AI-STROKE

Algorithm development through artificial intelligence for the triage of stroke patients in the ambulance with electroencephalography

RESEARCH PROTOCOL

PROTOCOL TITLE: 'AI-STROKE: Algorithm development through artificial intelligence for the triage of stroke patients in the ambulance with electroencephalography'

Protocol ID	NL75429.018.20
Short title	AI-STROKE
EudraCT number	Not applicable
Version	5.0
Date	14-04-2022
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse event
AI	Artificial intelligence
AIS	Acute ischemic stroke
AMC	Amsterdam UMC, location AMC
Amsterdam UMC	Amsterdam University Medical Centers
AVG	General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming)
CRF	Case report form
CT	Computed Tomography
EEG	Electroencephalography
EMS	Emergency medical service
EVT	Endovascular thrombectomy
ER	Emergency room
LVO	Large vessel occlusion
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsingscommissie (METC)
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
NPV	Negative predictive value
OLVG West	Onze Lieve Vrouwe Gasthuis, location Amsterdam West
PPV	Positive predictive value
ROC	Receiver operating characteristic
SAE	Serious adverse event
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.
VUMC	Amsterdam UMC, location VUMC
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk onderzoek met mensen)

SUMMARY

RATIONALE

Large vessel occlusion (LVO) stroke causes around 30% of acute ischemic strokes (AIS) and is associated with severe deficits and poor neurological outcomes.[1-4] Endovascular thrombectomy (EVT) enormously improves the prognosis of patients with LVO stroke, but its effect is highly time-dependent. Because of its complexity and required resources, EVT can be performed in selected hospitals only. In the Netherlands, approximately half of the EVT-eligible patients are initially admitted to a hospital incapable of performing EVT, and – once it has been ascertained that a patient requires EVT – the patient needs to be transported a second time by ambulance to an EVT-capable hospital.[5] This workflow leads to an average treatment delay of about 1 hour, which decreases the absolute chance of a good outcome of the patient by 5-15%.[5-7] To solve this issue, a prehospital stroke triage instrument is needed, which reliably identifies LVO stroke in the ambulance, so that these patients can be brought directly to an EVT-capable hospital. Electroencephalography (EEG) may be suitable for this purpose, since it shows almost instantaneous changes in response to cerebral blood flow reduction.[8, 9] Moreover, significant differences between EEGs of patients with an LVO and those of suspected AIS patients with a smaller or no vessel occlusion have been found.[10] A dry electrode EEG cap enables ambulance paramedics to perform an EEG in the prehospital setting, with significant reduced preparation time compared to conventional wet electrode EEG.[11, 12] An automatic LVO-detection algorithm will be the key to reliable, simple and fast interpretation of the EEG by paramedics, enabling direct admission of suspected AIS patients to the right hospital.

HYPOTHESIS

An EEG-based algorithm, developed with artificial intelligence (AI), will have sufficiently high diagnostic accuracy to be used by ambulance paramedics for prehospital LVO detection.

OBJECTIVE

The primary objective of this study is to develop one or more novel AI-based algorithms (the AI-STROKE algorithms) with optimal diagnostic accuracy for identification of LVO stroke in patients with a suspected AIS in the prehospital setting, based on ambulant EEG data.

STUDY DESIGN

AI-STROKE is an investigator-initiated, multicenter, diagnostic test accuracy study.

STUDY POPULATION

Part A: Adult patients with a (suspected) AIS, in the prehospital setting.

Part B: Adult patients with a (suspected) AIS, in the in-hospital setting.

INTERVENTION

A single EEG measurement with a dry electrode cap (approximately 2 minutes recording duration) will be performed in each patient. In addition, clinical and radiological data will be collected. EEG data will be acquired with a CE approved portable dry electrode EEG device.

MAIN END POINTS

- Primary end point: Based on the EEG data, and using the final diagnosis established by an adjudication committee as the gold standard, one or more novel AI-based EEG algorithms (the AI-STROKE algorithms) will be developed with maximal diagnostic accuracy (i.e. area under the ROC curve; AUC) to identify patients with an LVO stroke of the anterior circulation in a population of patients with suspected AIS.

