Artery**
REC	**Research Ethics Committee (=METC)**

RIGHT	**Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial**
SAE	**Serious Adverse Event**
SAP	**Statistical analysis plan**
SCAST	**Scandinavian Candesartan Acute Stroke Trial**
SICH	**Symptomatic Intracerebral Haemorrhage**
SMD	**Standardised Mean Difference**
SmPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TIA	**Transient Ischaemic Attack**
TOAST	**Trial of ORG 10172 in Acute Stroke Treatment**
UK	**United Kingdom**
USA	**United States of America**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Despite recent advances in the treatment of patients with acute stroke, about half of the patients have a poor outcome. Some studies have suggested that administration of glyceryl trinitrate (GTN) via a transdermal patch in the first hours after stroke onset increases the chance of a favourable outcome, possibly through an increase in intracranial collateral blood flow and a reduction in blood pressure. However, early treatment with GTN did not improve functional outcome in patients with presumed stroke in a recent large ambulance-based randomised clinical trial in the UK.

Objectives: The primary objective is to assess the effect of transdermal GTN, started within 3 hours of symptom onset in the prehospital setting, on functional outcome at 90 days in patients with acute ischaemic stroke or intracerebral haemorrhage. A secondary objective is to assess whether this effect is consistent across specific subgroups of patients, i.e., those with 1. ischaemic stroke; 2. ischaemic stroke treated with endovascular techniques; or 3. intracerebral haemorrhage.

Study design: Randomised, multicentre, open clinical trial with blinded outcome assessment.

Study population: 1400 adult patients in a maximum of 10 ambulance regions in the Netherlands with a probable diagnosis of acute stroke, as made by the paramedic in the prehospital setting; a score of 2 or 3 on the Face Arm Speech Test (FAST); systolic blood pressure ≥ 140 mm Hg; and a possibility to start the trial treatment within 3 hours of symptom onset.

Intervention: Patients will be randomly allocated to open-label GTN (5 mg/24 hours) administered as a transdermal patch by paramedics in the prehospital setting within 3 hours of stroke onset and continued for 24 hours, or to standard care alone.

Main study outcomes: The primary outcome measure is the score on the modified Rankin Scale at 90 days. Secondary outcomes include but are not limited to: collateral circulation on hospital admission, as assessed with CTA; quality of life assessed with the EuroQol 5D-5L; and home time: the number of nights among the first 90 since stroke onset that are spent in the patient's own home or a relative's home.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients included in this study will have a GTN patch for 24 hours if randomised to GTN and more frequent and intensive follow-up during hospital admission and at 90 days after stroke. No additional laboratory or imaging studies will be performed as part of this study. Based on previous studies of GTN in patients with acute stroke, we consider the risk associated with treatment as minimal. Study procedures (questionnaires and physical examination) will require an estimated 30 minutes of the patient's time in the first

week after stroke and 30 minutes at 90 days. We therefore consider the burden acceptable. Patients randomised to GTN may have a better outcome if this study will demonstrate benefit of treatment.

1. INTRODUCTION AND RATIONALE

1.1 Stroke incidence

Stroke is the second most common cause of death and the third most common cause of loss of disability-adjusted life-years (DALYs) worldwide.[1, 2] Three major types of stroke can be distinguished: about 80% are ischaemic, most often caused by occlusion of a cerebral artery or arteriole; about 15% are intracerebral haemorrhage, most often caused by a rupture of an artery into the brain; and about 5% are subarachnoid haemorrhage, most often caused by rupture of an intracranial aneurysm.[3, 4] Every year, some 1.3 million people in Europe and 25.000 people in the Netherlands have a first stroke.[5, 6] Twenty to 35% of the patients die in the first month after stroke, and around one third remain dependent on the help of others.[7, 8] Even in patients who survive a stroke with minor disabilities, quality of life is often substantially impaired.[9, 10]

1.2 Acute stroke treatment

Treatment options for patients with ischaemic stroke or intracerebral haemorrhage are limited.[11-14] For patients with ischaemic stroke, aspirin has a small benefit but can be used in a large number of patients;[15] intravenous thrombolysis (IVT) with alteplase has a modest benefit and can be used in a modest number of patients;[16] intra-arterial treatment (IAT) with a retrievable stent has a large benefit but can be used in a small number of patients;[17-21] and hemicraniectomy has a large benefit in patients aged 60 years or younger, but can be used in a very small number of patients with life-threatening space-occupying infarction.[22] For all strokes, organised care in a designated stroke unit has a modest effect on outcome and can be used in a large number of patients, but it is not clear which components of this stroke unit care drive the reduction in mortality and long-term dependency.[23] There are no other treatment options for patients with intracerebral haemorrhage of proven benefit, but early blood pressure lowering may improve outcome in a small number of patients (see below).[24] It is also illustrative that in randomised trials, the risk of a poor outcome (death or dependency) in patients treated with IVT within 3 hours of symptom onset was still 59%,[16] and in a large observational study 45%.[25] In the highly selected patient populations included in recent trials of IAT for acute ischaemic stroke, the risk of a poor outcome in patients randomised to the intervention arm ranged from 29 to 67%.[17-21] For these reasons, there is a clear need for additional effective treatment options that can be applied in broad populations of patients with acute stroke.

1.3 Hypertension in acute ischaemic stroke or intracerebral haemorrhage

About two thirds of patients presenting with an emergency department with acute stroke have an elevated blood pressure, defined as initial systolic blood pressure of 140 mm Hg or higher.[26] High blood pressures after ischaemic stroke or intracerebral haemorrhage have consistently been associated with a poor outcome.[27] However, the optimal blood pressure management in the acute phase of stroke has remained uncertain, despite several recent large clinical trials addressing this question.

1.4 Clinical trials of antihypertensive treatment in acute stroke

In the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS), which included a total of 4071 patients, blood pressure reduction with any of several antihypertensive medications started within 24 hours of stroke onset had no effect on the likelihood of death and major disability at 14 days or hospital discharge as compared with the absence of hypertensive medication (odds ratio, 1.00; 95% CI, 0.88 to 1.14; P = 0.98).[28]

Two phase III trials have tested intensive intravenous blood-pressure-lowering treatment in patients with intracerebral haemorrhage. In the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2), intensive lowering of blood pressure started within 6 hours of intracerebral haemorrhage (with a target systolic level of <140 mm Hg) was safe but did not result in a significant reduction in the rate of death or severe disability as compared with guideline-recommended treatment (with a target systolic level of <180 mm Hg). An ordinal analysis of scores on the modified Rankin Scale (mRS) however indicated improved functional outcomes with intensive lowering of blood pressure. In addition, haematoma volumes were smaller with intensive blood-pressure-lowering treatment.[24] In the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial, treatment within 4.5 hours of symptom onset of intracerebral haemorrhage to achieve a target systolic blood pressure of 110 to 139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140 to 179 mm Hg (relative risk, 1.04; 95% confidence interval, 0.85 to 1.27). In this trial, the percentage of patients with any serious adverse event during the 3 months after randomisation was higher in the intensive-treatment group than in the standard-treatment group (adjusted relative risk, 1.30; 95% CI, 1.00 to 1.69; P = 0.05).[29]

Two other trials have assessed the effects of blood-pressure-lowering treatment in populations of patients with either ischaemic stroke or intracerebral haemorrhage. In the Scandinavian Candesartan Acute Stroke Trial (SCAST) of 2029 patients with ischaemic stroke or intracerebral haemorrhage, treatment with the angiotensin-receptor blocker

candesartan started within 30 hours of stroke onset appeared associated with a higher risk of poor outcome (adjusted common odds ratio, 1.17; 95% CI, 1.00 to 1.38; P=0.048).[30] The Efficacy of Nitric Oxide in Stroke (ENOS) trial, discussed in more detail in paragraph 1.8, also found no overall benefit of transdermal glyceryl trinitrate (GTN) on functional outcome, if started within 48 hours of stroke onset. However, in patients treated within 6 hours of stroke onset, transdermal GTN did increase the chance of a good outcome.[31] The benefit of early administration of GTN could however not be confirmed in the phase III Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2). In this trial, transdermal GTN (5 mg once daily for 4 days), started within four hours of symptom onset, did not improve functional outcome in patients with presumed stroke.[32] RIGHT-2 is also discussed in more detail in paragraph 1.8.

1.5 Guidelines

Based on the data above, American guidelines for the treatment of acute ischaemic stroke state that “in patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg.”[12] For intracerebral haemorrhage, American guidelines state that “patients presenting with systolic blood pressures between 150 and 220 mm Hg and without contraindication to acute blood pressure treatment, acute lowering of systolic blood pressure to 140 mm Hg is safe and can be effective for improving functional outcome.”[14] The European guideline on intracerebral haemorrhage states that “in acute intracerebral haemorrhage within 6 h of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.”[13]

1.6 Blood pressure lowering, cerebral perfusion, and collaterals

A concern when lowering blood pressure in patients with acute stroke is a potential further reduction in cerebral blood flow. Under normal circumstances, intracranial blood vessels have the ability to keep cerebral blood flow relatively constant over a wide range of systemic blood pressures. In patients with acute stroke, this autoregulatory mechanism can be impaired, and cerebral tissue perfusion then depends at least in part on systemic blood pressure.[33, 34]

In the first minutes to hours after occlusion of a cerebral artery or arteriole, the infarct core of irreversibly damaged tissue is surrounded by a region with reduced blood supply that is potentially salvageable if reperfusion occurs: the so-called ischaemic 'penumbra.[35, 36] Blood supply to this penumbra is dependent on collateral arteries and arterioles. A substantial decrease in blood pressure in the presence of dysfunctional cerebral autoregulation may therefore lead to additional ischaemic damage. This is especially important because the above-mentioned high risk of a poor outcome in patients with ischaemic stroke treated with IVT or IAT may to a large extent be explained by the lack of salvageable brain tissue at the time the treatment is started. A major goal of treatment should therefore be to reduce the amount of irreversible ischaemic damage before arrival in the hospital, rather than increasing this by an uncontrolled reduction in blood pressure with unselected antihypertensive drugs.
In patients with occlusion of an intracranial artery, the extent of irreversible brain damage is strongly dependent on the time from occlusion and on the extent of collateral perfusion.[37]
Both in patients with ischaemic stroke in general, and in those treated with IVT or IAT, adequate collateral perfusion has independently been associated with smaller final infarct size and better functional outcomes.[37, 38] Maintaining or improving collateral blood flow could therefore improve functional outcomes in patients with ischaemic stroke through better preservation of salvageable brain tissue before recanalisation, and a reduction in collateral flow should be avoided. As mentioned above, treatment to support collateral blood flow should ideally be started as soon as possible after stroke onset, preferably in the prehospital setting by paramedics.

1.7 **Nitric oxide donors**

In patients with ischaemic stroke, blood pressure could be reduced and collateral flow promoted by the vasodilatory effects of nitric oxide donors.[37] Nitric oxide is a cerebral and systemic vasodilator that lowers blood pressure.[39] In meta-analysis of animal studies of acute ischaemic stroke, nitric oxide donors increased cerebral blood flow and reduced infarct size.[40 41] One nitric oxide donor with a well-established safety profile in patients with acute stroke is GTN. In healthy volunteers, GTN increased the estimated cerebral perfusion pressure despite a decrease in mean arterial pressure.[41] In two small studies in patients with acute stroke, GTN did not alter middle cerebral artery blood velocity or pulsatility index as assessed with transcranial Doppler,[42] nor did this change cerebral blood flow as assessed with Xenon computed tomography,[43] despite a substantial reduction in blood pressure.
In an in vitro study, GTN reversed platelet aggregation[44] and in patients with coronary artery disease, intravenous administration of GTN inhibited platelet aggregation.[45] By contrast,

transdermal GTN did not have an effect on platelet aggregation in patients with ischaemic stroke or intracerebral haemorrhage.[46]

1.8 GTN in acute stroke trials

GTN has been tested in four phase II stroke trials[42, 43, 46, 47] and two phase III trials,[31, 32] all including patients with either ischaemic stroke or intracerebral haemorrhage. The first three phase II trials and the first phase III trial had time windows to treatment that were far too broad (48 to 120 hours) to realistically reduce ischaemic damage and the fourth phase II trial was too small to reliably assess an effect on outcome. However, these did provide useful information on the safety and feasibility of treatment.

The phase III Efficacy of Nitric Oxide in Stroke (ENOS) trial[31] randomised 4011 stroke patients with raised systolic blood pressure (140 – 220 mm Hg) to 7 days of transdermal GTN (5 mg per day), started within 48 h of stroke onset, or to no GTN. Use of GTN lowered blood pressure (difference on day 1, –7.0/3.5 mm Hg; $P < 0.0001$) but did not lead to an overall improvement in functional outcome at 90 days. There was no increase in serious adverse events with GTN. The drug was also safe in patients with carotid occlusion or more severe stroke.

In the prespecified subgroup of 273 patients who were randomised within 6 hours of symptom onset, the first dose of GTN lowered blood pressure by 9.4/3.3 mm Hg ($P < 0.01$, $P = 0.064$). Importantly, GTN improved functional outcome on day 90 (adjusted common odds ratio, 0.51; 95% CI, 0.32 to 0.80). Of the patients treated with GTN, 51.4% had a poor outcome (mRS ≥ 3), as compared with 60.5% of controls (adjusted OR, 0.60; 95% CI, 0.32 to 1.13; $P = 0.11$). Significant beneficial effects were also seen with GTN for quality of life, cognition, and mood. GTN was safe to administer with less serious adverse events by day 90 (GTN, 18.8% versus no GTN, 34.1%) and a lower risk of death (hazard ratio, 0.44; 95% CI, 0.20 to 0.99; $P = 0.047$).[48] In the *post-hoc* subgroup of 61 patients with intracerebral haemorrhage randomised within 6 hours, GTN improved functional outcome (OR, 0.22; 95% confidence interval, 0.07–0.69; $P = 0.001$).[49]

The phase II Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT)[47] randomised 41 patients with probable acute stroke and systolic blood pressure >140 mm Hg to transdermal GTN (5 mg/24 hours) or no GTN, started within 4 hours of symptom onset and continued for 7 days, with the first dose given by paramedics in the prehospital setting. GTN reduced systolic blood pressure by 21 mm Hg (95% CI, -39 to 1) at 15 minutes and by 18 mm Hg (-32 to -2) at 2 hours after start of treatment. Early administration of GTN was safe, and improved functional outcome ($P = 0.040$). Of the

patients treated with GTN, 52% had a poor outcome (mRS ≥ 3), as compared with 75% of controls (P = 0.20).

Data of the above-mentioned five studies of GTN in a total of 4197 patients with acute stroke were combined in an individual-patient meta-analysis.[50] Not surprisingly, results were comparable to those reported for ENOS: GTN was safe but did not have an overall benefit on functional outcome at 90 days. In the 312 patients randomised within 6 hours of stroke onset, treatment with GTN improved functional outcome (OR, 0.52; 95% CI, 0.34 to 0.78) and reduced death (OR, 0.32; 95% CI, 0.14 to 0.78). Even within the first 6 hours of stroke onset, GTN appeared to be more beneficial with shorter durations to start of treatment (Figure 1).

