

Prehospital triage of patients with a suspected acute stroke

Prehospitale triage van patiënten met de verdenking op een acute beroerte

20-12-2023, versie 1.2

Full title of protocol	Prehospital triage of patients with a suspected stroke
Short title or Acronym	PRESTO-2
Protocol ID / Panama number	11129
Version	1.2
Date	December 20th, 2023
Project leaders	B. Roozenbeek, MD, PhD Erasmus MC Department of Neurology Dr. Molewaterplein 40, 3015GD, Rotterdam, NL Email: b.roozenbeek@erasmusmc.nl H. Kerkhoff, MD, PhD Albert Schweitzer hospital Department of Neurology Albert Schweitzerplaats 25, 3318AT, Dordrecht, NL Email: h.kerkhoff@asz.nl
Coordinating investigator	R.M. van de Wijdeven, MD Erasmus MC Department of Neurology Dr. Molewaterplein 40, 3015GD, Rotterdam, the Netherlands Email: r.vandewijdeven@erasmusmc.nl
Principal investigator[2] **(in Dutch: hoofdonderzoeker/ uitvoerder)** **<Multicenter research[3]: principal investigator per site>**	<u>Local principal investigators</u> P.J. van der Geest, MD Ambulance Rotterdam-Rijnmond Medical Manager Breslau 2, 2993LT Barendrecht, NL Email: patrick.vandergeest @vr-rr.nl J.C.M. IJzermans Ambulancedienst Zuid-Holland Zuid Research Nurse Vliedberg 2, 3356GA Papendrecht, Rotterdam, NL Email: jcm.ijzermans@ravzhz.nl
Sponsor[4] (in Dutch: verrichter/opdrachtgever)	Erasmus University Medical Center Rotterdam Dr. Molewaterplein 40 3015 CD Rotterdam, the Netherlands
Subsidizing party[5]	Erasmus MC, ZonMw, Dutch Heart Foundation

PROTOCOL SIGNATURE SHEET

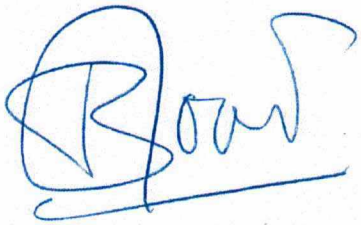
Name	Signature	Date
Sponsor or legal representative: P.A.E. Sillevis Smitt, MD, PhD Head of Department Dept of Neurology, Erasmus MC		21-12-2023
Project leaders: B. Roozenbeek, MD, PhD Neurologist Dept of Neurology, Erasmus MC H. Kerkhoff, MD, PhD Neurologist Dept of Neurology, Albert Schweitzer hospital	 	21/12/2023 21.12.2023

Table of Contents

List of abbreviations and relevant definitions 5
Summary 6
1. Introduction and rationale 8
2. Objective(s) 9
3. Study type 10
4. Study population 11
5. Methods 13
6. Incidental findings 15
7. Statistical analysis 16
8. Ethical considerations 18
9. Handling and storage of data / images / sound recordings / photos / film recordings 20
10. Handling and storage of human material 21
11. Exchange, sharing or transfer of data and/or human material and/or images 21
12. Amendments 21
13. End of study report Within one year after the end of the study a final study report will be submitted with the results of the study, including any publications/abstracts of the study. 21
14. Publication 21
15. References 22
16. Attachments 24

List of abbreviations and relevant definitions

CE	Conformité Européene
CTA	Clinical Trial Agreement
De novo biobank	A new data, human material or imaging collection
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreement
EVT	Endovascular thrombectomy
Exception consent	Form Care for data Template, in Dutch: Formulier uitzondering toestemming
FAST	Face Arm Speech Time
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation in Dutch: Algemene Verordening Gegevensbescherming
GPS	Global Positioning System
IC	Informed Consent
IVT	Intravenous thrombolytics
IFU	Instruction For Use
LVO	Large vessel occlusion
mRS	modified Rankin Scale
MTA	Material Transfer Agreement
NIHSS	National Institutes of Health Stroke Scale
NWTC	Non-WMO Review Committee; in Dutch: Niet WMO Toetsingscommissie
PSC	Primary stroke center
RACE	Rapid Arterial oCclusion Evaluation
ROAZ	Regionaal Overleg Acute Zorg
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet Algemene Verordening Gegevensbescherming
WGBO	Wet op de geneeskundige behandelingsovereenkomst
WMO	Medical Research Involving Human Subjects Act, in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