- Secondary end points:

    - AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the AI-STROKE algorithms based on ambulant EEG for diagnosis of LVO of the anterior circulation in suspected AIS patients in the prehospital setting;

    - AUC, sensitivity, specificity, PPV and NPV of existing EEG algorithms based on ambulant EEG for diagnosis of LVO of the anterior circulation in suspected AIS patients in the prehospital setting;

    - AUC, sensitivity, specificity, PPV and NPV of existing and newly developed EEG algorithms based on ambulant EEG for detection of LVO stroke of the posterior circulation, intracerebral hemorrhage, transient ischemic attack, and stroke mimics;

- Technical and logistical feasibility (e.g. in terms of EEG channel reliability) of paramedics performing ambulant EEG in patients with a suspected AIS in the prehospital setting.

NATURE AND EXTENT OF THE BURDEN AND RISKS ASSOCIATED WITH PARTICIPATION, BENEFIT AND GROUP RELATEDNESS

A single EEG will be performed in each patient. An EEG-measurement is a safe and non-invasive procedure, regularly performed in standard medical practice. The use of dry electrodes makes it possible to perform the measurement in less than five minutes. The dry electrodes will cause no to minimal discomfort, and only during the measurement. We expect no health risks, as we will use only CE marked products for performing the EEG. The treating physicians and the ambulance paramedics will not interpret the EEG recording, therefore the EEG results will not influence choices regarding diagnosis, treatment or the hospital to which the patient is presented. Deferred informed consent will be asked as soon as logistically feasible, preferably within 72 hours after arrival at the hospital or at discharge (whichever comes first). If informed consent is given, a case report form (CRF) will be filled out containing information on patient characteristics, medical history, medication use, physical and neurological examination performed by the treating physician, results of imaging studies, diagnosis and treatment as well as logistical and technical information, obtained from the patient, the treating physician and the Emergency Medical Service (EMS). There are no follow up visits. For the patient, there is no benefit of participation in the study.

1. INTRODUCTION AND RATIONALE

Acute ischemic stroke (AIS) is a major cause of death and disability worldwide.[13, 14] Large vessel occlusion (LVO) stroke causes around 30% of AIS and is associated with more severe deficits and worse neurological outcomes than other types of AIS.[1-4] In 2015, endovascular thrombectomy (EVT) became standard treatment for patients with LVO stroke. EVT improves the chance of good functional outcome in patients with an LVO, provided it is initiated within 6 hours, or in a selected population, within 24 hours after stroke symptom onset.[15-17] Early initiation of EVT within these time-ranges is extremely important, as each 9-minute delay results in a poor functional outcome in 1 of every 100 treated patients.[18] However, EVT is a complex procedure that can be performed in specialized hospitals only, so-called comprehensive stroke centers. In the Netherlands, approximately half of EVT-eligible patients are initially admitted to a hospital where this therapy is not available, and are – once it has been established that they are eligible for EVT – transferred to an EVT-capable hospital.[5] In other countries this proportion is even higher. In the Netherlands, this interhospital transfer delays treatment with about 1 hour and leads to an decrease in the absolute chance of functional independence of the patient by 5-15%.[5-7] Direct presentation of all suspected AIS patients to an EVT-capable hospital, however, is also not feasible, since only approximately 7% of these patients have an LVO. Therefore, a prehospital triage instrument that reliably identifies LVO stroke patients allowing direct transport to an EVT capable hospital, is much needed.