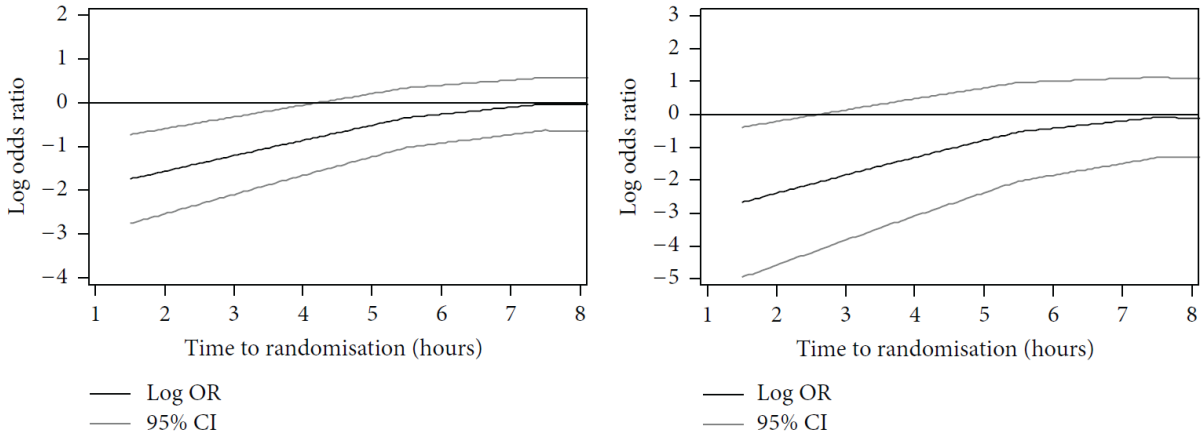

Figure 1: Effect of GTN by time to enrolment within 8 hours for score on the mRS (left) and death (right). Negative log odds ratios indicate benefit. Data from Bath *et al.* 2016.[50]

The phase III randomised Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial-2 (RIGHT-2) was based on the promising findings in the studies above. RIGHT-2 randomised 1149 adults with presumed stroke within 4 hours of onset who had a face-arm-speech test score of 2 or 3 and systolic blood pressure of 120 mm Hg or higher to transdermal GTN (5 mg once daily for 4 days) or a similar sham dressing. Treatment was started in the ambulance by paramedics, with treatment continued in hospital. The median time to randomisation was 71 min (IQR, 45 to 116). 597 (52%) patients had ischaemic stroke, 145 (13%) had intracerebral haemorrhage, 109 (9%) had transient ischaemic attack, and 297 (26%) had a non-stroke mimic at the final diagnosis of the index event. In the GTN group, participants' systolic blood pressure was lowered by 5.8 mm Hg compared with the sham group (p<0·0001), and diastolic blood pressure was lowered by 2.6 mm Hg (p=0·0026) at hospital admission. Early administration of GTN did not have an effect on functional outcome in patients with a final diagnosis of stroke or transient ischaemic stroke (adjusted common odds ratio for poor outcome (acOR), 1.25; 95% CI, 0.97 to 1.60; p=0·083), nor in the complete population (acOR, 1.04; 95% CI, 0.84 to 1.29; p=0·69). There was also no

difference in the risk of death at 90 days (19% vs 17%; acOR, 1.11; 95% CI, 0.84 to 1.47; p = 0·47) or in the risk of serious adverse events. Remarkably, GTN was associated with an improved functional outcome in patients with a stroke mimic (acOR, 0.54; 95% CI, 0.34 to 0·85; p=0·0081). This positive finding was not localised to any particular type of mimic.
In subgroup analysis, a tendency towards harm of GTN in RIGHT-2 was seen in patients with intracerebral haemorrhage, very early stroke (<1 h), and severe stroke. Furthermore, patients with intracerebral haemorrhage treated with GTN had larger haematoma size and more mass effect on hospital admission.
The discrepancy of the results of RIGHT-2 with those observed in the populations treated early in ENOS and RIGHT has several potential explanations. First, these might be due to chance rather than any true positive or negative effect of GTN. This is supported by the observation that GTN appeared to be beneficial in participants with a final diagnosis of a stroke mimic, irrespective of the underlying mimic diagnosis. Second, the difference between RIGHT-2 and ENOS-early or RIGHT might be real, due to intrinsic differences in their design: in RIGHT-2, patients were assigned far earlier (median 71 min) than in RIGHT and ENOS-early combined (median 257 min). Compared with these earlier trials, participants in RIGHT-2 were older and more likely to have premorbid dependency, diabetes, previous stroke, and ischaemic heart disease; and, among the patients with intracerebral haemorrhage, they were more likely to still be in a period of haematoma expansion. All these factors might have contributed to different effects of GTN on functional outcome, as was apparent for reductions in systolic blood pressure (6.2 mm Hg in RIGHT-2 vs 9.4 mm Hg in ENOS-early). Finally, studies showing a positive effect of GTN within 6 hours used a 7-day treatment period and had higher rates of adherence.

1.9 Pre-hospital stroke trials

Two previous trials of acute stroke treatment started by paramedics in the prehospital setting in the USA or the UK have shown that enrolment and treatment of patients with acute stroke in the field is a practical and feasible strategy for phase III trials, and that the proportion of enrolled patients with stroke-mimicking conditions (and not a stroke) can be as small as 4 to 12%.[47, 51] In these two trials, the median intervals between stroke onset and the start of study treatment were 45 and 60 minutes, respectively. In RIGHT-2, the median time from stroke onset to randomisation was 71 minutes.
For the present study, it is essential that the proportion of enrolled patients with a stroke-mimicking condition rather than a stroke is small. We will use the Face-Arm-Speech Test (FAST), which is used as a mnemonic to increase knowledge of stroke symptoms in the general population and to support diagnosis of stroke by paramedics. The FAST has been

used in clinical practice for many years by the Dutch ambulance organisations. In a UK study, paramedics using the FAST achieved high levels of detection and diagnostic accuracy of stroke.[52] Because patients with more severe strokes have a larger chance of occlusion of a proximal intracranial artery or intracerebral haemorrhage,[53, 54] and because these are the most likely to benefit from improved collateral circulation, patients should at least score 2 on the first three items of the FAST. This is also likely to increase the discriminatory power of the test, although this has not been tested.

1.10 **Conclusion**

In conclusion, there is a strong need for additional stroke treatments that can be used in a broad population of patients with acute ischaemic stroke or intracerebral haemorrhage. Very early blood pressure reduction with transdermal GTN appears a very promising option because this has shown to be safe in patients with acute ischaemic stroke or intracerebral haemorrhage; reduces blood pressure within 15 minutes of application, without a reduction in cerebral blood flow; as an NO donor, may improve cerebral collateral circulation before the start of recanalisation strategies; has been associated with time-dependent improvement of functional outcome in post-hoc analyses of previous acute stroke trials; and is cheap and easy to administer. The lack of benefit of GTN observed in RIGHT-2 may be explained by chance and does not preclude a beneficial effect in trials in a different stroke population, such as in The Netherlands, where rates of endovascular treatment are much higher. However, the tendency towards harm in specific subgroups does warrant close monitoring of safety in any future trial. Treatment with GTN in the prehospital setting has the advantage of strongly reducing the delay to treatment for a broad range of stroke patients to less than 1 hour after symptom onset, because this is simple and safe and does not require laboratory testing of the blood or imaging of the brain before the start of treatment.

2. OBJECTIVES

Primary objective

To assess the effect of transdermal GTN, started within 3 hours of symptom onset in the prehospital setting, on functional outcome at 90 days in patients with acute ischaemic stroke or intracerebral haemorrhage.

Secondary objectives

To assess whether the effects of transdermal GTN, started within 3 hours of symptom onset in the prehospital setting, on functional outcome at 90 days are consistent across specific subgroups of patients, i.e., those with 1. ischaemic stroke; 2. ischaemic stroke treated with endovascular techniques; or 3. intracerebral haemorrhage.

To assess the effect of GTN on collaterals, size of the ischemic core and salvageable brain tissue on admission to the hospital.

Tertiary objectives

To collect and analyse data regarding the deferred consent procedure and its association with patient recall and satisfaction at three months from randomisation.

To study the efficiency of national IAT implementation, given the availability of IAT hospitals and capacity, and travel times of ambulance services. To this end, we aim to collect data (time delays and diagnostics) from each step in the acute stroke pathway as input parameters for a simulation model. This way we can study the regional set-up of the IAT organisational model.

3. STUDY DESIGN

This is a multicentre, prospective randomised, open clinical trial with blinded outcome assessment (PROBE) of transdermal GTN in a dose of 5 mg/day for one day, in 1400 adult patients with suspected stroke. Patients will be recruited in a maximum of 10 ambulance regions in the Netherlands. Patients will be included in the study by a paramedic before hospital admission. Study treatment will be started in the prehospital phase, and continued in the admitting hospital. MR ASAP is part of a consortium of 5 acute stroke trials conducted by the Dutch 'Collaboration for New TReatments of Acute Stroke' (CONTRAST, see Appendix 1). The trial will be performed according to ICH-GCP principles, the Declaration of Helsinki as most recently amended in 2013, and national regulatory requirements. Because the majority of patients will be incapacitated and because the informed consent procedure should not delay the process of transporting the patient to the hospital, we will use a deferred consent procedure.

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of patients aged 18 years or older, in whom the attending paramedic makes the probable diagnosis of acute stroke with a moderately severe to severe deficit.
The trial will be conducted by members of the CONTRAST consortium. Although the trials draw from the pool of patients with acute ischemic stroke, there is no competition between the endovascular treatment trials in the collaboration (Appendix 2).

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age 18 years or older;
2. Probable diagnosis of acute stroke, as assessed by the paramedic in the prehospital setting;
3. Score of 2 or 3 on the Face Arm Speech Test (FAST, Appendix 3);
4. Systolic blood pressure ≥ 140 mm Hg;
5. Possibility to start the trial treatment within 3 hours of symptom onset;
6. Intention to transport the patient to one of the participating hospitals;
7. Written informed consent (deferred).

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Considerable pre-stroke dependency in activities of daily living, defined as staying in a chronic nursing home or rehabilitation centre;
2. Known pregnancy or lactation;
3. Indication for acute treatment with nitroglycerin or known use of nitroglycerin in the previous 12 hours;
4. Known hypersensitivity to GTN, nitrates in general, or the adhesives used in the patch
5. Glasgow Coma Scale < 8;
6. Known with any of the following heart disorders: myocardial insufficiency due to obstruction; aortic or mitral valve stenosis; constrictive pericarditis; hypertrophic obstructive cardiomyopathy; cardiac tamponade;
7. Known marked anaemia, defined as haemoglobin < 5 mmol/L;
8. Known closed angle glaucoma;

9. Known concomitant use of phosphodiesterase type-5 inhibitors, (e.g. sildenafil, tadalafil, vardenafil).

4.4 Sample size calculation

MR ASAP is powered to detect a statistically significant shift in the distribution of the scores on the mRS at 90 days in the overall study population, assuming an effect that leads to a 7% absolute risk reduction (ARR) for poor functional outcome (mRS 3 - 6) in the GTN group compared with controls (48% vs 41%). The risk of a poor functional outcome of 48% is based on findings in the Field Administration of Stroke Therapy – Magnesium (FAST-MAG) trial, a trial including 1700 patients with suspected stroke in the prehospital setting.[51] This effect is considerably smaller than the 23% ARR observed in the small phase II trial RIGHT,[47] with patients treated within 4 hours of stroke onset, and smaller than the 9% ARR in the subgroup of patients enrolled in ENOS[31] within 6 hours of symptom onset. We consider a 7% ARR sufficient to change clinical practice. We assume that the use of covariate adjustment will increase statistical efficiency by 20%, which is based on the R2 in the MR CLEAN trial data of an adjustment model containing age, pre-stroke mRS and items 4, 5a, 5b, 9 and 10 of the NIHSS that correspond to the FAST score.[55, 56]The sample size calculations are based on a simulation study with a proportional odds model. A total study size of 1280 patients then allows for a power of 80% to detect a difference at a 5% significance level in the scores on the mRS in patients treated with GTN as compared with controls. As we expect to include around 10% stroke mimics, in whom no treatment benefit is expected we increase this sample size with 10% and aim for inclusion of 1400 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product

Patients will be randomly allocated to open-label GTN (5 mg/24 hours) administered as a transdermal patch by paramedics in the prehospital setting within 3 hours of stroke onset and continued for 24 hours, or to standard care alone. If patients are randomised to treatment with GTN but prove not to have a transient ischaemic attack (TIA) or stroke after examination in the hospital, the patch will be removed. This will not be registered as a protocol deviation or protocol violation. In the unlikely scenario that a patient will be transferred to a hospital that does not participate in the study, the patch will be removed as soon as possible. This will be considered a protocol violation. In case the patient will be transported by the ambulance from one to another hospital, i.e. to receive intra-arterial treatment, and has not yet been included in MR ASAP but does fulfil all eligibility criteria, the patient can be included in MR ASAP.

5.2 Use of co-intervention

Patients in each study group will be treated according to national and international guidelines and local protocols of ischaemic stroke, intracerebral haemorrhage, or any other condition that may be diagnosed. Participation in this study is NOT a contra-indication to e.g., intravenous thrombolysis or intra-arterial treatment for ischaemic stroke or surgical treatment for intracerebral haemorrhage. Participation in this study does also not preclude inclusion in a subsequent intervention study, as long as this is not directed at blood pressure modification (see explanatory flowchart and text in Appendix 2).

5.3 Escape medication and early termination of active treatment

Any reduction or increase in blood pressure that requires treatment according to the treating physician or paramedic may be treated according to local or national protocols or guidelines. If symptomatic falls in blood pressure occur, a stepped approach to management may be practiced (as done in ENOS):[31]

- Monitor closely;
- Raise the patient's legs;
- Administer intravenous saline or colloid;
- Remove GTN patch.

Headache may also be treated according to local protocols and practice. If during the course of the first 24 hours it becomes apparent that the patient fulfils one of the exclusion criteria,

the patch will be removed. In case of discharge from the hospital within 24 hours, the patch will be removed. This will not be registered as a protocol deviation or protocol violation.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

Glyceryl trinitrate (GTN), also known as nitroglycerin, is a vasodilator used in cardiac diseases. It exerts a spasmolytic action on smooth muscle, particularly in the vascular system. This action is more marked on the venous capacitance vessels than the arterial vessels. By direct action and through the reduction of myocardial wall tension, GTN also lowers the resistance to flow in the coronary collateral channels and allows re-distribution of blood flow to ischaemic areas of the myocardium.

For details we refer to the relevant SmPC. Note that for this off-patent drug, a wide range of SmPCs is available, with subtle differences. Annual review of the SmPC will only lead to amendments to the study protocol in case of new clinical findings that are of direct relevance to the study population.

ATC-Code: C01DA02 Organic nitrates.

Indication

Prophylaxis of angina pectoris alone or in combination with other anti-anginal therapy.

Contraindications

- Known hypersensitivity to nitrates or to the adhesives used in the patch;
- Raised intracranial pressure including that caused by head trauma or cerebral haemorrhage;
- Acute circulatory failure associated with marked hypotension (shock);
- Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis or constrictive pericarditis;
- Marked anaemia;
- Closed angle glaucoma;
- Severe hypotensive conditions (systolic blood pressure less than 90 mm Hg);
- Severe hypovolaemia;
- Hypertrophic obstructive cardiomyopathy;
- Aortic stenosis and mitral stenosis;
- Constrictive pericarditis;
- Cardiac tamponade;
- Concomitant use of phosphodiesterase type-5 inhibitors. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) have been shown to potentiate the

hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contra-indicated;

6.2 Summary of findings from non-clinical studies

We refer to the SmPC, filed under D2.

6.3 Summary of findings from clinical studies

For findings in clinical studies of GTN in general, we refer to the SmPC, and for studies of GTN in patients with stroke we refer to chapters 1 and 13.

6.4 Summary of known and potential risks and benefits

We refer to the structured risk analysis in chapter 13.

6.5 Description and justification of route of administration and dosage

The route of administration and dosage as set out in paragraph 6.6. are based on the previous randomised trials ENOS[31] and RIGHT[47] of GTN in patients with acute stroke. In these trials, including a total of over 4000 patients, GTN as administered via a transdermal patch in a dose of 5 mg per day for a maximum duration of 7 days proved to be safe. GTN appeared only to be effective if started within 6 hours of stroke onset, and the potentially beneficial mode of action is therefore probably limited to the first hours. In addition, we aim at improving the collateral circulation before reperfusion in patients with ischaemic stroke, for which therapies (IVT; IAT) are started within the first six hours and have their effect during the first day. In patients with intracerebral haemorrhage, reduction of blood pressure is also likely to have largest effect during the first day. For these reasons, we have selected a maximum duration of treatment in MR ASAP of 24 hours rather than 7 days.

6.6 Dosages, dosage modifications and method of administration

GTN will be administered as a single patch which contains 18.7 mg GTN. The average amount of GTN absorbed from each patch in 24 hours is 5 mg. The patch will be applied to healthy, undamaged, relatively crease-free and hairless skin at the front or side of the chest, the upper arm, thigh, or shoulder. Skin care products should not be used before applying the patch. The patch will be removed after 24 ± 2 hours, or earlier if clinically indicated. If the patch will be detached inadvertently before the end of the 24-hour period, the same patch will be applied.

6.7 Preparation and labelling of Investigational Medicinal Product

The following information will be included on labels

a) name and telephone number of the chief investigator;
b) the name and strength of the product, pharmaceutical dosage form, route of administration, and quantity of dosage units;
c) the batch number to identify the contents and packaging operation;
d) “Uitsluitend voor in MR ASAP” (“only for MR ASAP”);
e) the storage conditions;
f) expiry date in month/year format and in a manner that avoids any ambiguity.