Summary

Rationale

In current practice, patients with a suspected stroke are transported by ambulance to the nearest stroke center capable of administering intravenous thrombolytics (IVT). If the diagnostic workup is performed in a primary (=non-intervention) stroke center and shows a large vessel occlusion (LVO) as cause of the ischemic stroke, the patient is transferred to an intervention center to undergo endovascular treatment (EVT). These transfers delay the start of EVT and decrease the chances of recovery. An alternative strategy could be to transport every patient with suspected stroke directly to an intervention center. This approach delays treatment with intravenous thrombolytics in patients not eligible for EVT. Triage of patients eligible for EVT in the prehospital setting may eliminate the need for interhospital transfers, expediting time to EVT and improving long-term functional outcome. The Stroke Triage App has been developed to provide a substantiated transportation advice to paramedics. The Stroke Triage Apps compares the two transportation strategies (transfer to primary stroke center and transfer to intervention center) and returns the strategy which yields the highest estimated probability of good long-term functional outcome.

Objective(s)

The overall objective of the PRESTO-2 study is to evaluate the implementation of the Stroke Triage App, a decision support tool for individualized prehospital triage of patients with suspected stroke. We defined the following specific objectives:

1. To assess whether implementation of prehospital triage by means of the Stroke Triage App reduces the onset-to-groin time in patient with ischemic stroke caused by large vessel occlusion.

2. To evaluate the effect of implementation of prehospital triage on the number of required ambulance transportations and the distribution of suspected ischemic stroke patients among hospitals in the intervention region.

Study type

For the first specific objective, we will perform an implementation study using a before-and-after intervention design with difference-in-differences analysis. We will use data from an intervention region and a control region. For the second specific objective, we will conduct a cohort study with simulation.

Study population

1. All consecutive adult patients (≥18 years) with a clinical diagnosis of ischemic stroke in the 12 months prior and 12 months after implementation of the Stroke Triage App, in the intervention region and the control region.

2. All consecutive adult patients (≥18 years) with a suspected stroke for whom the Stroke Triage App was utilised by paramedics to facilitate prehospital triage in the 12 months after implementation of the Stroke Triage App in the intervention region.

Methods

Paramedics use the Stroke Triage App in the ambulance to obtain routing advice. Prehospital data will be enriched with data from the ambulance call reports and hospital electronic files. Primary outcome is the reduction in onset-to-groin time, assessed by calculating the difference-in-differences estimator through the use of a difference-in-differences linear regression model.

Burden and risks

The burden on participants is minimal. The study procedures take place in the prehospital setting and consist of a short neurological examination (2 extra items compared to current clinical practice) and transport to a hospital. There is a small risk that standard treatment with intravenous thrombolysis will be minimally delayed, but it is expected that this is outweighed by the time gained to standard treatment with endovascular thrombectomy.

Recruitment and consent

Patients are recruited in the prehospital setting by paramedics. Due to the nature of the study, an appeal is made to the exception of Section 7:458(1)(b) of the Dutch Civil Code, as stated in Chapter 5 Section 5.4 of the 2022 Code of Conduct for Health Research, for an exemption for the need of informed consent in accordance with the code of conduct 2022.

1. Introduction and rationale

Every year, more than 30,000 patients with a stroke are hospitalized in the Netherlands. [1] Treatment with intravenous alteplase (IVT) is an effective treatment for patients with ischemic stroke, but the effectiveness depends on the speed of administration. [2-5] Approximately one quarter of patients with acute ischemic stroke have a proximal intracranial large vessel occlusion (LVO). The effect of IVT in this group of patients is small. [6-9]

For patients with an LVO, endovascular thrombectomy (EVT) is an effective treatment.[6, 9-11] This is a complex treatment that is only available in specialized intervention centers. Like with IVT, there is a strong time-dependent treatment effect, with treatment being more effective the earlier it is initiated.[12] An important cause of delay is a transfer between hospitals. This occurs when patients with an LVO stroke are first transported to the nearest primary stroke center (PSC) where EVT is not possible.[13, 14] A transfer can be prevented by recognizing patients with a LVO stroke in the ambulance and transporting them immediately to an intervention center. This can be done through prehospital triage. To this end, prehospital stroke scales have been developed. These scales can be used to estimate the likelihood of LVO. Several of these prehospital stroke scales have been prospectively validated, showing that some scores can detect the presence of LVO with good accuracy. Of these scales, the Rapid Arterial oCclusion Evaluation (RACE) scale performed best in several studies. This was also the case in the PRESTO study, conducted by our group within our Acute Care (ROAZ) region. [8, 14-16]