Several diagnostic tools have previously been proposed for this purpose, but none have been found suitable. Clinical scales, containing items for scoring the severity of neurological deficit, have low diagnostic accuracy.[19] Ambulances equipped with an imaging system for computed tomography (CT) and CT-angiography have high diagnostic accuracy, but issues regarding safety, clinical efficacy and cost-effectiveness make broad implementation unlikely.[20] Electroencephalography (EEG) may be suitable for LVO-detection, since multiple studies have shown almost instantaneous changes in the EEG-signal in response to reduction of the cerebral blood flow.[8, 9] These changes often include a decrease in higher frequencies followed by an increase in lower frequencies, and can be quantified by EEG measures based on frequency band power.[21] Multiple studies have shown that such quantitative EEG (qEEG) measures, e.g. the delta/alpha ratio, discriminate between AIS patients and healthy controls.[22-24] Based on functional magnetic resonance imaging data, it is also known that the functional connectivity is affected in patients with AIS.[25-27] One case-control study quantified this property by EEG coherence and phase synchronization and found reduced values in both the ipsi- and contralateral hemispheres of AIS patients compared to healthy controls.[24] Recently, a small study performed a single EEG in suspected stroke patients and

showed differences in frequency band power ratios between patients with an LVO (infarct volume > 20 cc) and a smaller or no vessel occlusion. [10] These results indicate the possibility of EEG as an instrument for identification of patients with an LVO.

Although regular wet electrode EEG has a long preparation time and requires experienced lab technicians, a dry electrode EEG cap dramatically reduces preparation time and can be applied by relatively unexperienced users.[11, 12] Preliminary results of our pilot study (ELECTRA-STROKE; NL65939.018.18; clinicaltrials.gov, NCT03699397) suggest that dry electrode EEG is indeed a promising method for LVO-detection and can be performed by ambulance paramedics within minutes, with only minimal training. The EEG setup used in our pilot study is shown in Figure 1. The next step towards a complete, implementable triage instrument is the development of an algorithm that automatically and reliably detects LVO stroke and eventually gives a binary outcome: LVO or no LVO. This algorithm should have both a high specificity and high sensitivity for LVO-detection. A high sensitivity prevents EVT-eligible patients to be admitted to a hospital incapable of EVT, which would result in treatment delay and worse functional outcome. A high specificity may be even more important, in order to prevent false-positive cases to be admitted to an EVT-capable hospital, since this would delay initiation of regular (non-EVT) treatment for these patients and would overburden the EVT-capable hospitals. Moreover, a high specificity may enable direct presentation of EVT-eligible patients to the angiography room, thereby further reducing time to treatment.

We aim to develop an algorithm for LVO-detection using artificial intelligence (AI), as AI is state of art in the automated analysis of medical signals and images. For EEG-signal analysis, the application of AI has grown in recent years and has shown to reach high accuracy in cerebral disease classification, especially in the field of epilepsy.[28, 29] To our knowledge, no EEG-based algorithm developed for detection of LVO stroke, or even an EEG data base suitable for AI-algorithm development for this purpose, is currently available. We hypothesize that an EEG-based algorithm developed using AI can accurately predict the likelihood of an LVO stroke in suspected AIS patients and therefore allows ambulance paramedics to reliably identify EVT-eligible patients in the prehospital setting.

Figure 1. An example of a dry electrode EEG system. A. The dry electrode EEG cap (Waveguard touch, Eemagine [Berlin, Germany]). B/C. Portable and lightweight EEG suitcase, including the dry electrode EEG cap, as used in the ELECTRA-STROKE study.

A 

B 

C 

2. OBJECTIVES

The primary objective of this study is to develop one or more novel AI-based algorithms (the AI-STROKE algorithms) with optimal diagnostic accuracy for identification of LVO stroke in patients with a suspected AIS in the prehospital setting, based on ambulant EEG data.

The secondary objectives are:

- Assessing the diagnostic accuracy of existing EEG algorithms for identification of LVO stroke in patients with a suspected AIS in the prehospital setting;
- Improving the applicability and reliability of the dry electrode EEG cap for use in the prehospital setting;
- Assessing the logistical and technical feasibility of ambulance paramedics performing ambulant EEGs, using an improved dry electrode EEG cap, in the prehospital setting in patients with a suspected AIS.

3. STUDY DESIGN

AI-STROKE is an investigator-initiated, multicenter, diagnostic test accuracy study.