6.8 Drug accountability

The IMPs will be labelled and distributed to the ambulance services by the central pharmacy at UMC Utrecht. Each participating service will store the patches under prespecified, secured conditions. Each ambulance will have just two patches on board. As soon as one of these has been used, this will be replaced from the central storage. In each patient randomised to GTN, the batch number, subject identification number, and the time the patch is removed from the patient will be recorded by the investigator’s team at the admitting hospital. After removal, the patch will be destroyed according to local regulation.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/outcomes

Of the following parameters, only NIHSS at 24 hours and Barthel Index, EuroQol, home time, and patient location at 90 days are additional measurements as compared to standard care.

8.1.1 Main study outcome

The primary outcome measure is the score on the modified Rankin Scale (mRS)[57] at 90 days (± 14 days). The mRS is the preferred disability parameter for clinical trials in stroke.[58] The mRS is an ordinal hierarchical scale incorporating six categories from 0 up to and including 5, and describes the range of disability encountered post stroke. 'Death' is assigned a score of 6.

8.1.2 Secondary study parameters/outcomes

On admission to the hospital:

- Vital signs: first measured systolic and diastolic blood pressure, pulse, and body temperature;
- Collateral circulation, as assessed with CTA (only in patients in whom CT angiography is performed as part of routine clinical care);
- Lesion size: volume of the perfusion deficit (only in patients in whom CT perfusion is performed as part of routine clinical care) or ICH on the initial CT;

At 24 hours (± 4 hours):

- Treatment with intravenous thrombolysis;
- Intra-arterial treatment;
- Vital signs: systolic and diastolic blood pressure, pulse, and body temperature;
- Neurological deficit, as assessed with the NIHSS;

At 7 days (± 1 day) or at discharge, if earlier:

- SAEs in the first 7 days or until discharge, if earlier;

At 90 days (± 14 days):

- Death;
- Dichotomized mRS of 0-1 vs. 2-6;
- Dichotomized mRS of 0-2 vs. 3-6;
- Dichotomized mRS of 0-3 vs. 4-6;
- Disability assessed with the score on the Barthel Index[59] (BI);
- Quality of life assessed with the EuroQol 5D-5L (EQ-5D-5L);

- Home time: the number of nights among the first 90 days since stroke onset that are spent in the patient's own home or a relative's home. Where final follow-up occurs earlier, the last known placement will be extrapolated to 90 days;[60]
- Patient location over first 90 days (± 14 days): hospital; rehabilitation service; chronic nursing facility; home.

8.1.3 Other study parameters

Baseline characteristics, assessed as part of routine clinical care at the time of the initial assessment by the paramedics. The last assessments before study inclusion should be reported.

- Age; sex;
- Vital signs: systolic and diastolic blood pressure, and pulse;
- Score on the Glasgow Coma Scale;
- Score on the FAST;
- Time of stroke onset according to paramedics;
- Date and time of randomisation.

Baseline characteristics, assessed as part of usual clinical care at the time of hospital admission:

- Comorbidities/medical history: atrial fibrillation; diabetes mellitus; hypertension; pre-stroke mRS;
- Concurrent drugs: use of any blood-pressure-lowering drug in the 3 days before randomisation;
- Dates and times according to treating physician: stroke onset, hospital admission;
- Vital signs: blood pressure; pulse; body temperature;
- Neurological examination: NIHSS (see paragraph 8.3.4 and Appendix 4); (expected) location of the lesion (left or right hemisphere; posterior fossa);
- Laboratory examinations (see paragraph 8.3.6);
- Imaging results: stroke type: ischaemic stroke, intracerebral haemorrhage, or other relevant finding (see paragraph 8.3.7);
- Treatment restrictions (see paragraph 8.3.9);
- Stroke treatment: IVT with alteplase; IAT.

First 7 days or until discharge, if earlier:

- Vital signs: blood pressure and pulse at hourly intervals in the first 6 hours, at 2-hourly intervals between 6 and 24 hours, and daily thereafter;

- Final diagnosis (ischaemic stroke; intracerebral haemorrhage; other diagnosis);
- Cause of ischaemic stroke according to TOAST criteria;[61]
- Treatment restrictions.
- Stroke treatment: early blood pressure reduction as acute treatment of intracerebral haemorrhage; surgery for intracerebral haemorrhage or decompressive hemicraniectomy for ischaemic stroke.

Safety parameters in first 7 days or until discharge, if earlier:

- Any serious adverse event (see paragraph 9.2.2);
- Hypotension requiring clinical intervention;
- Hypertension requiring clinical intervention;
- 'Symptomatic intracerebral haemorrhage (sICH) scored according to the Heidelberg Bleeding Classification,[62] with the addition of sICH that led to death and that was identified as the predominant cause of the neurologic deterioration.

Prehospital data that will be recorded:

Time of symptom onset/last seen well, time of call for help, time of 112 call, referrer of stroke, suspected diagnose (referrer), urgency code ambulance (A1/A2/B), time of arrival ambulance on site, time of departure ambulance towards hospital, name and postal code ambulance destination, time of arrival ER. When transfer from a primary stroke centre to an intervention centre takes place, we will also collect departure time of the primary stroke centre and arrival time at the ER of the intervention centre.

8.2 Randomisation, blinding and treatment allocation

Patients will be randomly allocated to open-label GTN 5 mg/day for one day, started within 3 hours of symptom onset, or to usual care. Randomisation will be through a web-based allocation service which will also allocate a unique study number to each patient.
Patients, paramedics, and treating nurses and physicians will be aware of the treatment allocation but the assessors of outcome at 90 days will remain blinded until the database has been locked. Information on treatment allocation will be kept separate from the main study database. The independent trial statistician will combine data on treatment allocation with the clinical data in order to report to the data safety monitoring board (DSMB). The treatment allocation code will not be broken until the database will have been locked, after the last patient has completed the final follow-up and all data have been cleaned.

8.3 Study procedures

8.3.1 Baseline characteristics

See item 8.1.3. Baseline characteristics assessed by the paramedic will be included in the pre-hospital eCRF via a mobile device that is connected to the internet. The system will then also allocate a unique patient number.

8.3.2 Vital signs

Blood pressure and pulse will be assessed at baseline in the prehospital setting and at hospital admission. Where assessed as part of routine clinical practice during hospital admission, blood pressure and pulse will be collected at hourly intervals (± 30 minutes) in the first 6 hours, at 2-hourly (± 30 minutes) intervals between 6 and 24 hours, and at 24-hour (± 4 hours) intervals thereafter. Body temperature will be collected at hospital admission and at 24 (± 4) hours. Both rectal and tympanic thermometry are allowed, but the method of thermometry will be noted in the eCRF. The assessment of vital signs will be discontinued at hospital discharge.

8.3.3 Face-Arm-Speech Test (FAST)

FAST is used as a mnemonic to increase knowledge of stroke symptoms in the general population and to support diagnosis of stroke by paramedics. The FAST has been used in clinical practice for many years by the Dutch ambulance organisations. In a UK study, paramedics using the FAST achieved high levels of detection and diagnostic accuracy of stroke.[52] In the present study, the score on the FAST will be assessed in the prehospital setting by the paramedic as part of routine clinical care, before inclusion in the study.

8.3.4 National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance (Appendix 4).[63] Scores range from 0 to 42, with higher scores indicating a more severe deficit. The score on the NIHSS will be assessed at hospital admission and at 24 (± 4) hours after study inclusion.

8.3.5 Modified Rankin Scale (mRS)

The mRS is the preferred functional outcome measure in clinical stroke studies.[57] The mRS is an ordinal hierarchical scale that describes the range of disabilities encountered post stroke, incorporating six categories from 0 (complete recovery) up to and including 5 (severe disability).[57] 'Death' is assigned a score of 6 (Appendix 5). The mRS will be assessed at 7 (± 1) days or at hospital discharge, if earlier, by a member of local study team, and at 90 (± 14)

days. Assessment of outcome on the mRS at 90 days will be performed by independent assessors, blinded to the allocated and actually received treatment. Their assessment will be based on standardised reports of a telephone interview by trained research personnel who are not aware of treatment allocation. Telephone assessment of the mRS with a structured interview has a good agreement with face-to-face assessment and can thus be used reliably in the setting of a clinical trial.[64]

8.3.6 Laboratory tests

If assessed at baseline as part of routine clinical practice, results from the following laboratory tests will be collected: INR; serum glucose; estimated glomerular filtration rate; C-reactive protein (CRP).

8.3.7 Imaging: lesion type and size; collateral circulation

Brain CT or MRI will be performed as part of routine clinical care in each patient with suspected stroke. Results (e.g., visible ischaemic damage; intracerebral haemorrhage) will be noted in the eCRF. It is foreseeable that the majority of patients will also have CT angiography and perfusion of the brain, and a substantial minority DSA as part of routine clinical care in the context of IAT. No additional imaging will be performed as part of the present study. All imaging performed in the first week will be sent in a coded fashion to a central image institute for central evaluation of (where appropriate) perfusion deficits, arterial occlusion, early ischaemic damage, early lesion size, collateral circulation, and final lesion size. These evaluations will be performed blinded to treatment allocation. Algorithms for the assessment of these parameters will be developed during the course of the study.

8.3.8 Medication

The times of the start and termination of study medication will be recorded. During the first 3 days (or up to discharge, if earlier), the use of any other antihypertensive drug will be recorded.

8.3.9 Treatment restrictions

The presence of any treatment restriction will be recorded at baseline and during the first 7 days of hospital admission, and will be classified as 1. Do not resuscitate; 2. Do not intubate and ventilate; 3. Withholding other treatments that may prolong life; 4. Withholding food; 5. Withholding fluids; and 6. Palliation with morphine or a benzodiazepine. Any combination of these strategies is possible.

8.3.10 Barthel Index (BI)

The BI is an ordinal scale used to measure performance in 10 activities of daily living (ADL).[59, 65, 66] Test scores range from 0 to 100, with higher scores indicating better performance in these activities (Appendix 6). The BI will be assessed during the telephone interview at 90 days (± 14 days).

8.3.11 EuroQoL (EQ-5D-5L)

The EuroQoL 5-dimensions 5-level (EQ-5D-5L) questionnaire is a standardised measure of health outcome that has been used extensively in patients with stroke (Appendix 7).[17, 21, 67] It is easy to understand and takes a few minutes to complete. The questionnaire is primarily designed for self-completion by patients, but if the patient is impaired in writing, the EQ-5D-5L may be completed by a representative of the patient or by the trial nurse, both as instructed by the patient. If the patient will not be able to complete the questionnaire because of aphasia or cognitive impairment, the patient's representative will do this instead of the patient. The EQ-5D-5L will be assessed during the telephone interview at 90 days (± 14 days).

8.3.12 Patient location

The location of the patient at noon of the relevant day during the Hospital Phase and follow-up phase will be recorded and classified as: hospital; rehabilitation service; chronic nursing facility; home (own or relative's). 'Home time,' defined as the number of nights among the first 90 since stroke onset that are spent in the patient's own home or a relative's home is a secondary outcome, for which the resource use will be censored at 90 days. Where final follow-up occurs earlier, the last known placement will be extrapolated to 90 days.[60]

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. The reason for withdrawal, if available, will be recorded in the eCRF. Data from non-consenting subjects will only be used when there is no written objection from the subject or representative. In an effort to describe the non-consenting population we will ask the subject or his/her representative to allow the use of routinely collected data in a coded manner. If no consent for the use of these data is obtained, only the following will be noted: study number, treatment allocation and refusal.

8.5 Replacement of individual subjects after withdrawal

For each patient that withdraws before the final outcome assessment, an additional patient will be included.

8.6 Follow-up of subjects withdrawn from treatment

In patients who discontinue their allocated treatment, this event will be recorded, including the reason for discontinuation if available. Further treatment will be at the discretion of the treating physician. Follow-up will be carried out as planned.

Due to the deferred consent procedure, study medication has been administered to patients randomised to GTN before informed consent has been obtained. Therefore it is not ethical, for the safety of all patients in the study, to eliminate all information of patients who do not provide informed consent in case of a serious adverse event in the first 7 days, or death during the full study period (both important safety variables for the study). Eliminating these records could result in an underestimation of the true risk of the study treatment and reduce the validity of the data and could lead to major safety concerns for all patients in case patients with a poor outcome will selectively withdraw from study participation. To overcome this safety concern, we will register for non-consenting patients only the variables: patient's study number, date of randomisation, study treatment, final diagnosis, investigator reported serious adverse events in the first 7 days (or until hospital discharge, if earlier), in-hospital mortality (yes/no). All other information will completely be erased from the patient's study record. The link to the study database will be erased from the medical record.

8.7 Premature termination of the study

If the Sponsor, the Investigator(s), or Regulatory Authorities discover any condition during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor and the Investigator(s). The Sponsor has the right to terminate the participation of either an individual site or the complete study at any time. This action may be taken based on the recommendation of the independent DSMB.

Reasons for terminating may include, but are not limited to, the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to subjects;
- Subject enrolment is unsatisfactory;
- Data recording is inaccurate or incomplete to an unacceptable extent;
- Investigator(s) do not adhere to the protocol or applicable regulatory guidelines in conducting this study;

- Submission of knowingly false information from the study site to the Sponsor or regulatory authorities;
- Results of an interim analysis supporting terminating the study.

In the event that the study is terminated early, the Sponsor will provide specific guidance to investigational sites regarding the end-of-study procedures.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs, and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the IMP. Because the IMP has been marketed and used for over a hundred years and has a well-known safety profile, AEs will not be recorded unless they are serious (SAE or SUSAR).

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All SAEs occurring between randomisation and day 7 have to be reported to the study Sponsor within 24 hours of Investigator's first awareness about the event, except for expected SAEs (see below). Any AE that occurs for the first time after day 7 is highly unlikely to be related to the IMPs. However, any SAE occurring between day 7 and the end of follow-up on day 90 (± 14 days) for which a causal relationship between the IMP and the SAE is

considered at least a reasonable possibility should also be reported. This includes the reporting of SUSARs (see below).
The sponsor will report all unexpected SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other unexpected SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Expected SAEs are events that are known to occur in the conditions under study or with the IMP used in the trial as defined in its SmPC. As mentioned above, the IMP has been marketed and used for over a hundred years and has a well-known safety profile. Expected SAEs are defined in the protocol (Appendices 8 and 9). Expected SAEs are excluded from expedited reporting but should be documented in the eCRF within 7 days of the Investigator's first awareness about the event. Expected SAEs will be included as line listing in the annual safety report to the accredited METC.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:
1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
- Summary of Product Characteristics (SmPC) for an authorised medicinal product.

All SUSARS occurring between randomisation and the end of follow-up at day 90 (± 14 days) have to be reported by the local Investigator to the study Sponsor within 24 hours of Investigator's first awareness about the event. The sponsor will report the following SUSARs through the web portal *ToetsingOnline* to the METC in an expedited fashion:
- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line listing) that will be submitted once every half year to the METC. This line listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or *ToetsingOnline* is sufficient as notification to the competent authority.

In the event this becomes applicable, the Sponsor will report all SUSARs to the competent authorities in other Member States in an expedited fashion, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and (in the event this becomes applicable) competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions in the present study, ordered by organ system;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All SAEs occurring between randomisation and day 7, and all SUSARs occurring between randomisation and the end of follow-up at day 90 (± 14 days) will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will oversee the safety of patients in the trial and the efficacy of the intervention under study. They will work in accordance with a dedicated charter and will follow processes recommended by the DAMOCLES statement. The DSMB will meet in person or by telephone at least annually. With respect to safety, the DSMB will conduct unblinded interim analyses after every 100 patients have completed follow-up, until at least patient number 1000. With respect to efficacy, the DSMB will conduct unblinded interim analyses after 900 patients had their final follow-up. DSMB members will receive listings of all SAE reports as well as unblinded aggregate summaries of data by treatment group for review in closed meetings. Feedback, blind to treatment, will be provided in open meetings and in written conclusions to the sponsor and the MR ASAP project leaders.

10. STATISTICAL ANALYSIS

10.1 Statistical analysis plan (SAP)

The analysis and reporting of the trial will be in accordance with CONSORT guidelines. Before follow-up will have been completed, a statistical analysis plan (SAP) will be developed that will specify: (i) Hypotheses to be tested; (ii) Treatment effects to be estimated in order to satisfy the primary and secondary objectives of this trial; (iii) Technical description of the statistical methodology and procedures for performing the statistical analysis of outcome measures and SAE data; (iv) Primary, secondary, and sensitivity analyses; and (v) Subgroup analyses. The SAP will be signed off by the trial Executive Committee and then uploaded on the public area of the trial website. The final statistical analysis will be performed once recruitment has ceased, final follow-up has been completed, final data have been checked and any errors corrected, and the database has been locked.

All analyses will be performed according to the intention-to-treat principle. Baseline data by treatment allocation will be reported with statistical procedures. Missing values for baseline characteristics will be reported. Missing baseline characteristics will be imputed using regression imputation.