Prehospital stroke scales are being implemented in some regions in the Netherlands and beyond. The following procedure is used in these regions: when the total score of the prehospital stroke scale for a patient is higher than a defined cutpoint, the decision is made to transport this patient directly to the intervention center. When the score falls below this cutpoint, the patient is transported to the nearest hospital.[17, 18] However, this method does not take into account essential regional characteristics. Previous research showed that not only the probability of having an LVO, but also the driving times to hospitals, the workflow times within hospitals, and the transfer times between hospitals are important factors in determining the optimal transportation strategy.[14] The Stroke Triage App brings the aforementioned factors together in a multivariable decision model to aid ambulance staff in determining the best transport strategy for each individual patient.[19] This application will be implemented in the ROAZ Southwest Netherlands.

Based on simulation studies with the data from the PRESTO study, we expect that the implementation of the Stroke Triage App in the ROAZ Southwest Netherlands will lead to faster treatment of patients with EVT, without leading to a substantial delay of treatment with IVT.[20] In this document, we describe the protocol for scientific evaluation of the implementation of the Stroke Triage App in the ROAZ Southwest Netherlands: the PRESTO-2 study.

2. Objective(s)

The overall objective of the PRESTO-2 study is to evaluate the implementation of the Stroke Triage App, a decision support tool for individualized prehospital triage of patients with potential stroke. The specific objectives are the following:

Specific Objective 1:

Evaluation of the effectiveness of the Stroke Triage App implementation in reducing the time to EVT.

Specific Objective 2:

Evaluation of the consequences of the implementation of the Stroke Triage App for the number of ambulance transportations and the distribution of stroke patients across hospitals in the region.

3. Study type

3.1. **Study type**

☐ Retrospective
☐ Prospective
☒ Combination Retrospective/Prospective

3.2. **Single center / Multicenter**

☐ Single center
☒ Multicenter

3.3 **Check all the applicable boxes**

☒ Medical records (re-use of data from healthcare, including AI)
☐ Case report
☐ Re-use data from research
☒ Evaluations of quality of healthcare (retrospective)
☐ Research with additional use of residual material from regular healthcare
☐ Research with re-use of human material from research or existing biobank
☐ De novo biobank
☒ Phase IV research
☒ Healthcare evaluation research (prospective)
☒ Research with medical devices
☐ Research with In Vitro Diagnostic Tests
☐ Other research, describe

4. Study population

4.1. Study population

☒ Adults (16 years and older)
☐ Minors (younger than 16 years)
☒ Incapacitated adults (16 years and older)
☐ Incapacitated minors (younger than 16 years)

4.2. Population (base)

Specific Objective 1:

All consecutive adult patients (≥18 years) with a clinical (in-hospital) diagnosis of ischemic stroke in the 12 months prior and 12 months after implementation of the Stroke Triage App, in the intervention region and the control region. The intervention region consists of the ambulance regions Rotterdam-Rijnmond and Zuid-Holland Zuid. The control region is defined as the ambulance region Amsterdam-Amstelland.

Specific Objective 2:

All consecutive adult patients (≥18 years) with a suspected stroke (based on a positive FAST-test (≥1 point)) with onset of symptoms within the last 24 hours for whom the Stroke Triage App was utilized by paramedics to facilitate prehospital triage in the 12 months after implementation of the Stroke Triage App in the intervention region.

4.3. Inclusion criteria

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

Specific Objective 1:

Adult patients (≥18 years) with a clinical diagnosis of ischemic stroke in the 12 months prior and 12 months after implementation of the Stroke Triage App, in the intervention region and the control region.

Specific Objective 2:

Adult patients (≥18 years) with a suspected stroke (based on a positive FAST-test (≥1 point)) with onset of symptoms within the last 24 hours for whom the Stroke Triage App was utilized by paramedics to facilitate prehospital triage in the 12 months after implementation of the Stroke Triage App in the intervention region.