PART A: ALGORITHM DEVELOPMENT AND VALIDATION IN THE PREHOSPITAL SETTING

This part is carried out by two ambulance services (Ambulance Amsterdam and Ambulance Noord-Holland Noord). These ambulances almost exclusively transport suspected AIS patients to the following hospitals: AMC, VUMC, OLVG West and Noordwest Ziekenhuisgroep, location Alkmaar. The ambulance services and these hospitals are therefore all participating centers in this study. A single EEG will be performed in patients with a suspected AIS as assessed by the ambulance paramedic, or with a radiologically confirmed LVO (in case of transport to an EVT center). The acquired data will be used for development and validation of one or more AI-algorithms for LVO-detection and validation of existing EEG-algorithms.

PART B: ALGORITHM DEVELOPMENT AND VALIDATION IN THE EMERGENCY ROOM

This part is carried out in the emergency room (ER) of AMC. A single EEG will be performed in patients with a suspected AIS as assessed by the ambulance paramedic that presents the patient to the ER, or with a radiologically confirmed LVO and who are transported to the AMC for EVT. We will use the data for training and validation of one or more AI-algorithms for LVO-detection and validation of existing EEG-algorithms.

At the start of the study, EEG data of suspected AIS patients will be limited. In this phase, we will use existing fully anonymized EEG data, obtained as part of standard medical care, and data from the ELECTRA-STROKE study for pretraining of the AI-algorithms (see chapter 10).

In both study parts a single EEG is performed. After informed consent is given, information is collected on patient characteristics, medical history, medication use, physical and neurological examination performed by the treating physician, imaging studies, diagnosis and treatment as well as logistical and technical information, obtained from the patient, the treating physician and the Emergency Medical Service (EMS). There are no follow up visits.

Each patient will be enrolled once. If the patient has already been included in the study in the prehospital setting, no EEG will be performed in part B. The study will run until the maximum number of inclusions is reached (as specified in chapter 4.4) or earlier when the steering committee decides that an accurate and stable algorithm can be developed with the data collected up till that point. Two interim analyses will take place as described in chapter 10, at which time the steering committee may decide to prematurely stop the recruitment in the study.

Based on findings in our pilot ELECTRA-STROKE study, we are optimizing the EEG-hardware to improve the reliability and applicability of the dry electrode EEG cap in acute care settings. We will assess the technical and logistical feasibility of performing EEGs using the optimized EEG-hardware in patients with a suspected AIS in the ambulance.

4. STUDY POPULATION

4.1 POPULATION (BASE)

PART A

We will recruit patients with a suspected AIS or a known LVO of the anterior circulation, in the ambulance, who meet the criteria described in chapter 4.2 and 4.3.

PART B

We will recruit patients with a suspected AIS or a known LVO of the anterior circulation, presented to the ER of the AMC, who meet the criteria described in chapter 4.2 and 4.3.

4.2 INCLUSION CRITERIA

PART A AND B

All subjects must meet all of the following criteria:

- Suspected AIS, as assessed by the attending ambulance paramedic, or a known LVO stroke;
- Onset of symptoms or last seen well < 24 hours before EEG acquisition;
- Age of 18 years or older;
- Written informed consent by patient or legal representative (deferred).

4.3 EXCLUSION CRITERIA

A potential subject who meets any of the following criteria will be excluded from participation in this study (parts A and B):

- Skin defect or active infection of the scalp in the area of the electrode cap placement;

- (Suspected) COVID-19 infection.

4.4 SAMPLE SIZE CALCULATION

We aim to develop and validate a novel algorithm for diagnosis of LVO stroke. In the prehospital and in-hospital setting together, EEG-measurements will be performed in a maximum of 1192 patients.

Using preliminary data of the ongoing ELECTRA-STROKE study (clinicaltrials.gov, NCT03699397), we identified two independent EEG predictors for LVO stroke: the theta-alpha ratio and the weighted phase lag index. For optimal algorithm development, using conventional statistical methods, 20-50 events (i.e. LVO strokes) per predictor are required in the derivation cohort.[30] Thus, with conventional statistics, 40-100 patients with an LVO stroke would be required for algorithm development. Based on an incidence of 12% for LVO stroke among patients with a suspected AIS[31], and assuming a dropout rate of 30% (either due to missing consent or failed EEG registration), 484-1192 patients with a suspected AIS are required.