10.2 Primary outcome

The primary effect estimate will be a shift in the mRS score at 90 days (± 14 days) assessed by means of ordinal logistic regression, and will be expressed as a common odds ratio with 95% confidence interval. The assumption of proportional odds will be assessed using the likelihood ratio test. The statistical analyses will be performed according to the intention-to-treat principle and adjusted for relevant baseline characteristics including age, sex, stroke type, score on the FAST at study inclusion, time of symptom onset to randomisation, pre-stroke score on the mRS, and ambulance region.

10.3 Secondary outcomes

Binary logistic regression will be used for binary outcomes, including death, unfavourable outcome, and SAEs. Ordinal logistic regression will be used for ordered categorical data and multiple regression will for continuous outcomes. Wilcoxon rank sum test will be used for continuous outcome measures which are not normally distributed.

10.4 Subgroup analyses

Comparison of the primary outcome in the intervention group vs. control will be performed in the following pre-specified subgroups:

- Age (≤70, > 70 years);
- Sex (male, female);
- Stroke type (ischaemic stroke, intracerebral haemorrhage);
- In patients with ischaemic stroke: visible occlusion of the proximal intracranial arteries (internal carotid artery (ICA); basilar artery (BA); first or second segment middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (PCA));
- Intravenous thrombolysis (yes; no);
- Intra-arterial treatment (yes; no);
- Blood pressure, dichotomised at the median;
- Stroke severity at presentation in the hospital;
- Time to treatment (<90 minutes; ≥ 90 minutes).

10.5 Interim analyses

See paragraph 9.5. Interim analyses will only be performed by the DSMB.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The trial will be performed according to ICH-GCP principles, the Declaration of Helsinki as most recently amended in 2013, and the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

This study evaluates the effect of an acute treatment in an emergency situation concerning a life-threatening disorder. In the acute stage, the very large majority of the patients will lack the capacity to decide on participation in this trial. The large majority of the patients' legal representatives will also lack this capacity because of the emergency situation, the necessity for urgent treatment and the emotional stress of the situation. Conversely, participation in the trial may be of direct benefit to the patient.
The executive committee feels that the emergency situation, the vulnerable patient group and the importance of early treatment provide ethically and legally valid reasons for an emergency procedure where obtaining consent after the study procedure takes place (deferred consent). The trial cannot practically and ethically be carried out without deferred consent, nor can the trial be investigated in any other patient group than the one mentioned above.

In patients suspected to have acute stroke who have the possibility for treatment within six hours of symptom onset, the aim and task of the paramedics is to stabilise the patient and to transport him/her as quickly as possible to a hospital for diagnosis and stroke treatment.[68, 69] This prevents the paramedic from obtaining informed consent for study participation before enrolment into the study. For this reason, we will use a deferred informed consent procedure, i.e., informed consent will be obtained after enrolment in the study. This is reasonable because of the proven safety of the IMP (see chapter 12), the lack of invasive study procedures, and the time-dependent benefit of GTN suggested in previous studies (see paragraph 1.8). Not all patients will be able to provide consent themselves due to neurological disability and legal representatives might not be available in the acute setting. Also, part of acute stroke patients is eligible for intra-arterial thrombectomy, where immediate application of the treatment will lead to additional benefit; for every hour delay, the absolute benefit of treatment (probability of recovery to independent living) decreases by 6%.[70]

When there is no apparent emergency situation and there is sufficient time to inform patients or their representatives about their treatment, this is the appropriate route in deriving informed consent. However, as set out above, all patients with (the clinical suspicion of) acute stroke are at any time in an emergency situation. Therefore, all patients or representatives will be approached for deferred consent.

As soon as possible but deemed reasonable and appropriate by the investigator, informed consent will be obtained in accordance with the Declaration of Helsinki, ICH-GCP, the Data Protection Directive (Directive 95/46/EC), and national and local regulations. The Sponsor will prepare the informed consent form (ICF) and provide the documents to the CA and REC for approval.
Before informed consent can be provided, the investigator or an authorised member of the investigational staff must explain to potential study subjects and/or their legal representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects and/or their legal representatives will be informed their participation is voluntary and they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects and/or their legal representatives will be told that alternative treatment strategies are available if they refuse to take part and that such refusal will not prejudice future treatments. Finally, they will be told the local and central investigators will maintain a subject identification register for the purposes of long-term follow-up and that their medical records may be accessed by health authorities and authorised sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulation. By signing the ICF the subject and/or the legal representative is authorising such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations if needed, or to obtain information about his or her vital status.

If the subject is considered mentally competent to provide consent, the subject will be informed and asked for consent. However, if the subject lacks decision-making capacity, the investigator will search for a legal representative available. Every 24 hours, the investigator will assess whether the subject or the legal representative is capable of making a decision about participation in this trial in the current situation. If not, every 24 hours later will be evaluated if informed consent can be obtained. If there is no legal representative available, study procedures will be continued until a proxy is present.

The subject and/or his/her legal representative will be given sufficient time to read the ICF and the opportunity to ask questions. However, this time period is limited to the duration of the hospital admission. After this explanation, consent should be appropriately recorded by means of the subject's or the legal representative's personally dated signature and authorised study staff's personally dated signature. After obtaining the consent, a copy of the ICF must be given to the subject.

Copies or a second original of the signed ICF will be given to the subject and the original will be maintained with the subject's records. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated if necessary. All subjects for whom this is relevant should be informed of the new information and give their consent to continue the study.
If a patient who has been enrolled into the study refuses to participate and sign the ICF, or if his/her legal representative refuses this in case of the patient's incapacity, participation into the study will be terminated immediately. Data from non-consenting subjects will only be used when there is no written objection from the subject or representative. In an effort to describe the non-consenting population we will ask the subject or his/her representative to allow the use of routinely collected data in a coded manner. The refusal and the reason, if available, will be recorded in the patient's clinical chart.

If a patient has died before deferred consent has been obtained, his/her representative will be informed about the study treatment the patient may have received, trial procedures and use of the collected data. A separate information letter will be sent to a representative of the patient.

A flowchart of the deferred consent procedure can be found in Appendix 10.

11.3 **Objection by incapacitated subjects**

MR ASAP will include subjects aged 18 years or older, who may lack the capacity to provide informed consent. A vital criterion for valid consent by the patient for inclusion in a clinical trial is the patient's decision-making capacity. The criteria for assessing decision-making capacity vary, but generally include four interrelated capacities: to understand relevant information, to appreciate the current situation and consequences of decisions, to use sufficient reasoning to make decisions, and to communicate a choice.[71, 72] MR ASAP will include patients with moderately severe to severe stroke because these patients are at the highest risk of a poor outcome.[73-76] The large majority of patients with moderately severe to severe stroke have a diminished decision-making capacity because of a reduced level of

consciousness, aphasia, or another cognitive disorder. Patients with stroke but with a maintained capacity to provide informed consent will have considerably smaller lesions and will have a stroke severity at the less severe end of the spectrum.[77, 78] Results of trials obtained in patients with the capacity to provide consent can therefore not be extrapolated to patients who cannot give consent. For these reasons, the trial Executive Committee feels that it is ethically appropriate to include incapacitated patients in this trial if the informed consent of their legally designated representative has been obtained.
Incapacitated subjects will be provided study information in a way that is adequate in view of their capacity to understand it. The explicit wish of an incapacitated subject who is capable of forming an opinion to refuse participation in, or to withdraw from, MR ASAP at any time, will be respected by the investigator. No incentives or financial inducements will be given to the patients or their legally designated representatives.
This policy is in line with 'regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use' because data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods; MR ASAP relates directly to the medical condition from which the patient suffers; and there are scientific grounds for expecting that participation in the clinical trial may produce a direct benefit to the incapacitated subject outweighing the risks and burdens involved if the patient will receive active trial treatment. On participants not receiving active trial treatment, MR ASAP will impose minimal burden.

Incapacitated patients will be provided with trial information and will be asked to give informed consent as soon as they will have regained their decision-making capacity. We refer to Appendix 10.

11.4 **Benefits and risks assessment, group relatedness**

We refer to Chapter 13.

11.5 **Compensation for injury**

Ambulance organisations will be regarded as a participating study sites, as defined by the Central Committee on Research Involving Human Subjects (Dutch: CCMO). The sponsor and each of the participating study sites have a liability insurance which is in accordance with article 7 of the WMO.

The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 **Incentives**

No incentives will be given to subjects for participation in this study. Reimbursement for travel to the investigational site incurred by the subject caused directly by the study or its procedures may be provided at reasonable and fair terms.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Clinical data will be captured using an eCRF, developed with the electronic data capture system OpenClinica, which is a fully web-based system that meets all ICH-GCP requirements for electronic data entry with respect to safeguarding data integrity and data security. Required data for this study are to be obtained from the subject's medical notes/source documents where the information was first recorded and then entered into the eCRF. Data from the eCRF will be encoded and stored in a study database. Only authorised and trained site staff will be allowed to enter data into the eCRF and make changes to eCRF data.

All eCRF data should be verifiable to a source at the investigational site or accessible by the site staff.

Data points that are not considered part of the eCRF (e.g. derived data points and administrative data points) will be automatically calculated or entered by authorised staff of the Sponsor or its designee.

All changes made to the eCRF data will be captured via an electronic audit trail, indicating at least date and time of change, the reason for changing the data, the individual that made the change and the old and new data value.

Source documents may include but are not limited to the following original documents, data, and records:

- Ambulance and hospital records
- Medical histories and narrative statements relating to the subject's progress
- Clinical and office charts
- Operative reports
- Laboratory notes/reports
- Memoranda and telephone notes/records
- ECG recording
- Pharmacy dispensing records
- Recorded data from automated instruments
- Copies of transcriptions certified after verification as being accurate copies

On request the Investigator shall provide the Sponsor access to any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or regulatory queries or requests for audit or inspections, it is also necessary to have access to the

complete study records, provided that subject confidentiality is protected. The Investigator(s) will be responsible for ensuring eCRF data completeness and accuracy. The eCRFs will be reviewed by a monitor from the Sponsor or its designee for completeness and accuracy. Source document verification will be performed. The eCRF data will also be reviewed internally by the Sponsor's Data Management, Medical and Scientific staff or their designee and, if necessary, the investigational sites will be queried for corrections and/or clarifications. Once data are concluded to be complete and accurate, the eCRF data will be locked, meaning that the data will become read-only. The Investigator(s) are required to approve the eCRF data of their site through provisioning of an (electronic) signature before the data is used for final analysis. The Sponsor will ensure that eCRF data is accessible and verifiable by the investigational site and install adequate back-up and security measures to prevent loss of data or unauthorised access to the data.

Copies of pertinent records in connection with the study, including eCRFs and queries, as well as subject charts, laboratory data, etc., will be maintained at the investigational site.

In compliance with ICH-GCP guidelines, Investigator(s) will maintain all eCRFs and all source documents supporting data collected from each subject, as well as all study documents as specified in ICH-GCP Section 8, Essential Documents for the conduct of a Study, and all study documents as specified by the applicable regulatory requirement(s). Subject records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but for at least 15 years. If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or regulatory authority inspection.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

12.2 **Monitoring and Quality Assurance**

MR ASAP will be monitored by an independent monitor according to ICH-GCP guidelines and relevant national regulations. Before initiation of the trial, the monitors will receive training about stroke, the study protocol, and the eCRF. This training will also include training for the site (initiation) visit procedures and monitoring forms to be used during the study conduct. Trained monitors will perform monitoring activities according to the Monitoring Plan and will supervise the maintenance of the Investigator Site File (ISF).

Monitoring of the trial will be done according to the criteria laid down in the MR ASAP Monitoring Plan, which will be developed by the project leaders in collaboration with the monitoring organisation All monitoring activities will be on-site. Each of the active sites (i.e., open and enrolled at least one patient in the previous year) will be visited at least once a

year during the course of the trial. On-site data monitoring will include the verification of data with source documents, considering critical aspects of the trial such as: informed consent, inclusion and exclusion criteria, and (serious) AEs. A monitoring report will be written at the end of each monitoring visit. The last monitoring visit will also be the close-out visit. In addition, continuous remote monitoring with telephone and web-based monitoring 'visits' will be performed in order to assure resolution of all queries.

12.3 **Amendments**

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 **Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 **Temporary halt and (prematurely) end of study report**

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 **Public disclosure and publication policy**

The trial is registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) and ISRCTN Register (ISRCTN99503308). The study database will be closed within one month after the last scheduled follow-up date of the last included patient. A manuscript which at least describes the study and the answer to the primary research question will be submitted to a major clinical journal within 3 months from closure of the database. The manuscript will be shared with the funder(s) one month before submission, but the funder(s) will have no influence on its contents. Anonymous data can be requested from the PI with a detailed description containing the aims and methods of the study for which the data are intended to be used. Data will be made available for this purpose at least 18 months after publication of the main report. Data may also be shared with non-commercial parties for scientific purposes, including individual patient meta-analyses.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

We refer to paragraph 5 of the SmPC. Glyceryl trinitrate is a well-known active substance, used in clinical practice for more than a hundred years.

b. Previous exposure of human beings with the test product and products with a similar biological mechanism

We refer to paragraph 1.8 for details about the use of GTN in clinical trials of acute stroke, and to the SmPC for details on the clinical use of GTN in general. In short, GTN has been tested in four phase II stroke trials[42, 43, 46, 47] and two phase III trials,[31, 32] including a total of 5346 patients with ischaemic stroke or intracerebral haemorrhage. Details are provided under 'e' below. Details of other trials of antihypertensive treatment in patients with acute stroke are provided in paragraph 1.4.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

The effects on L-arginine (the precursor for NO) and NO donors on cerebral blood flow and infarct size in animal stroke models have been summarized in a systematic review and meta-analysis.[40] A total of 25 studies were identified, with a median of 41 animals per study. L-Arginine and NO donors reduced total cerebral infarct volume in permanent (standardized mean difference (SMD), -1.21; 95% CI, -1.69 to -0.73, $p < 0.01$) and transient models of ischaemia (SMD, -0.78, 95% CI -1.21 to -0.35, $p < 0.01$). Drug administration increased cortical CBF in permanent (SMD +0.86, 95% CI 0.52-1.21, $p < 0.01$) but not transient models (SMD +0.34, 95% CI -0.02 to 0.70, $p = 0.07$). The effects of GTN have not be assessed in ex-vivo human cell material.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

We refer to the SmPC.

e. Analysis of potential effect

In an individual-patient meta-analysis[50] of four phase II stroke trials[42, 43, 46, 47] and one phase III trial[31] of GTN in a total of 4197 patients with ischaemic stroke or intracerebral haemorrhage, GTN was associated with increased rates of headache (369/2033, 18.2%

versus 171/2026, 8.4%) and clinical hypotension (i.e., hypotension requiring medical intervention, 55/2033, 2.7% versus 15/2026, 0.7%). There were no differences in the rates of death, neurological deterioration, recurrent stroke, clinical hypertension, or serious adverse events by the end of the 7 to 12 days of randomised treatment. GTN did not have an overall benefit on functional outcome at 90 days. The effects of GTN on functional outcome were consistent among relevant subgroups of patients, except for sex and time to randomisation (Figure 2).