4.4. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
None.

4.5. Sample size calculation

Specific Objective 1:

Given the nature of this implementation study, in which data are collected from patients with a clinical diagnosis of ischemic stroke 12 months before and 12 months after implementation of the Stroke Triage App, a power calculation has been conducted instead of a sample size calculation.(20) Based on registry data, the mean (±SD) onset-to-groin time is currently 224.5 (±94.1) minutes. Based on modelled data, where the Stroke Triage App algorithm has been applied to a prospectively collected cohort of prehospital suspected stroke patients, the mean effect of implementation of triage with the Stroke Triage App algorithm on the primary outcome measure (onset-to-groin time in patients undergoing EVT for ischemic stroke with LVO) in the intervention region is estimated to be -31 minutes. Assuming a low intra-cluster correlation coefficient (ICC) of 0.01, 96 EVTs annually per region would be required to reach a power of 80%. It is estimated that approximately 300 EVTs take place per region annually, which corresponds to a power of >99% at a predefined alpha of 0.05.

Specific Objective 2:

A sample size calculation is not applicable.

5. Methods

5.1. Research methods

Paramedics will use the Stroke Triage App in the ambulance to obtain routing advice for suspected stroke patients. The input required for this advice is the time of symptom onset and the RACE score. Driving times are automatically calculated through Global Positioning System (GPS) tracking. The data gathered by the Stroke Triage App will be enriched by extraction of data from ambulance call reports and hospital medical records.

5.2. Standard clinical care versus extra for research

All of the data (i.e. patient characteristics, (neurological) examinations, imaging and laboratory tests) that are collected for the purpose of this study are obtained during standard clinical care at the discretion of the attending paramedics and attending physician. The study is designed in such a way that no additional data has to be obtained solely for the purpose of research.

5.3. Burden and risks

Implementation of the triage algorithm in the Stroke Triage App is expected to lead to faster onset-to-groin times, at the expense of a minimal delay in onset-to-needle times. The benefits are expected to outweigh these side effects. From a broader health care perspective, fewer acute interhospital transfers are expected to be required, reducing the burden to ambulance services. The preclinical data consists of modelling studies where the triage algorithm in the Stroke Triage App is applied to cohorts of suspected stroke patients. One such study was conducted with a simulated patient cohort in the United States. The study showed that our triage algorithm yielded the highest increase of good outcomes (+1.8% to +2.4%) when compared to other triage paradigms.[21] We modelled the effect of implementation of our triage algorithm within our own study region, using a cohort of prospectively collected suspected stroke patients in the prehospital setting. We found that 33% of patients undergoing endovascular thrombectomy (EVT) would be treated faster by 31 minutes on average, and that 16% of patients undergoing intravenous alteplase would be treated faster by 8 minutes on average. On the other hand, 7% of EVT patients would be treated 27 minutes slower on average, while 19% of IVT patients would be treated 9 minutes slower on average (*unpublished data)*. It is important to interpret these numbers in the context of the time-dependent treatment effect of both treatments. The probability of good functional outcome in patients undergoing EVT decreases by approximately 5.2-6.0% for each hour delay to initiating treatment, compared to approximately a 2.5% decrease for each hour delay in patients undergoing IVT.[9, 21-23] In summary, when expediting EVT by a minute at the expense of delaying IVT by a minute, this yields an overall net benefit from a health care perspective. The numbers above show that the expected gains from implementing prehospital triage heavily outweigh the expected side effects.

5.4. **Medical device(s) / In vitro diagnostic tests**

The Stroke Triage App is a medical device as defined by the Medical Device Regulation. It is classified as a Risk Class 1 device (Annex VIII, Chapter III). As such, CE-certification will be acquired by the manufacturer of the product.

The Stroke Triage App aims to provide an advice for transporting suspected stroke patients to the nearest primary stroke center or to the nearest intervention center for diagnosis. At these centers, patients will be diagnosed for treatment options. If the Stroke Triage App is unavailable, transportation strategy will be reverted to current practice, which is the drip-and-ship transportation strategy. This strategy dictates transportation of patients to the nearest hospital. The Stroke Triage App rationalizes the routing decision to be made.

No in vitro diagnostic tests will be used.