5. TREATMENT OF SUBJECTS

PART A AND B

A single dry electrode cap EEG will be performed in the prehospital setting (part A) or at presentation in the ER (part B). As soon as feasible, preferably within 72 hours after arrival at the hospital or at discharge (whichever comes first), deferred informed consent is asked (see chapter 11). If informed consent is obtained, information on patient characteristics, medical history, medication use, physical and neurological examination performed by the treating physician, imaging studies, diagnosis and treatment as well as logistical and technical information regarding the patient's transport, treatment and the EEG measurement, obtained from the patient, the treating physician and the EMS will be collected. There are no follow up visits.

6. INVESTIGATIONAL PRODUCT

Not applicable, since no investigational product(s) will be used in this study.

7.NON-INVESTIGATIONAL PRODUCT

7.1 NAME AND DESCRIPTION OF NON-INVESTIGATIONAL PRODUCT

We will use the Waveguard™ touch dry electrode EEG cap and compatible eego™ mini amplifier (ANT Neuro B.V., Hengelo, Netherlands) to record and amplify the EEG signal, respectively. Both products are CE marked as medical devices in the European Union (Appendices 1 and 2) and will be used within the intended use as described in the user manuals (Appendices 4 and 5). To acquire the EEG signals from the amplifier, we plan to use CE marked NeuroCenter® EEG software (CE class IIa; Appendix 3 and 6) from Clinical Science Systems (ISO 9001 and ISO 13485 certified).

7.2 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES

This is not relevant, as the Waveguard™ dry electrode cap and eego™ amplifier are both CE marked products that have been safely used in clinical studies (see chapter 7.3). NeuroCenter® EEG software is a CE class IIa product.

7.3 SUMMARY OF FINDINGS FROM CLINICAL STUDIES

The Waveguard™ dry electrode cap and eego™ amplifiers have both been safely used in several clinical studies, with no reported adverse events.[11, 12, 32, 33] Two small studies that compared the Waveguard™ dry electrode cap with conventional wet electrode EEG reported similar (good) wearing comfort as well as similar signal quality based on power spectral density analysis, with significantly less preparation time for the dry electrode cap.[11, 12]

7.4 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS

Since an EEG-measurement is a safe and non-invasive procedure that is regularly performed in standard medical practice, and we only use CE marked products, we expect no health risks and no to minimal discomfort (during the measurement).[11, 12] The caps will be cleaned and disinfected as recommended in by the manufacturer.

8. METHODS

8.1 STUDY PARAMETERS/END POINTS

8.1.1 MAIN STUDY PARAMETER/END POINT

Based on the EEG data one or more novel AI-based EEG algorithms (the AI-STROKE algorithms) will be developed with optimal diagnostic accuracy for identification of LVO stroke in patients with a suspected AIS in the prehospital setting. For the purpose of the study, an LVO is defined as an occlusion of:

- Intracranial part of the internal carotid artery (ICA)
- First segment or proximal part of the second segment of the middle cerebral artery (M1 and proximal M2, respectively)
- First segment of the anterior cerebral artery (A1)

The final diagnosis of all patients will be established by an adjudication committee, which will consist of a vascular neurologist and neuroradiologist, and will be based on available clinical and imaging data.

8.1.2 SECONDARY STUDY PARAMETERS/END POINTS

Secondary end points of this study are:

- AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the AI-STROKE algorithms based on ambulant EEG for diagnosis of LVO of the anterior circulation in suspected AIS patients in the prehospital setting;
- AUC, sensitivity, specificity, PPV and NPV of existing EEG algorithms based on ambulant EEG for diagnosis of LVO of the anterior circulation in suspected AIS patients in the prehospital setting;
- AUC, sensitivity, specificity, PPV and NPV of existing and newly developed EEG algorithms based on ambulant EEG for detection of LVO stroke of the posterior circulation, intracerebral hemorrhage, transient ischemic attack, and stroke mimics;
- Technical and logistical feasibility (e.g. in terms of EEG channel reliability) of paramedics performing ambulant EEG in patients with a suspected AIS in the prehospital setting.