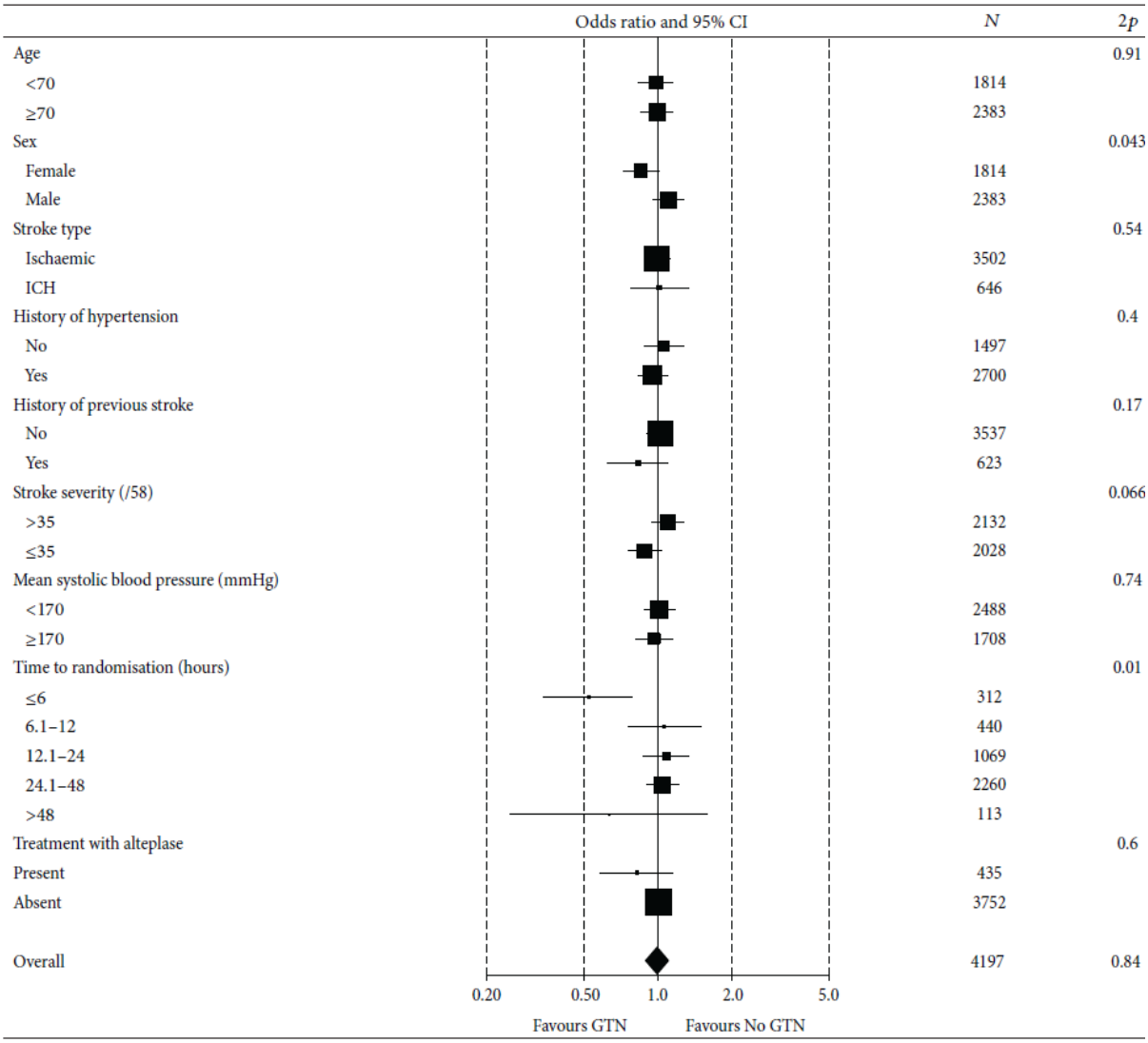

Figure 2: Effect of GTN versus no GTN on functional outcome at 90 days in subgroups of patients. Figure from Bath *et al.* 2016.[50]

More details can be obtained from the large phase III Efficacy of Nitric Oxide in Stroke (ENOS) trial,[31] which randomised 4011 stroke patients with raised systolic blood pressure (140–220 mm Hg) to 7 days of transdermal GTN (5 mg per day), started within 48 h of stroke onset, or to no GTN. Use of GTN lowered blood pressure (difference on day 1, –7.0/3.5 mm Hg; P<0·0001) but did not lead to an overall improvement in functional outcome at 90 days. There was no increase in serious adverse events with GTN (Table 1). The drug was also safe in patients with carotid occlusion or more severe stroke. Serious adverse events occurred in 271 (14%) patients randomised to GTN and in 261 (13%) patients randomised to control (OR, 1.05; 95% CI, 0.88 to 1.26).

In the prespecified subgroup of 273 patients who were randomized within 6 hours of symptom onset, the first dose of GTN lowered blood pressure by 9.4/3.3 mm Hg (P<0.01, P=0.064). Importantly, GTN improved functional outcome on day 90 (adjusted common odds

ratio, 0.51; 95% CI, 0.32 to 0.80). Of the patients treated with GTN, 51.4% had a poor outcome (mRS ≥ 3), as compared with 60.5% of controls (adjusted OR, 0.60; 95% CI, 0.32 to 1.13; P=0.11). In this subgroup treated early, there was no interaction in effect of GTN on outcome based on sex. If anything, male patients appeared to do better than females. Significant beneficial effects were also seen with GTN for quality of life, cognition, and mood. GTN was safe to administer with less serious adverse events by day 90 (GTN 18.8% versus no GTN 34.1%) and death (hazard ratio, 0.44; 95% CI, 0.20 to 0.99; P=0.047).[48] In the *post-hoc* subgroup of 61 patients with intracerebral haemorrhage randomised within 6 hours, GTN improved functional outcome with a shift in the modified Rankin Scale (OR, 0.22; 95% confidence interval, 0.07–0.69; P=0.001).[46]

The phase II Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT)[47] randomised 41 patients with probable acute stroke and systolic blood pressure >140 mm Hg to transdermal GTN (5 mg/24 hours) or no GTN, started within 4 hours of symptom onset and continued for 7 days, with the first dose given by paramedics in the prehospital setting. GTN reduced systolic blood pressure by 21 mm Hg (95% CI, -39 to 1) at 15 minutes and by 18 mm Hg (-32 to -2) at 2 hours after start of treatment. Early administration of GTN was safe, and improved functional outcome (P=0.040). Of the patients treated with GTN, 52% had a poor outcome (mRS ≥ 3), as compared with 75% of controls (P=0.20).

The phase III randomised Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial-2 (RIGHT-2) was based on the promising findings in the studies above. RIGHT-2 randomised 1149 adults with presumed stroke within 4 h of onset who had a face-arm-speech-time score of 2 or 3 and systolic blood pressure of 120 mm Hg or higher to transdermal GTN (5 mg once daily for 4 days) or a similar sham dressing. Treatment was started in the ambulance by paramedics, with treatment continued in hospital. The median time to randomisation was 71 min (IQR, 45 to 116). 597 (52%) patients had ischaemic stroke, 145 (13%) had intracerebral haemorrhage, 109 (9%) had transient ischaemic attack, and 297 (26%) had a non-stroke mimic at the final diagnosis of the index event. In the GTN group, participants' systolic blood pressure was lowered by 5.8 mm Hg compared with the sham group (p<0·0001), and diastolic blood pressure was lowered by 2·6 mm Hg (p=0·0026) at hospital admission. Early administration of GTN did not have an effect of functional outcome in patients with a final diagnosis of stroke or transient ischaemic stroke (adjusted common odds ratio for poor outcome (acOR), 1.25; 95% CI, 0.97 to 1.60; p=0·083), nor in the complete population (acOR, 1.04; 95% CI, 0.84 to 1.29; p=0·69). There was also no difference in the risk of death at 90 days (19% vs 17%; acOR, 1.11; 95% CI, 0.84 to 1.47; p = 0·47) or in the risk of serious adverse events. Remarkably, GTN was associated with an

improved functional outcome in patients with a stroke mimic (acOR, 0.54; 95% CI, 0.34 to 0·85; p=0·0081). This positive finding was not localised to any particular type of mimic. The observed tendency towards harm of GTN in RIGHT-2 was particularly seen in patients with intracerebral haemorrhage, very early stroke (<1 h), and severe stroke [Figure 3]. Furthermore, patients with intracerebral haemorrhage treated with GTN had larger haematoma size and more mass effect on hospital admission.

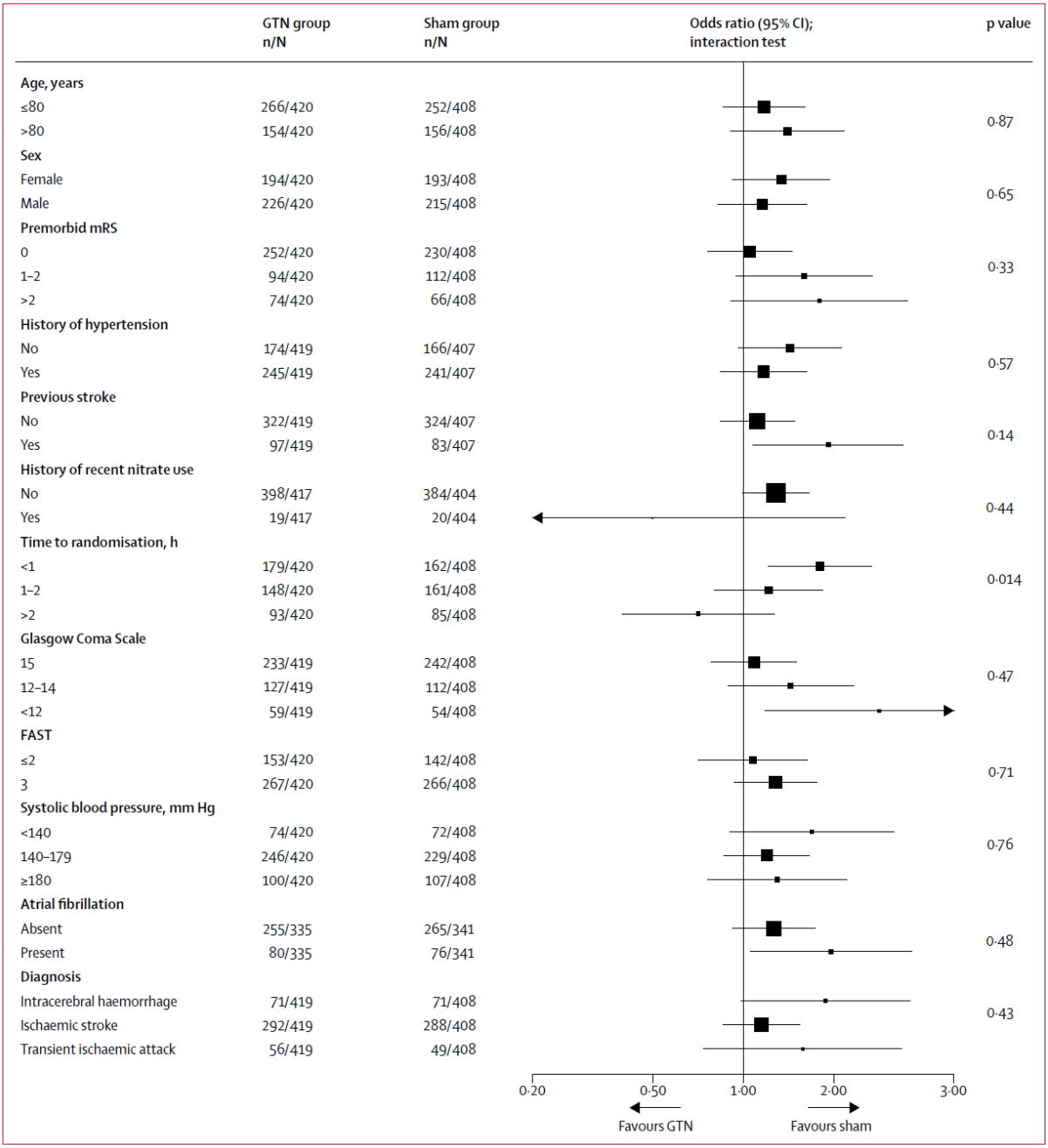

Figure 3: Effect of GTN versus sham on mRS score at day 90 in patients with a final diagnosis of stroke or TIA.

The investigators of RIGHT-2 have given several explanations for the potential hazard of GTN in patients with intracerebral haemorrhage. First, the earliest stage in haemostasis is vasoconstriction and GTN might prevent this protective response and so lead to very early haematoma expansion. Unfortunately, it is not known whether these mechanisms also play a role in patients with intracranial haemorrhage rather than extracranial haemorrhage. Second, GTN could have amplified haematoma expansion through inhibition of platelet aggregation. However, although an antiplatelet effect has been observed in an in vitro study[44] and in patients with coronary disease,[45] this was not observed in patients with ischaemic stroke or intracerebral haemorrhage.[46] Third, an older study in baboons has suggested that GTN raises intracranial pressure, particularly if intracranial pressure is already elevated.[79] However, other studies did not find a negative effect of GTN on cerebral blood flow or cerebral perfusion pressure in patients with recent stroke.[42, 43, 80]

f. Pharmacokinetic considerations

We refer to the SmPC.

g. Study population

We refer to Chapter 4. The study population will consist of 1400 patients aged 18 years or older, in whom the attending paramedic makes the probable diagnosis of acute stroke with a moderately severe to severe deficit.

h. Interaction with other products

For potential interactions, we refer to paragraph 4.5 of the SmPC. Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, sapropterin and major tranquillisers, as well as the consumption of alcohol, may potentiate the hypotensive effect of the preparation. Nitroglycerin may potentiate the effect of dihydroergotamin which could theoretically lead to coronary vasoconstriction in patients with coronary disease. This has not led to concern in the large phase III ENOS trial,[31] in which the concurrent use of these substances was not prohibited.

Patients who use phosphodiesterase inhibitors (e.g. sildenafil) are excluded from participation in this study.

i. Predictability of effect

In patients randomised within four hours of onset of symptoms in RIGHT-2, the effects of GTN appeared to depend on the time to start of treatment, stroke severity, and final diagnosis (Figure 3). In previous randomised trials of GTN in patients with acute stroke, its

effects on functional outcome in patients treated within 6 hours of symptom onset were consistent among relevant subgroups of patients. There are no markers to reliably predict the effects of the IMP in the prehospital setting.

j. Can effects be managed?

Any reduction or increase in blood pressure that requires treatment according to the treating physician or paramedic may be treated according to local or national protocols or guidelines. If symptomatic falls in blood pressure occur, a stepped approach to management may be practiced (as done in ENOS):[31]

- Monitor closely;
- Raise the patient's legs;
- Administer intravenous saline or colloid;
- Remove GTN patch.

Headache may also be treated according to local protocols and practice.

13.2 Synthesis

Even with the current treatment options available, about half of the patients with acute stroke have a poor prognosis. For this reason, there is a strong need for additional stroke treatments that can be used in a broad population of patients with acute ischaemic stroke or intracerebral haemorrhage. Very early blood pressure reduction with transdermal GTN is a promising option because this has been shown to have an acceptable safety profile in randomised trials in patients with acute ischaemic stroke or intracerebral haemorrhage;[32, 50] reduces blood pressure within 15 minutes of application, without a reduction in cerebral blood flow;[42, 43, 47] as an NO donor, may improve cerebral collateral circulation before the start of recanalisation strategies;[40] has been associated with time-dependent improvement of functional outcome in post-hoc analyses of previous acute stroke trials;[50] and is cheap and easy to administer. Treatment with GTN in the prehospital setting has the advantage of strongly reducing the delay to treatment for a broad range of stroke patients to less than 1 hour after symptom onset, because this is simple and safe and does not require laboratory testing of the blood or imaging of the brain before the start of treatment. The lack of benefit of GTN observed in RIGHT-2 may be explained by chance and does not preclude a beneficial effect in the different stroke population of MR ASAP, where rates of endovascular treatment are likely to be much higher. Although the tendency towards harm in specific subgroups in RIGHT-2 may also be due to the play of chance, this does warrant close monitoring of safety by the independent DSMB. Finally, the antiplatelet effects of GTN observed in an in vitro study and in patients with coronary disease were not reproduced in patients with ischaemic

stroke or intracerebral haemorrhage. In patients with intracerebral haemorrhage, any mild antiplatelet effect may be offset by the benefit of an early reduction in blood pressure. We therefore consider the balance of potential risks and benefits of GTN in patients with acute stroke in favour of the potential benefits. In addition, based on the analyses described under item ‘e’ above, we consider the risk of participation in this study as negligible, as defined by the NFU Guideline version 2.0.

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15. APPENDICES

15.1 Appendix 1 – CONTRAST

15.1.1 CONTRAST logo

CONTRAST

Collaboration for New Treatments of Acute Stroke

15.1.2 Research leaders CONTRAST

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15.1.3 Overall scientific summary CONTRAST

MR ASAP will be carried out by members of Collaboration for New TReatments of Acute Stroke (CONTRAST). The overarching aim of CONTRAST is to improve outcome of patients with stroke by creating a consortium that blends mechanistic, basic scientific projects with pragmatic randomized clinical trials with a firm view of the future of Dutch Stroke Research beyond the coming five years.

The CONTRAST consortium will perform five large randomized clinical trials in acute stroke patients in the Netherlands, to test novel treatment strategies, aimed at preservation of ischemic tissue and to improve outcome after intra-arterial treatment by focusing on the optimization of IAT and the expansion of its indication.

1. Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP): pre-hospital augmentation of collateral blood flow and blood pressure reduction;

2. Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of concomitant MEDication: heparin, antiplatelet agents, both or neither (MR CLEAN-MED): antithrombotics to prevent microvascular occlusion after IAT;

3. Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion. (MR CLEAN-NO IV): immediate IAT without preceding thrombolysis;

4. Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals: MR CLEAN-Late (MR CLEAN-LATE): IAT in the 6 to 24 hour time window;

5. A prospective, multicenter, randomized open, blinded end-point clinical trial of minimally-invasive surgery, steroids or both in patients with spontaneous, non-traumatic supratentorial ICH in the Netherlands (DUTCH ICH Trial): microsurgical hematoma evacuation and dexamethasone in patients with ICH.