6. Incidental findings

6.1. Chance of incidental findings

Is there a chance of incidental findings?

☐ Yes

☒ No

6.2. Procedures

Not applicable.

7. Statistical analysis

7.1 Main study parameters/endpoints

Specific Objective 1:

Time from symptom onset to groin puncture (=start EVT) in patients with an ischemic stroke who are treated with EVT.

7.2 Secondary study parameters/endpoints

Specific Objective 1:

• Time from symptom onset to needle (=start of IVT) in patients with ischemic stroke who were treated with IVT

• Percentage of patients with ischemic stroke treated with IVT within the regular time window of 4.5 hours after the onset of symptoms or 'last seen well' and percentage treated outside this treatment window (extended window)

• Percentage of patients with ischemic stroke treated with EVT within the regular time window of 6 hours after the onset of symptoms or 'last seen well' and percentage treated outside this treatment window (extended window)

• modified Rankin Scale (mRS) score after 3 months

Specific Objective 2:

• Number and case mix of patients with ischemic stroke with and without occlusion, TIA, intracerebral haemorrhage and stroke mimics in participating hospitals (primary hospitals vs. intervention centers)

• Number and percentage of ischemic stroke patients without EVT-eligible occlusion who were taken to an intervention center and bypassed a primary stroke center

• Number and percentage of stroke patients with EVT-eligible occlusion who were not immediately taken to an intervention center

• Compliance with Stroke Triage App advice

• Number of required acute ambulance transports (A1/A2-transports, prior to reperfusion therapy)

• Number of subacute ambulance transports (B-transports, for transfer after reperfusion therapy or after it has become apparent that there is no indication for reperfusion therapy)

7.3 Other study parameters

Other study parameters that will be collected are:

Baseline characteristics:

Age, date of birth (hashed bye one-way hashing), sex, vital functions (blood pressure, pulse, rhythm, saturation), Glasgow Coma Scale (GCS) score, individual components of GCS-score (i.e. eye, motor and verbal scores), Face Arm Speech Time (FAST) test, pupil score, serum glucose in ambulance, date and time of ambulance notification, date and time of ambulance departure to location, date and time of ambulance arrival, date and time of ambulance departure, date and time of arrival at first hospital, destination hospital, date and time of transfer request (if applicable), date and time of departure at first hospital (if applicable), date and time of arrival at intervention center (if applicable), medical history, total National Institutes of Health Stroke Scale (NIHSS) score, individual components of the NIHSS (i.e. level of consciousness, best gaze, visual, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, dysarthria, extinction and inattention), diagnosis at Emergency Department, treatment with IVT, time of IVT, treatment with EVT, time of EVT, duration of hospitalization, discharge location, diagnosis at discharge, modified Rankin Scale score after 3 months.

Input and output variables of the Stroke Triage App:

Ambulance ridenumber, the ambulance service, time of login, type of onset, total RACE-score, individual components of the RACE-scale (i.e. side of deficits, facial paresis, paresis of arm, paresis of lag, cephalic and eye deviation and aphasia or agnosia), GPS of pick-up location, onset-to-ambulance departure time, time of triage request, duration of triage, time of advice, driving time to all regional hospitals, nearest hospital, nearest intervention center, door-to-needle-time and door-to-groin-time of nearest hospitals, door-in-door-out time of nearest hospital, transfer time of nearest hospital, probability of LVO ischemic stroke based on RACE-score, probability of non-LVO ischemic stroke based on RACE-score, probability of receiving IVT, probability of receiving EVT, probability of early reperfusion after IVT, adaptable sensitivity margin of the model, the predicted probability of good functional outcome for the nearest hospital, the predicted probability of good functional outcome for the nearest intervention center, the hierarchical advice of the model, the advice returned to user by the model, whether the advice was followed by the user (if not, why not).

7.4 Analysis

Specific objective 1:

The statistical analysis will be performed after inclusion of the last patient, after the data has been checked, errors have been corrected and the database has been locked. Missing data will be imputed using simple imputation (if <5% missing) or multiple imputation by means of a regression model (if ≥5% missing). We will estimate the effect of the implementation of the Stroke Triage App on the primary and secondary outcomes using differences-in-differences analysis. This analysis compares the differences before and after implementation in the implementation region with the differences in the same time period in the control region where no implementation takes place. This method corrects for unobserved confounders and (other) time-related differences in acute stroke care. For the primary outcome, we will calculate the difference-in-differences estimator by means of a difference-in-differences linear regression model. The statistical analysis will be further elaborated in a separate Statistical Analysis Plan.