15.1.4 MR ASAP logo

15.2 Appendix 2 – Patient flow and selection into the CONTRAST trials

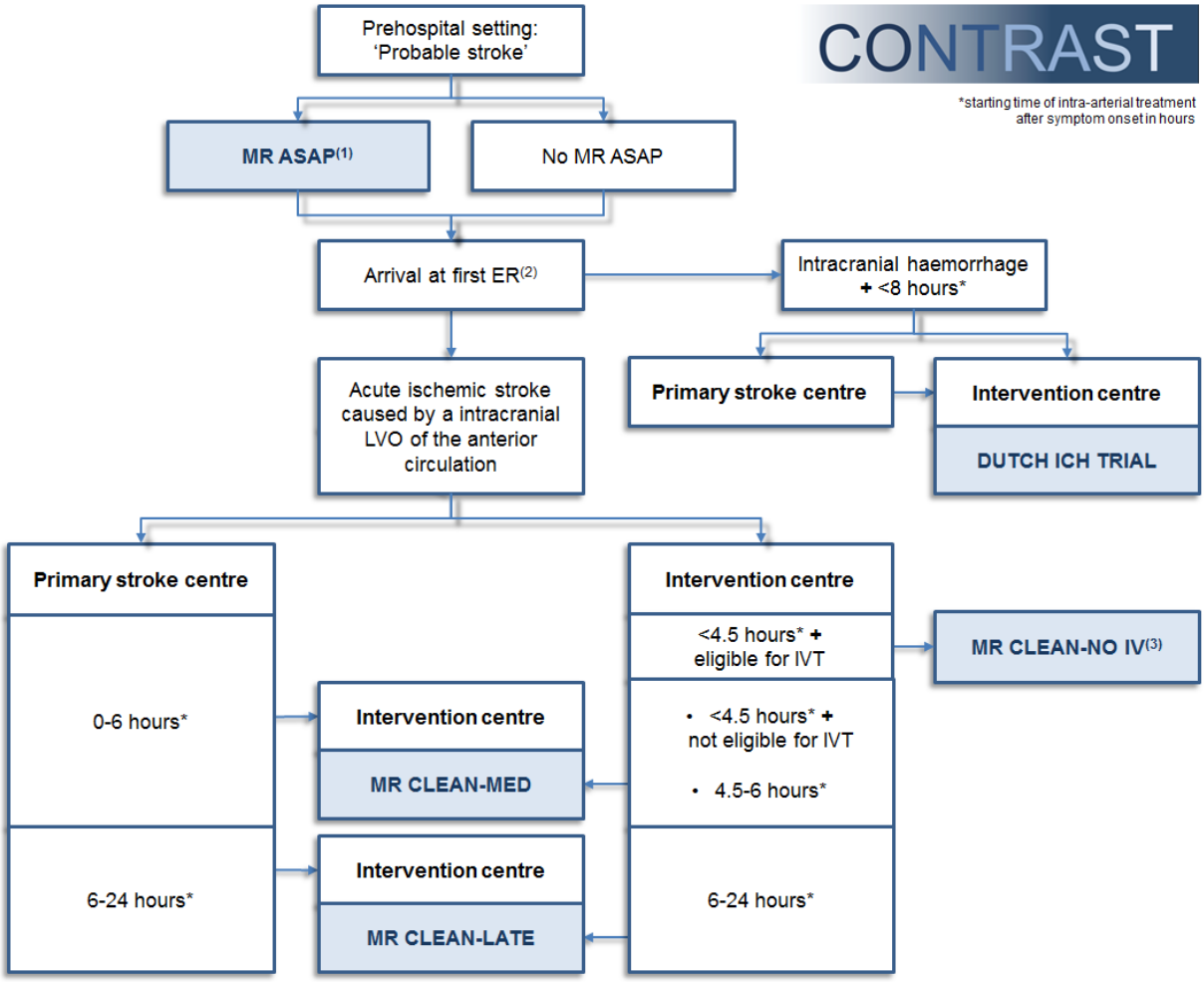

Figure 3: Patient flow and selection into the CONTRAST trials

Participating centres may largely be similar for all five RCT's. Therefore, patient selection into the proper trial is represented in the following flow chart.

Glossary

MR ASAP: Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch; ER: Emergency Room; DUTCH ICH TRIAL: A prospective, multicenter, randomized open, blinded end-point clinical trial of minimally-invasive surgery, steroids or both in patients with spontaneous, non-traumatic supratentorial ICH in the Netherlands; MR CLEAN-MED: Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither; MR CLEAN-NO IV: Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion; IVT: intravenous thrombolysis with alteplase; MR CLEAN-LATE: Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals

Considerations

(1) The CONTRAST studies are independent RCT's. Patients who have been included in MR ASAP may also be included in one of the intervention trials for ischemic or for haemorrhagic stroke. Being eligible for two trials at the same time raises questions whether the trials influence each other's results. Therefore, we will perform pre-specified subgroup analyses to test for interaction between the different performed treatments. Further, part of the potential treatment effect in MR ASAP will be represented in the baseline characteristics measured at inclusion in the second trial, such as collaterals, blood pressure and NIHSS, which we will adjust for in all analyses.

(2) At the first ER (either a primary stroke centre or a participating intervention centre), all patients with a probable diagnosis of acute stroke will undergo non-contrast CT to differentiate between acute cerebral infarction or acute intracranial haemorrhage. When the first ER is a primary stroke centre and the patient could be eligible for the DUTCH ICH TRIAL, MR CLEAN-MED or MR CLEAN-LATE study, the patient should be transferred to a participating intervention centre (where inclusion in one of these studies, randomization and treatment takes place).

(3) Patients arriving at a primary stroke centre first, will never be eligible for the MR CLEAN-NO IV, since intravenous thrombolysis with alteplase (IVT) cannot be withheld until after patient transfer to the participating intervention centre. Patients who are eligible for inclusion in MR CLEAN-NO IV (primary presentation at intervention centre, <4.5 hours + eligible for IVT) will not be included in MR CLEAN-MED. Patients presenting at the primary stroke canter within 6 hours (both eligible or not eligible for IVT), could be eligible for the MR CLEAN-MED. Importantly by this scheme, competition between the intervention trials will not occur.

15.3 **Appendix 3 – FAST**

FAST is used as a mnemonic to increase knowledge of stroke symptoms in the general population and to support diagnosis of stroke by paramedics. The FAST has been used in clinical practice for many years by the Dutch ambulance organisations. In a UK study, paramedics using the FAST achieved high levels of detection and diagnostic accuracy of stroke.[52]

F	Face Drooping – Does one side of the face droop or is it numb? Ask the person to smile. Is the person's smile uneven?
A	Arm Weakness – Is one arm weak or numb? Ask the person to raise both arms. Does one arm drift downward?
S	Speech Difficulty – Is speech slurred? Is the person unable to speak or hard to understand? Ask the person to repeat a simple sentence, like "The sky is blue." Is the sentence repeated correctly?
T	Time to call 112 – If someone shows any of these symptoms, get the person to the hospital immediately. Check the time so you'll know when the first symptoms appeared.

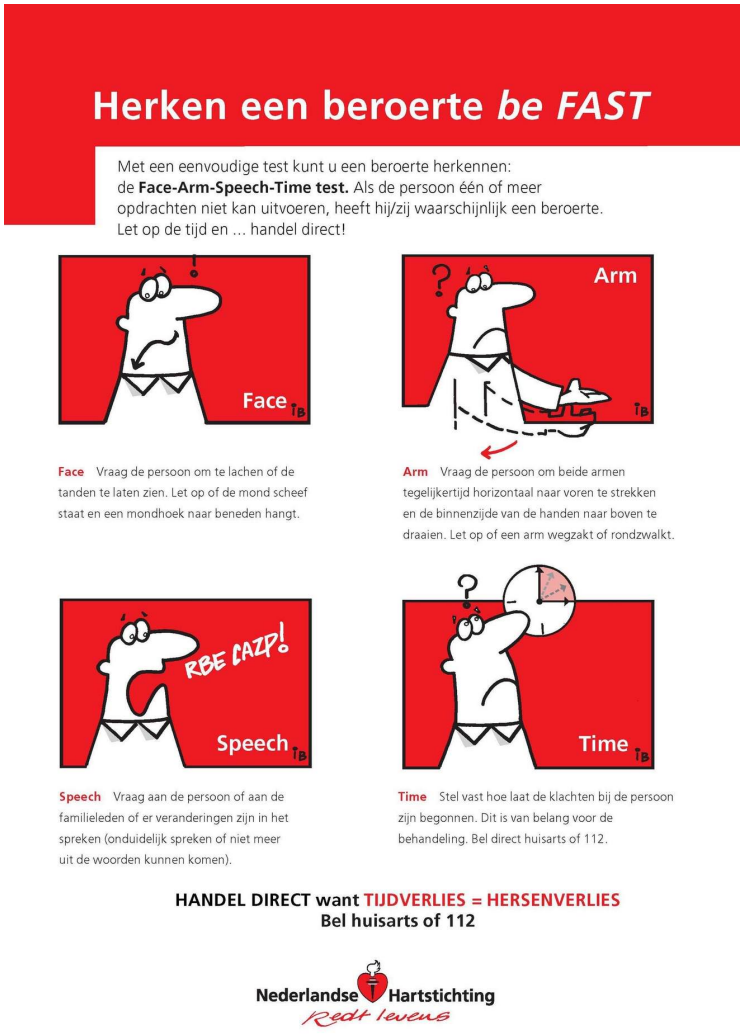

Figure 4: Patient information about FAST by Dutch Heart Foundation

15.4 Appendix 4 – NIHSS

The NIHSS is an ordinal hierarchical scale to evaluate the severity of stroke by assessing a patient's performance.[63] Scores range from 0 to 42, with higher scores indicating a more severe deficit.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition
1a. Level of consciousness. The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; required repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is not partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal clues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be a 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal**. 1 = **Partial gaze palsy**; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation;** or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual. Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving finger appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patients receives a 1, and the results are used to respond to item 11.	0 = **No visual loss**. 1 = **Partial hemianopia**. 2 = **Complete hemianopia**. 3 = **Bilateral hemianopia** (blind including cortical blindness)
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly response or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling) 2 = **Partial paralysis** (total or near-total paralysis of lower face) 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).
5. Motor arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift**; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity**; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity**; limb falls. 4 = **No movement**. UN = **Amputation** or joint fusion: explain: **5a = Left Arm**. **5b = Right arm**.

6. Motor leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; leg holds 30-degree position for full 5 seconds. 1 = **Drift**; leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity**; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity**; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: **6a. Left Leg** **6b. Right Leg.**
7. Limb ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent**. 1 = **Present in one limb**. 2 = **Present in two limbs**. UN = **Amputation** or joint fusion, explain:
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, 'severe or total sensory loss', should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal**; no sensory loss. 1 = **Mild-to-moderate sensory loss**; patients feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss**; patient is not aware of being touched in the face, arm and leg.

9. Best language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia**; normal 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conservation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia**; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia**: no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal**. 1 = **Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood by some difficulty. 2 = **Severe dysarthria**: patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier. Explain:
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality**. 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality**; does not recognize own hand or orients to only one side of space.

15.5 Appendix 5 – mRS

The modified Rankin Scale[57] (mRS) is an ordinal hierarchical scale ranging from 0 to 5, with higher scores indicating more severe disability. A score of 6 has been added to signify death.

0. No symptoms.
1. No significant disability. Able to carry out all usual activities despite some symptoms.
2. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3. Moderate disability. Requires some help, but able to walk unassisted.
4. Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted.
5. Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6. Dead.

15.6 Appendix 6 – BI

The Barthel Index (BI) is an ordinal scale used to measure performance in 10 activities of daily living (ADL).[59, 65, 66] Test scores range from 0 to 100, with higher scores indicating better performance in these activities.

FEEDING

0 = unable

5 = needs help cutting, spreading butter, etc., or requires modified diet

10 = independent

BATHING

0 = dependent

5 = independent (or in shower)

GROOMING

0 = needs to help with personal care

5 = independent face/hair/teeth/shaving (implements provided)

DRESSING

0 = dependent

5 = needs help but can do about half unaided

10 = independent (including buttons, zips, laces, etc.)

BOWELS

0 = incontinent (or needs to be given enemas)

5 = occasional accident

10 = continent

BLADDER

0 = incontinent, or catheterized and unable to manage alone

5 = occasional accident

10 = continent

TOILET USE

0 = dependent

5 = needs some help, but can do something alone

10 = independent (on and off, dressing, wiping)

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance

5 = major help (one or two people, physical), can sit

10 = minor help (verbal or physical)

15 = independent

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards

5 = wheelchair independent, including corners, > 50 yards

10 = walks with help of one person (verbal or physical) > 50 yards

15 = independent (but may use any aid; for example, stick) > 50 yards

STAIRS

0 = unable

5 = needs help (verbal, physical, carrying aid)

10 = independent

Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

15.7 Appendix 7 – EuroQoL

The EuroQoL 5-dimensions 5-level (EQ-5D-5L) questionnaire is a standardised measure of health outcome that has been used extensively in patients with stroke.[17, 21, 67]

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

15.8 **Appendix 8 – Known side effects of GTN**

Very common (>10% of patients): Headache. Nausea, vomiting.

Common (1-10% of patients): Hypotension and/or light-headedness on standing. These symptoms may be associated with dizziness, drowsiness, reflex tachycardia, and a feeling of weakness.

Infrequently (less than 1% of patients): Flushing and allergic skin reaction (e.g. rash), which may be severe. Exfoliative dermatitis has been reported.
Uncommonly collapse may occur (sometimes accompanied by bradyarrhythmia and syncope). Uncommonly severe hypotension may lead to enhanced angina symptoms.
A few reports of heartburn, most likely due to a nitrate-induced sphincter relaxation, have been recorded.
Allergic skin reactions to GTN and ingredients (>0.1% but <1%). Slight itching or burning at the site of application. Slight reddening usually disappears without therapeutic measures after the patch has been removed. Allergic contact dermatitis and application site erythema, pruritus, burning, irritation are uncommon.

Unknown frequency: Cardiac disorders like palpitation and disorders related to skin and subcutaneous tissue like generalized rash. Heart rate increase. During the treatment with these patches, a temporary hypoxaemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease this may lead to a myocardial hypoxia.

Other: Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

15.9 Appendix 9 – Common (potentially) serious complications after stroke

Based on: [81-84]

Cardiac

Angina
Arrhythmia
Atrial fibrillation
Angina pectoris
Bradycardia
Cardiac arrest
Cardiomyopathy
Heart failure
Myocardial infarction
Tachycardia

Central nervous system

Brain oedema
Cerebral herniation
Cerebellar herniation
Delirium
Depression
Epileptic seizure
Haemorrhagic transformation of the infarct
Headache
Haematoma expansion
Hydrocephalus
Intraventricular extension of haemorrhage
Increased intracranial pressure
Progressive stroke / Stroke in evolution
Recurrent ischaemic stroke
Recurrent intracerebral haemorrhage
Recurrent stroke
Retinal ischaemia
Sleep disorder

Status epilepticus
Transient ischaemic attack
Transient monocular blindness

Gastro-intestinal

Constipation
Dysphagia
Faecal incontinence
Gastro-intestinal haemorrhage
Ileus
Melena
Mucosal irritation
Nausea
Rectal haemorrhage
Stress ulcer
Vomiting

General / other

Anaemia
Arterial hypertension
Arterial hypotension
Deep vein thrombosis
Dehydration
Fall (and consequences)
Fatigue
Fever
Haematuria
Hip fracture
Hyperglycaemia
Infections
Pain
Pressure sore
Renal failure
Sepsis
Syncope

Undernutrition
Urinary incontinence
Urinary tract infection

Pulmonary

Aspiration
Bronchitis
Central periodic breathing
Chronic obstructive pulmonary disease
Dyspnoea
Obstructive sleep apnoea
Oxygen desaturation
Pneumonia
Pulmonary embolism
Pulmonary oedema
Respiratory failure / arrest
Respiratory tract infection

15.10 Appendix 10 – Flowchart of deferred consent procedure

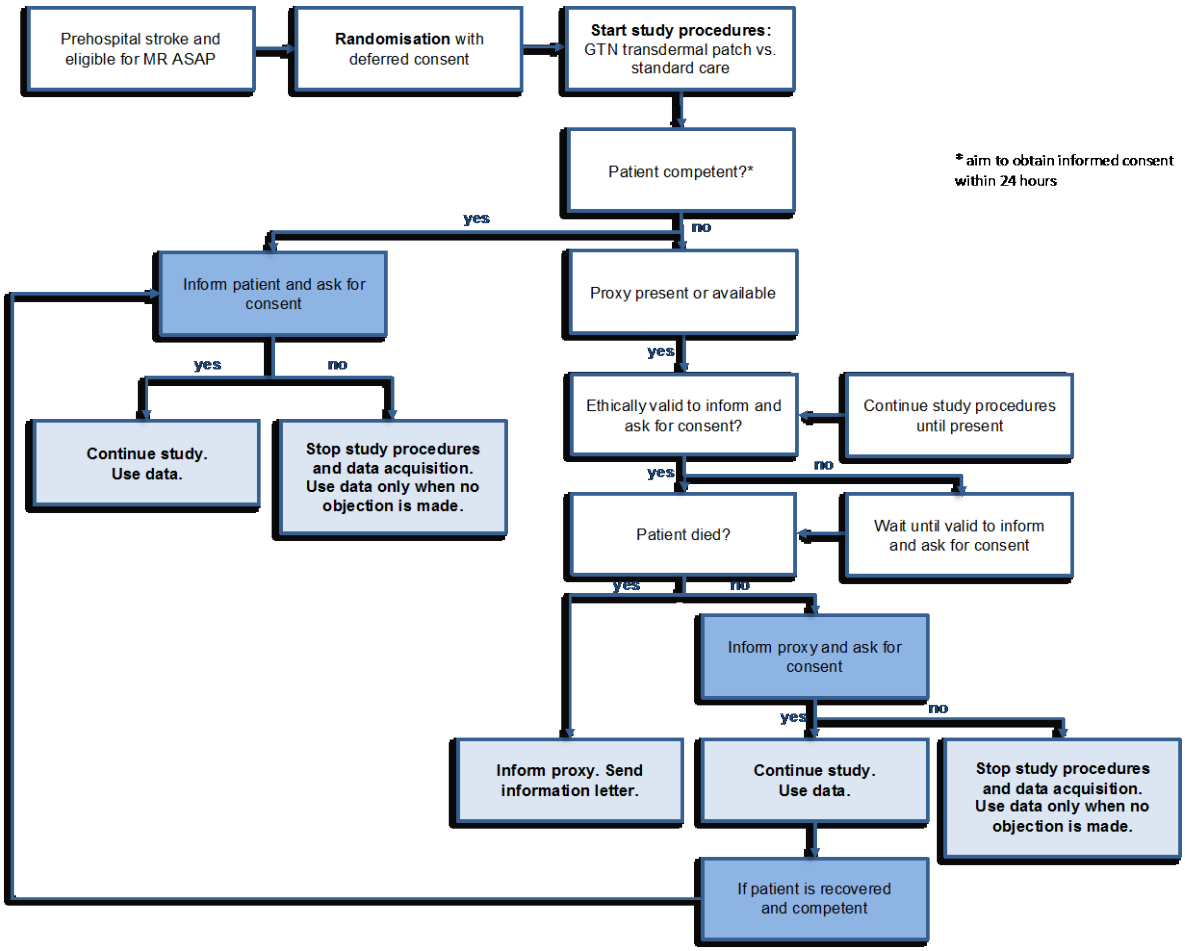

Figure 5: Flowchart of deferred consent procedure specific for the MR ASAP trial. Based on the flowchart proxy-deferred consent in emergency critical care research, by T. Jansen, E. Kompanje, et al.[85]

Glossary: MR ASAP: Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch; GTN: glyceryl trinitrate

15.11 Trial organisation

The MR ASAP trial is embedded in the CONTRAST consortium. It has an independent leadership, which reports progress in form of milestones to the CONTRAST Scientific committee. Funding is provided through the CONTRAST Consortium based on these milestones.

The Steering committee of the trial consists of all local Principal Investigators (PI) of the participating centers. Each participating center has two PIs: a vascular neurologist and a neuro-interventionist. The Steering committee will meet a least annually. Final decisions concerning protocol changes, publication and reporting will be made by the Steering committee. The Steering committee is chaired by the central PIs of the trial. Decisions will be made in consensus, but if unavoidable by majority vote. Day to day conduct of the trial will be managed by the trial coordinators, who will be supervised by the central PIs of the trial.
The Executive committee of the trial consists of the central PIs of the trial and a representation of local PIs. They meet regularly, discuss trial progress and prepare information for the Steering committee.

The Writing committee consists of the Executive committee and local PIs of the five collaborating centers that have contributed the most patients to the trial in the first two years of trial execution. The task of the Writing committee is to prepare the main publication which will be drafted by the study coordinators, supervised by the two central PIs. Typically, the main paper will be authored by the study coordinators (first), the local PIs, the committee members, and the central PIs. Authorship has to comply with the criteria of the International Committee of Medical Journal Editors (IMCJE), http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

The other trial committees are not trial specific and will be formed in collaboration with the four CONTRAST randomised clinical trials: MR ASAP, MR CLEAN-LATE, MR CLEAN-MED and MR CLEAN-NO IV. These are: the Outcome assessment committee, the Imaging committee, and the Adverse event committee. The committees work for and report to the other three CONTRAST trials.

The Outcome assessment committee consists of at least 3 members, all seasoned neurologists, their task is to evaluate all coded and masked structured reports of outcome assessments at three months of patients in the trials. In this way, the blind assessment is maintained. The chair of this committee will not assess reports, as he is involved as PI in one of the trials.

The Imaging committee is chaired by the CONTRAST WP leaders and consists of neuroradiologists from the collaborating centers. Their task is to assess and evaluate masked baseline and follow-up imaging, which is made per protocol and stored in a central web-based database. Assessments will be stored in Research forms and entered in the clinical database. And will be accessible to investigators after approval by the Steering committee.

The Adverse event committee consists of at least 3 members, including a neurologist and a neuro-interventionist. Their task is to oversee the review and reporting process of all reported serious adverse events. The chair of this committee will not assess reports, as he is involved as PI in one of the trials. The committee will regularly report to the four Steering committees.

15.12 **Appendix 12 – Deferred consent in acute stroke trials**

Deferred consent in acute stroke trials - CONTRAST

Concept research protocol

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Background and rationale

The informed consent procedure is considered fundamental for inclusion in a randomised clinical trial. However, the informed consent procedure in acute stroke research is challenging.

Acute stroke patients are often incapacitated and not able to provide their own consent prior to enrolment. Many patients have a decreased decision making capacity due to severe neurological deficits. In a Dutch registry with data of all patients who underwent endovascular treatment for acute ischemic stroke, 88% had neurological symptoms (aphasia, neglect, lowered consciousness level or confusion) interfering with their capacity to decide about participation in a clinical trial (unpublished data).

According to the 'time is brain' principle and time to treatment effects of endovascular treatment and intravenous thrombolysis, treatment should be initiated as soon as possible.(1) Each hour delay to reperfusion is associated with an increase in absolute risk of death or disability of 6-7%.(2)

As an alternative, a legal representative can be asked to give consent for participation in the trial. However, family members are often not available in the acute setting.(4,5) They might be too overwhelmed to understand the provided information to give valid consent, and experience psychological stress.(6) Also, not all patients want their family members to be their surrogate and many proxies do not know what the patient's wishes are for acute medical research.(7,8,9)

A person who gives consent should be able to understand information, balance benefits and risks and comprehend the severity of the illness. The capacity to consent for enrolment in a trial is subjectively estimated by the researcher or clinician. The comprehension of stroke patients and their proxies of the methods of the trial after providing (prospective) consent is diminished, as shown in a few studies.(10–13) Moreover, data is lacking on whether acute stroke patients and their proxies judge themselves capable of consenting to a clinical trial.

Deferred consent

An alternative for prospective (proxy) informed consent is deferred consent. In this procedure, consent is asked after enrolment in the study. In the Netherlands, deferred consent is possible in emergency situations. According to the Medical Research Human Subjects Act (Dutch: WMO), procedures of the clinical trial may be undertaken without consent as long as circumstances prevent the giving of consent and if inclusion in the trial may benefit the person in urgent need of medical treatment. No data on deferred consent in acute stroke research has been published yet.

The COllaboration for New Treatment of Acute Stroke (CONTRAST) investigates novel treatment strategies, aimed at preservation of ischemic tissue and improvement of functional outcome in patients with acute ischemic stroke. The CONTRAST consortium entails three trials on endovascular treatment and one prehospital trial. In these trials we will use a deferred consent procedure (figure 1).

Benefits and drawbacks of deferred consent

- Effect on treatment delays.

  The use of the deferred consent procedure might reduce time to study (drug) treatment,

with potential beneficial effects, and reduce delay to standard stroke treatments since the CONTRAST trials will study adaptations of endovascular treatment. No disadvantages of deferred consent on treatment delays are expected.

- Influence on decision-making competence.
  Decision-making competence is based on factual understanding, evidencing a choice (consent or refusal), and reasoning and appreciation of the situation. In the acute phase of an emergency situation, patients and relatives are in emotional distress and can be considered temporarily incompetent in these three points. Hence, patients and their relatives can be regarded temporarily incompetent for valid proxy consent in an emergency situation.(6) Deferment of the conversation might lead to a more ethically valid informed consent and a better informed decision.
  Still, there is no consistency in the duration of the acute phase of the emergency situation. The moment patients and proxies regain decision-making competence is not defined. Also, patients and proxies might not regard themselves competent of making a decision in the day(s) after the emergency situation.
  In addition, some patients and proxies will feel capable of making a decision and could object to the deferred consent procedure itself because they not understand the reasons for the postponement of asking consent. This could interfere with the decision they will make.

- Patient enrolment and selection bias.
  It might increase patient enrolment and reduce selection bias resulting in better generalizable study results. Meanwhile, should many patients and proxies object against enrolment, this could likewise contribute to selection bias.

Main objective

The aim of the current study is to increase knowledge about the deferred consent procedure in acute stroke research. We will collect and analyse data on logistics of the procedure and on patient recall, satisfaction, and comprehension at three months from randomization.

Specific objectives

1. To estimate the proportions of patients and proxies that give consent for and object against enrolment in acute stroke trials using deferred consent procedures;
2. To map the workflow and timeline of the deferred consent procedure;
3. To explore the personal feeling of capability of patients and proxies to provide consent for participation in an acute stroke controlled trial;
4. To explore appreciation of patients and proxies of the deferred informed consent procedure;
5. To investigate recall and comprehension by patients and proxies of study methods of the acute stroke trial for which they provided deferred consent;
6. To compare the observations on 1-5 with data from previous acute stroke trials.

Methods

Study design
This study will be a descriptive, observational substudy nested in 4 acute stroke trials within the CONTRAST consortium. We will prospectively collect data on logistics of the deferred consent procedure and ask patients and proxies to fill out questionnaires.

Study population
Patients and their proxies participating in one or two of the CONTRAST trials.

Inclusion criteria
- Participation in at least one of the CONTRAST trials.
    - Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP)
    - Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands. The effect of concomitant MEDication: heparin, antiplatelet agents, both or neither (MR CLEAN-MED)
    - Intravenous treatment followed by intra-arterial treatment versus direct intra-arterial treatment for acute ischemic stroke caused by a proximal intracranial occlusion. (MR CLEAN-NO IV)
    - Multicenter Randomized Clinical Trial of Endovascular Stroke treatment in The Netherlands for Late arrivals: MR CLEAN-Late (MR CLEAN-LATE)

Exclusion criteria
Proxies of deceased patients will not be interviewed.

Duration of data collection
We aim to collect data on deferred consent of 300 patients during the first year of enrolment in the CONTRAST trials. Data collection will start 3 months after the first inclusion in the study.

Patient recruitment

Patients / proxies who provided consent for participation in the trial

During the 3 month telephone follow-up of the CONTRAST trial, the subject who provided consent will be asked to participate in this substudy. The purpose of the study will be explained and the study procedures will be described. Questionnaire 1 will be sent to their home address. The feeling of capability for giving consent, appreciation of the informed consent process and recall and comprehension will be explored in this questionnaire.
For participation in this substudy, no additional written informed consent from individual subjects is needed.

Patients / proxies who withheld consent for participation in the trial

The patient or proxy who refused to give deferred consent for participation in the CONTRAST trial will be approached. The purpose of the study will be explained and the study procedures will be described. They will be asked to only fill out Questionnaire 2, which concerns the reasons for not giving consent. It will be emphasized that it is not mandatory to answer. No additional questionnaires or interviews will be carried out within this patient group.

Study procedures

Baseline information

The following baseline characteristics, already collected in the CONTRAST trials, will be used: age, sex, baseline NIHSS - including NIHSS subitems, stroke type, study site and treatment arm (intervention vs. control). The 3 month modified Rankin Scale score (mRS) will also be used.
Additionally we will document the educational level of the subject who provided consent.

1. Patient enrolment

The CONTRAST trials use different deferred informed consent forms (ICFs):

1) Patient: the patient is mentally competent to provide consent, as estimated by the researcher/clinician

2) Proxy (partner or family member): the patient is not mentally competent to provide consent, as estimated by the researcher/clinician, and the researcher/clinician believes it is ethically valid to inform and ask for consent

In case the patient has deceased before consent could be asked, the data which has been documented so far may be used in an anonymous fashion for study purposes and the proxy will be informed (figure 1).
The following data will be documented regarding patient enrolment:

- the number of patients providing consent vs. not providing consent + reasons for not providing consent
- the number of proxies providing consent vs. not providing consent + reasons for not providing consent
- the number of patients who deceased before consent could be asked
- the number of patients that withdrew their consent within 3 months

2. Deferred consent workflow and timeline

The study protocols of the CONTRAST trials state that deferred informed consent will be obtained within the first 24 hours after enrolment. In the MR ASAP trial, the nitroglycerin patch will be removed after 24 hours. However, when a patient refuses to provide consent, the patch will be removed directly. For the subsequent CONTRAST trials, the first follow-up CT scan will be performed 24 hours after randomisation (Figure 1).

We will document time intervals from symptom onset until consent has been obtained. The timeline will contain the following time measurements, if applicable.

1. MR ASAP: onset – randomisation/treatment – ER – inclusion in subsequent CONTRAST trial – IVT – IAT – start IC conversation – signature patient/proxy
2. MR CLEAN-NO IV: onset – inclusion in MR ASAP – ER – randomisation – IVT – IAT – start IC conversation – signature patient/proxy
3. MRCLEAN-MED: onset – inclusion in MR ASAP – ER – IVT – randomisation – IAT – start IC conversation – signature patient/proxy
4. MRCLEAN-LATE: onset – inclusion in MR ASAP – ER – IVT – randomisation – IAT – start IC conversation –signature patient/proxy

ER: emergency room; IVT: intravenous thrombolysis; IAT: intra-arterial treatment; IC: informed consent

On the ICF we will record date and time of:

- start of informed consent conversation; and
- signature of patient or proxy.

The remaining time measurements will be recorded in the electronic case report form (eCRF).
We will compare of the numbers and time intervals of patient vs. proxy consent in our study with data from the Multicenter Randomized CLinical trial of Endovascular treatment for Acute Ischemic stroke in the Netherlands (MR CLEAN).

3. Capability of patients and proxies of providing consent for participation

After 3 months the primary outcome of the CONTRAST trials will be assessed during a telephone interview by a blinded assessor. During the follow-up interview the patient or proxy will be asked if they would like to continue participating in this substudy. Questionnaire 1 will be sent to their home address with the questions regarding this objective and objective 4 and 5.

4. Appreciation of patients and proxies of the deferred informed consent procedure

See objective 3.

5. Recall and comprehension of study methods of the trial

See objective 3.

Statistical analysis

Results will be reported for the trials separately and the CONTRAST trials all together. This is an observational study. We will describe the distribution of consent process variables, as well as time and logistics parameters. We will relate characteristics of the neurological deficit, as measured with the NIHSS scale with the legal capability status of the patient. Finally, we will compare the consent parameters, including time intervals, with data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN). Variables will be compared with Chi square test for categorical variables and Mann-Whitney for continuous variables. A p-value below 0.05 will be considered statistically significant.

Ethical considerations

This study will be performed according to ICH-GCP principles, the Declaration of Helsinki as most recently amended in 2013, and national regulatory requirements, as the European trial Directive and the European privacy regulation. We are awaiting approval by the institutional review board of the Erasmus MC University Medical Center.