Specific objective 2:

The statistical analysis will be performed after inclusion of the last patient, after the data has been checked, errors have been corrected and the database has been locked. Categorical variables are reported as numbers and percentages. Normally distributed continuous data is reported as mean with standard deviations (±SD). Non-normally distributed continuous data is reported as median with interquartile range (IQR). Missing data will be imputed using simple imputation (if <5% missing) or multiple imputation using a regression model (if ≥5% missing). We will report the observed outcomes in the study cohort. We will then conduct an analysis in which we simulate what would have happened to the cohort outcomes if all patients had first been taken to the nearest hospital, in accordance with the ambulance protocol that was in place prior to the implementation of the Stroke Triage App ('drip-and-ship' model). We will compare the observed outcomes with the simulated outcomes in order to be able to make a statement about the effects of the implementation of the Stroke Triage App on these outcomes. The statistical analysis will be further elaborated in a separate Statistical Analysis Plan.

8. Ethical considerations

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (October 2013), Gedragscode Gezondheidsonderzoek 2022, the Dutch Medical Treatment Contracts Act (WGBO), and the General Data Protection Regulation (GDPR). The Medical Device Regulations (MDR, EU no 2017/745) is not applicable, as the Stroke Triage App is a CE-certified application used within the scope of its the intended purpose. This study is part of post-market clinical follow-up and does not comprise additional invasive or burdensome procedures compared to standard of care. As such, it falls outside the scope of chapter VI of the MDR.

8.2 Informed consent

Will the subjects be asked for informed consent?

☐ Yes *(Upload Participant Information Letter and Informed Consent)*

☐ No, consent already given in previous study *(Upload Participant Information Letter and Informed Consent previous study)*

☒ No, this research will be performed under the exception consent *(Upload form Care for data Template, in Dutch: Formulier uitzondering toestemming)*

☐ Other (e.g. partly, indirectly) *Please describe the situation.*

8.3 Recruitment and informed consent procedures

Patients will be recruited by paramedics in the ambulance. Informed consent will not be acquire, instead an appeal is made to the exception in the Dutch Civil Code, as stated in Chapter 5 Section 5.4 of the 2022 Code of Conduct for Health Research.(21) For a further elaboration see chapter 8.4.

8.4 Exception consent

Specific Objective 1:

For this part of the study, we will use non-personally identifiable data collected as part of a national quality registry (Dutch Acute Stroke Audit) in which all Dutch hospitals participate. This data is collected with an exemption of patient consent, as is common practice in clinical audits. Hospitals are free to determine who carries out the data registration (for example (research) nurses, data managers or neurologists), but the final responsibility lies with the neurologist.

Specific Objective 2:

For this part of the study, paramedics include patients with suspected stroke. Many patients with a stroke have a language impairment, anosognosia or other cognitive symptoms that complicate an informed consent procedure. A representative of the patient is often not immediately present in the prehospital setting. Moreover, a proper informed consent procedure takes time, and this time is not available in the ambulance.

Taking informed consent at a later time ('deferred consent') during hospitalization is burdensome for both the patient and family, and would have to be conducted by the attending physician within the context of the WGBO. Because the patients spread in various directions after the initial ambulance ride, a disproportionate number of healthcare providers/physicians from a multitude of specialties (neurologists, emergency physicians, internists, geriatricians,

cardiologists and general practitioners) must be involved in order for the deferred consent procedure to take place.

Because 'consent cannot reasonably be requested given the nature and purpose of the research', an appeal is made to the exception of Section 7:458(1)(b) of the Dutch Civil Code, as stated in Chapter 5 Section 5.4 of the 2022 Code of Conduct for Health Research.(21) The magnitude of the effort that must be made by a large number of healthcare providers to obtain consent from the participating patients is disproportionate in relation to the relatively limited sensitivity of the collected personal data and the associated limited infringement of the personal living atmosphere.

Moreover, the risks of participating in the study are minimal and using a deferred consent procedure could reasonably be presumed to lead to a drop-out of selected groups of patients due to geographical and/or clinical characteristics. This could jeopardize the validity and the reliability of the results and may lead to erroneous conclusions, making it unethical to conduct the study altogether.