Nature and extent of the burden of participation

The study procedures will require an estimated maximum of 30 minutes of the subject's time at 3 months (Questionnaire 1) and 5 minutes of the subject's time during hospital admission (Questionnaire 2) and. We therefore consider the burden minimal.

Handling of data and documents

The results of this substudy will be reported during the active enrolment in the CONTRAST trials. The conclusions of this substudy may have consequences for the actual consent study procedures.

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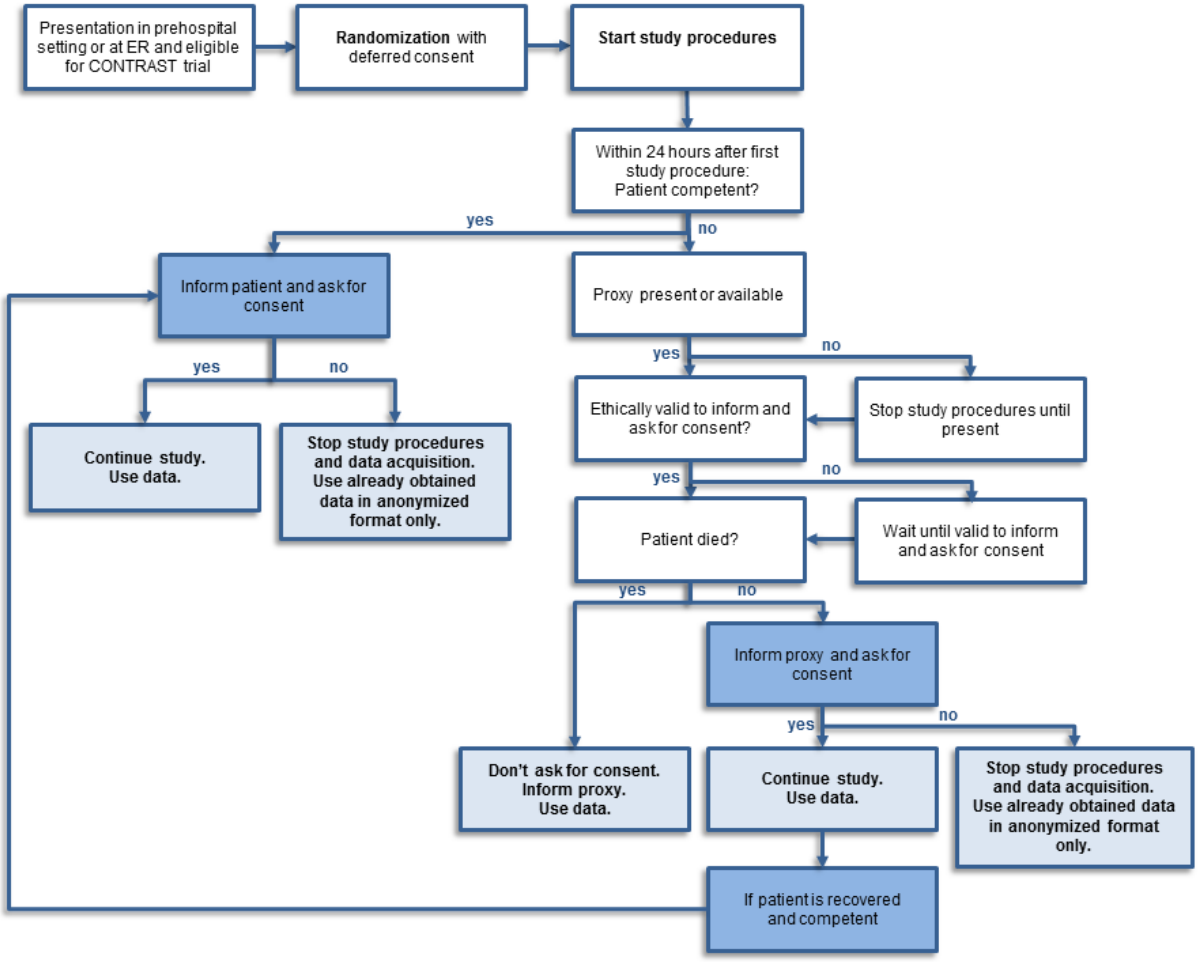
Figure 1


Presentation in prehospital setting or at ER and eligible for CONTRAST trial
Randomization with deferred consent
Start study procedures
Within 24 hours after first study procedure: Patient competent?
yes
no
Inform patient and ask for consent
Proxy present or available
yes
no
yes
no
Continue study. Use data.
Stop study procedures and data acquisition. Use already obtained data in anonymized format only.
Ethically valid to inform and ask for consent?
Stop study procedures until present
yes
no
Patient died?
Wait until valid to inform and ask for consent
yes
no
Inform proxy and ask for consent
yes
no
Don't ask for consent. Inform proxy. Use data.
Continue study. Use data.
Stop study procedures and data acquisition. Use already obtained data in anonymized format only.
If patient is recovered and competent

Questionnaire 1 – patient – after 3 months

Enquêtevragen als patiënt toestemming heeft gegeven voor deelname aan het onderzoek.
[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Algemeen

Wat is uw hoogst genoten opleiding? (keuze)

- □ geen
- □ basisschool
- □ lager beroepsonderwijs (LBO, VMBO)
- □ middelbaar algemeen voorbereidend onderwijs (MAVO)
- □ middelbaar beroepsonderwijs (MBO)
- □ hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- □ hoger beroepsonderwijs (HBO)
- □ kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- □ (post) wetenschappelijk onderwijs
- □ weet niet / wil ik niet zeggen

Vragen over uw kennis en begrip over de methode van het onderzoek

1. Vindt u zelf dat u voldoende weet over het onderzoek?

   I. Ik vind dat ik voldoende weet over het **doel** van het onderzoek

      □ Ja

      □ Nee

   II. Ik vind dat ik voldoende weet over de **opzet** van het onderzoek

      □ Ja

      □ Nee

2. Heeft u de informatiebrief gelezen?

   □ Ja

   □ Nee

3. Heeft u de informatiebrief begrepen?

    □ Ja

    □ Nee

4. Welke behandeling werd in dit onderzoek getest? (vrije tekst)

5. Hoe werd besloten welke behandeling u kreeg? (vrije tekst)

6. Welke behandeling heeft u of uw naaste gekregen? (vrije tekst)

7. Waren er risico's en nadelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

8. Waren er voordelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)

9. Was deelname aan het onderzoek vrijwillig of verplicht?

    □ Vrijwillig

    □ Verplicht

10. Was het mogelijk uw toestemming voor deelname aan het onderzoek in te trekken?

    □ Ja

    □ Nee

11. Wie had toegang tot uw persoonlijke gegevens en ziektegeschiedenis? (vrije tekst)

<u>Vragen over uw waardering over de toestemmingsprocedure</u>

12. Voelde u zich destijds in staat om te beslissen over deelname aan dit onderzoek?

    □ Ja (ga naar vraag 16)

    □ Nee (ga hieronder verder)

13. Wie had u liever deze beslissing willen laten maken?

    □ Mijn behandelend arts

    □ Een familielid, namelijk: ……

    □ Toestemming voor dit onderzoek vind ik niet nodig

14. Waarom voelde u zich niet in staat om te beslissen over deelname aan dit onderzoek? (meerdere antwoorden mogelijk)

    I. Ik vond het te veel informatie

    II. Ik begreep de uitleg niet goed

    III. Ik voelde mij gestresst

    IV. Deze vraag kwam te snel na de beroerte

    V. Ik heb te weinig bedenktijd gehad

    VI. Anders, namelijk: ……

15. Had u genoeg tijd om een beslissing te maken?

    □ Ja

    □ Nee

16. Had u liever gewild dat de vraag voor deelname aan het onderzoek op een ander moment was gekomen?

    □ Ja (ga naar de volgende vraag)

    □ Nee (ga naar vraag 19)

17. Zo **ja**, op welk moment had u liever gewild dat deze vraag aan u was gesteld? (één keuze)

    □ Eerder: nog vóór alle studiehandelingen, inclusief de behandeling

    □ Eerder na de studiehandelingen: binnen 12 uur in plaats van binnen 24 uur

    □ Later: binnen 72 uur in plaats van binnen 24 uur

18. Had u het goed vonden als een familielid voor u deze beslissing had gemaakt?

    □ Ja

    □ Nee

19. Welke beslissing zou uw familielid hebben gemaakt, als uw familielid voor u deze beslissing had gemaakt?

    □ Meedoen met het onderzoek

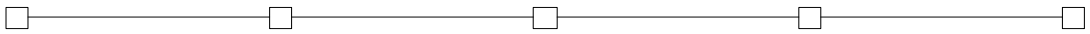
□ Niet meedoen met het onderzoek

20. Als de toestemmingsprocedure op een later tijdstip had plaatsgevonden (bijvoorbeeld binnen 72 uur in plaats van binnen 24 uur), zou u ermee akkoord gaan als er dan ook meer studiehandelingen (zoals bloedprikken of een CT-scan van het hoofd) zouden zijn uitgevoerd?

□ Ja

□ Nee

21. Hoe ervaart u de uitgestelde toestemmingsprocedure? (onderstaande Likert schaal + vrije tekst)



heel negatief redelijk negatief neutraal redelijk positief heel positief

Questionnaire 1 – proxy – after 3 months

Enquêtevragen als proxy (familielid of partner) toestemming heeft gegeven voor deelname aan het onderzoek.

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Algemeen

- Geslacht

  □ Man

  □ Vrouw

- Leeftijd (vrije tekst)

Wat is uw hoogst genoten opleiding? (keuze)

□ geen

□ basisschool

□ lager beroepsonderwijs (LBO, VMBO)

□ middelbaar algemeen voorbereidend onderwijs (MAVO)

□ middelbaar beroepsonderwijs (MBO)

□ hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)

□ hoger beroepsonderwijs (HBO)

□ kandidaats/propedeuse wetenschappelijk onderwijs (WO)

□ (post) wetenschappelijk onderwijs

□ weet niet / wil ik niet zeggen

Vragen over verloop toestemmingsprocedure en methode van het onderzoek

1. Vindt u zelf dat u voldoende weet over het onderzoek?

   I. Ik vind dat ik voldoende weet over het **doel** van het onderzoek

      □ Ja

      □ Nee

   II. Ik vind dat ik voldoende weet over de **opzet** van het onderzoek

□ Ja

□ Nee

2. Heeft u de informatiebrief gelezen?

□ Ja

□ Nee

3. Heeft u de informatiebrief begrepen?

□ Ja

□ Nee

4. Welke behandeling werd in dit onderzoek getest? (vrije tekst)
5. Hoe werd besloten welke behandeling u kreeg? (vrije tekst)
6. Welke behandeling heeft u of uw naaste gekregen? (vrije tekst)
7. Waren er risico's en nadelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)
8. Waren er voordelen verbonden aan meedoen aan het onderzoek? (ja/nee + vrije tekst)
9. Was deelname aan het onderzoek vrijwillig of verplicht?

□ Vrijwillig

□ Verplicht

10. Was het mogelijk uw toestemming voor deelname aan het onderzoek in te trekken?

□ Ja

□ Nee

11. Wie had toegang tot uw persoonlijke gegevens en ziektegeschiedenis? (vrije tekst)

<u>Vragen over uw waardering van de toestemmingsprocedure</u>

12. Voelde u zich destijds in staat om te beslissen over deelname aan dit onderzoek?

□ Ja (ga naar vraag 16)

□ Nee (ga hieronder verder)

13. Wie had u liever deze beslissing willen laten maken?

□ Mijn behandelend arts

□ Een familielid, namelijk: ……

□ Toestemming voor dit onderzoek vind ik niet nodig

14. Waarom voelde u zich niet in staat om te beslissen over deelname aan dit onderzoek? (meerdere antwoorden mogelijk)

I. Ik vond het te veel informatie

II. Ik begreep de uitleg niet goed

III. Ik voelde mij gestresst

IV. Deze vraag kwam te snel na de beroerte

V. Ik heb te weinig bedenktijd gehad

VI. Anders, namelijk: ……

15. Had u genoeg tijd om een beslissing te maken?

□ Ja

□ Nee

16. Had u liever gewild dat de vraag voor deelname aan het onderzoek op een ander moment was gekomen?

□ Ja (ga naar de volgende vraag)

□ Nee (ga naar vraag 19)

17. Zo **ja**, op welk moment had u liever gewild dat deze vraag aan u was gesteld? (één keuze)

□ Eerder: nog vóór alle studiehandelingen, inclusief de behandeling

□ Eerder na de studiehandelingen: binnen 12 uur in plaats van binnen 24 uur

□ Later: binnen 72 uur in plaats van binnen 24 uur

18. U hebt als familielid de beslissing voor uw naaste gemaakt. Welke beslissing zou uw naaste zelf hebben gemaakt?

    □ Meedoen met het onderzoek

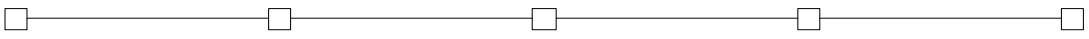
    □ Niet meedoen met het onderzoek

19. Als de toestemmingsprocedure op een later tijdstip had plaatsgevonden (bijvoorbeeld binnen 72 uur in plaats van binnen 24 uur), zou u ermee akkoord gaan als er dan ook meer studiehandelingen (zoals bloedprikken of een CT-scan van het hoofd) zouden zijn uitgevoerd?

    □ Ja

    □ Nee

20. Hoe ervaart u de uitgestelde toestemmingsprocedure? (onderstaande Likert schaal + vrije tekst)



heel negatief | redelijk negatief | neutraal | redelijk positief | heel positief

Questionnaire 2 – patient

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]

Enquêtevragen als patiënt om uitgestelde toestemming is gevraagd voor deelname aan de CONTRAST trial en geen toestemming heeft gegeven.

Wat was de reden dat u geen toestemming heeft gegeven? (meerdere opties mogelijk)

- ☐ Dit wil ik niet zeggen
- ☐ Ik wil niet dat er gegevens verzameld worden van mij
- ☐ Ik vond het te veel informatie
- ☐ Ik begreep de uitleg niet goed
- ☐ Ik voelde mij gestresst
- ☐ Deze vraag komt te snel na de beroerte
- ☐ Ik heb te weinig bedenktijd gehad
- ☐ Ik vind dat iemand anders, namelijk de behandelend arts deze beslissing voor mij moet maken
- ☐ Ik vind dat iemand anders, namelijk mijn partner en/of ander familielid deze beslissing voor mij moet maken
- ☐ Anders, namelijk: …..

Wat is uw hoogst genoten opleiding? (keuze)

- ☐ geen
- ☐ basisschool
- ☐ lager beroepsonderwijs (LBO, VMBO)
- ☐ middelbaar algemeen voorbereidend onderwijs (MAVO)
- ☐ middelbaar beroepsonderwijs (MBO)
- ☐ hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- ☐ hoger beroepsonderwijs (HBO)
- ☐ kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- ☐ (post) wetenschappelijk onderwijs

□ weet niet / wil ik niet zeggen

Questionnaire 2 – proxy

[voor start vragenlijst: informatie deferred consent en redenen voor dit onderzoek]
Enquêtevragen als proxy (familielid of partner) om uitgestelde toestemming is gevraagd voor deelname aan de CONTRAST trial en geen toestemming heeft gegeven.

Wat was de reden dat u geen toestemming heeft gegeven? (niet verplicht)

- ☐ Dit wil ik niet zeggen
- ☐ Ik wil niet dat er gegevens verzameld worden van mijn partner/familielid
- ☐ Ik vond het te veel informatie
- ☐ Ik begreep de uitleg niet goed
- ☐ Ik voelde mij gestresst
- ☐ Deze vraag komt te snel na de beroerte
- ☐ Ik heb te weinig bedenktijd gehad
- ☐ Ik vind dat iemand anders, namelijk de behandeld arts deze beslissing moet maken
- ☐ Ik vind dat iemand anders, namelijk een ander familielid deze beslissing moet maken
- ☐ Anders, namelijk: …..

- Geslacht
  - ☐ Man
  - ☐ Vrouw
- Leeftijd (vrije tekst)
- Wat is uw hoogst genoten opleiding? (keuze)
  - ☐ geen
  - ☐ basisschool
  - ☐ lager beroepsonderwijs (LBO, VMBO)
  - ☐ middelbaar algemeen voorbereidend onderwijs (MAVO)

- □ middelbaar beroepsonderwijs (MBO)
- □ hoger algemeen voorbereidend, wetenschappelijk onderwijs (HAVO, VWO)
- □ hoger beroepsonderwijs (HBO)
- □ kandidaats/propedeuse wetenschappelijk onderwijs (WO)
- □ (post) wetenschappelijk onderwijs
- □ weet niet / wil ik niet zeggen