Because of the aforementioned reasons, an opt-out procedure will be used. The attending paramedic will provide an information leaflet in which the patient is informed about the study. This leaflet also states that data has been collected in the ambulance and that routinely collected data from the hospital will be requested for further analysis. Patients or their next of kin are given the opportunity to object to the use of this data for the study. When a patient or next of kin objects, all data will be destroyed and this patient will no longer be included in the study. The letter should be signed and sent by land mail (free of charge) or as an attachment to an e-mail to the trial office.

9. Handling and storage of data / images / sound recordings / photos / film recordings

9.1 Data / images / sound recordings / photos / film recordings

A combination of prehospital data and hospital data will be gathered for the purpose of this study. No images, sound recordings, photos or film recordings will be gathered. All data gathered for the purpose of this study has been obtained for regular healthcare purposes. For an exhaustive list of collected parameters, please refer to chapters 7.2 and 7.3.

9.2 Privacy protection

To protect the subject's privacy, no directly identifiable data will be entered into the Stroke Triage App or gathered from the ambulance call reports or hospital electronic files.

The ride number will be used as a pseudonym to couple data from the Stroke Triage App with the ambulance call reports. The destination hospital, date and time of arrival will be extracted and date of birth will be extracted from the ambulance call report. The date of birth will be hashed by one-way hashing. A one-way hash function is a mathematical function that generates a fingerprint of the input, but there is no way to get back to the original input. If the input is the same then the hash is always the same. If it changes at all, the output hash is completely different. A hash can be used to verify that input A is identical to input B but cannot be used to get the input back from the output like with another mathematical function. The destination hospital, date and time of arrival will then be used to identify the correct patient record. The one-way hashed date of birth serves as a final verification that the correct individual has been identified.

9.3 Handling and storage of data

Data that is entered into or automatically generated by the Stroke Triage App will be stored on a server (LogiqCare, ISO27001 and NEN 7510 certified) owned by the developer of the application, ORTEC. This data is only accessible to authorized Erasmus MC users. These authorizations are managed by ORTEC. Access and changes to the data are logged. Access is granted to the researchers conducting the study. Subjects' records are coded with a unique study ID and a subject identification code is safeguarded to facilitate tracing data to individual subjects as long as necessary. The key to the code will be safeguarded by the coordinating investigator.

The data mentioned above will be enriched with data from the ambulance call reports and hospital electronic files.

All data will be stored for the duration of 10 years in accordance with the Erasmus MC guidelines.

9.4 Handling and storage of images / sound recordings / photos / film recordings

No images, sound recordings, photos or film recordings will be collected for the purpose of this study.

9.5 Approval of access to data / images / sound recordings / photos / film recordings

Approval of access to data will be granted by ORTEC upon request by the study's Principal Investigator.

10. Handling and storage of human material

No human material will be collected for the purpose of this study, therefore this section is not applicable.

11. Exchange, sharing or transfer of data and/or human material and/or images

Data from ambulance services and hospitals will be shared with the Erasmus MC. All participating organizations are in the EU, data will not be shared outside of the EU. Data transfers will be facilitated by data transfer agreements.

12. Amendments

Version number	Change	Date
1	Initial version	28-08-2023
1.1	- Replaced waiver of consent for exemption - Changed the opt-out procedure	16-10-2023
1.2	- Changed inclusion criteria to patients with onset of symptoms within 24 hours	20-12-2023

13. End of study report

Within one year after the end of the study a final study report will be submitted with the results of the study, including any publications/abstracts of the study.

14. Publication

Do you have the intention to submit the study results in a manuscript for publication in a journal:

☒ Yes

☐ No, *please motivate*

15. References

1. de Boer AR, van Dis I, Wimmers RH, Vaartjes I, Bots ML. Hart- en vaatziekten in nederland, 2020, cijfers over incidentie, prevalantie, ziekte en sterfte. 2020
2. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329
3. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019;380:1795-1803
4. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587
5. Tsivgoulis G, Katsanos AH, Malhotra K, Sarraj A, Barreto AD, Kohrmann M, Krogias C, Ahmed N, Caso V, Schellinger PD, et al. Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. *Neurology*. 2020;94:e1241-e1248
6. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F, investigators T. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (thrace): A randomised controlled trial. *Lancet Neurol*. 2016;15:1138-1147
7. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. *N Engl J Med*. 2013;368:893-903
8. Duvekot MHC, Venema E, Rozeman AD, Moudrous W, Vermeij FH, Biekart M, Lingsma HF, Maasland L, Wijnhoud AD, Mulder L, et al. Comparison of eight prehospital stroke scales to detect intracranial large-vessel occlusion in suspected stroke (presto): A prospective observational study. *Lancet Neurol*. 2021;20:213-221
9. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723-1731
10. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708-718
11. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11-21
12. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A meta-analysis. *JAMA*. 2016;316:1279-1288
13. Menon BK, Sajobi TT, Zhang Y, Rempel JL, Shuaib A, Thornton J, Williams D, Roy D, Poppe AY, Jovin TG, et al. Analysis of workflow and time to treatment on thrombectomy outcome in the endovascular treatment for small core and proximal occlusion ischemic stroke (escape) randomized, controlled trial. *Circulation*. 2016;133:2279-2286
14. Venema E, Boodt N, Berkhemer OA, Rood PPM, van Zwam WH, van Oostenbrugge RJ, van der Lugt A, Roos Y, Majoie C, Lingsma HF, et al. Workflow and factors associated with delay in the delivery of intra-arterial treatment for acute ischemic stroke in the mr clean trial. *J Neurointerv Surg*. 2018;10:424-428

15. Nguyen TTM, van den Wijngaard IR, Bosch J, van Belle E, van Zwet EW, Dofferhoff-Vermeulen T, Duijndam D, Koster GT, de Schryver E, Kloos LMH, et al. Comparison of prehospital scales for predicting large anterior vessel occlusion in the ambulance setting. *JAMA Neurol*. 2021;78:157-164
16. Perez de la Ossa N, Carrera D, Gorchs M, Querol M, Millan M, Gomis M, Dorado L, Lopez-Cancio E, Hernandez-Perez M, Chicharro V, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: The rapid arterial occlusion evaluation scale. *Stroke*. 2014;45:87-91
17. Abilleira S, Perez de la Ossa N, Jimenez X, Cardona P, Cocho D, Purroy F, Serena J, Roman LS, Urra X, Vilaro M, et al. Transfer to the local stroke center versus direct transfer to endovascular center of acute stroke patients with suspected large vessel occlusion in the catalan territory (racecat): Study protocol of a cluster randomized within a cohort trial. *Int J Stroke*. 2019;14:734-744
18. Kass-Hout T, Lee J, Tataris K, Richards CT, Markul E, Weber J, Mendelson S, O'Neill K, Sednew RM, Prabhakaran S. Prehospital comprehensive stroke center vs primary stroke center triage in patients with suspected large vessel occlusion stroke. *JAMA Neurol*. 2021;78:1220-1227
19. Venema E, Lingsma HF, Chalos V, Mulder M, Lahr MMH, van der Lugt A, van Es A, Steyerberg EW, Hunink MGM, Dippel DWJ, et al. Personalized prehospital triage in acute ischemic stroke. *Stroke*. 2019;50:313-320
20. Duvekot MHC, Garcia BL, Dekker L, Nguyen TM, van den Wijngaard IR, de Laat KF, de Schryver E, Kloos LMH, Aerden LAM, Zylicz SA, et al. Prehospital stroke triage: A modeling study on the impact of triage tools in different regions. *Prehosp Emerg Care*. 2023:1-9
21. Venema E, Burke JF, Roozenbeek B, Nelson J, Lingsma HF, Dippel DWJ, Kent DM. Prehospital triage strategies for the transportation of suspected stroke patients in the united states. *Stroke*. 2020;51:3310-3319
22. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935
23. Fransen PS, Berkhemer OA, Lingsma HF, Beumer D, van den Berg LA, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al. Time to reperfusion and treatment effect for acute ischemic stroke: A randomized clinical trial. *JAMA Neurol*. 2016;73:190-196

16. Attachments

☐ Participant information letter and Informed consent document

☒ Care for data Template – Formulier uitzondering toestemming

☐ Questionnaires

☒ Data Management Plan

☐ Data Transfer Agreement

☐ Material Transfer Agreement

☒ Clinical Trial (Site) Agreement

☐ Other, *please describe*