8.2 BLINDING

In this diagnostic accuracy study, the treating clinical team and the paramedics are not blinded for the EEG recording. However, they are not trained nor instructed to interpret the EEG results in this study.

8.3 STUDY PROCEDURES

All collected data and study procedures are listed in the following table. There are no follow up visits. Items that are not part of standard medical procedure/treatment are bold.

	PART A	**PART B**
Patient characteristics*	<24 hours after arrival in hospital or at discharge (whichever comes first)	<24 hours after arrival in hospital or at discharge (whichever comes first)
Past medical history	<24 hours after arrival in hospital or at discharge (whichever comes first)	<24 hours after arrival in hospital or at discharge (whichever comes first)
Medication use	<24 hours after arrival in hospital or at discharge (whichever comes first)	<24 hours after arrival in hospital or at discharge (whichever comes first)
Physical and neurological examination by treating physician	At arrival in ER	At arrival in ER
National Institute of Health Stroke Scale (NIHSS) score	At arrival in ER	At arrival in ER
Brain imaging results, if available	At arrival in ER (if necessary, as judged by treating physician)	At arrival in ER (if necessary, as judged by treating physician)
Dry electrode cap EEG	**At arrival of the ambulance**	**At arrival in ER**
Final diagnosis, as judged by the adjudication committee (as specified in Appendix 7)	At discharge	At discharge
Treatment with IVT and/or EVT	At arrival in ER (if necessary, as judged by treating physician)	At arrival in ER (if necessary, as judged by treating physician)
Times regarding stroke logistics**	**Collected during first 24 hours after symptom onset**	**Collected during first 24 hours after symptom onset**

*Age, sex, estimated quantity and length of hair on the head of the participant.
**Time of: last seen well or witnessed stroke onset, 112-call, ambulance arrival on site, ambulance departure to hospital, ambulance arrival at hospital, start neuro-imaging (if any), start IVT/EVT (if any), transfer times from other primary hospital (if applicable), putting on EEG cap, start EEG measurement, stop EEG measurement.

8.4 WITHDRAWAL OF INDIVIDUAL SUBJECTS

Subjects can deny or withdraw consent 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.

8.5 REPLACEMENT OF INDIVIDUAL SUBJECTS AFTER WITHDRAWAL

Since our sample size calculation includes an expected dropout rate, we do not intend to replace subjects that have withdrawn from the study. However, if the drop-out rate is higher than anticipated or when the number of LVO stroke patients is lower than expected, the steering committee (as specified in Appendix

7) may decide on replacement at a later stage. Records will be kept of all reasons for withdrawal and these will be reported along with the study results.

9. SAFETY REPORTING

9.1 TEMPORARY HALT FOR REASONS OF SUBJECT SAFETY

In accordance with section 10, subsection 4 of the Medical Research Human Subjects Act (in Dutch: WMO), the sponsor will suspend the study if there is sufficient ground to suspect that continuation of the study may jeopardize the health or safety of the subjects. 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 ensure 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 investigational product or the intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded.

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;
- Any other important medical event that did not result in any of the outcomes listed above due to but could have been based upon appropriate judgement by the investigator.

The sponsor will report the 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 SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

Stroke often results in complications such as infections, delirium, constipation, decubitus wounds, swallowing difficulties and falls, as well as in hospitalization and death. Because we expect no health risk related to participation in this study, these events will be reported to the accredited METC that approved the protocol in a yearly line listing until the last patient has completed the study.

Furthermore, the following situations will not be reported as (S)AEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by study treatment as judged by the clinical investigator and where admission did not take longer than anticipated;
- Admission and treatment for the index stroke (i.e. the stroke which lead to inclusion of the patient);
- Admission for diagnosis or therapy of a condition that existed before inclusion to this study and has not increased in severity or frequency as judged by the clinical investigator;
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present at the start of the study that do not worsen.

9.3 FOLLOW UP OF ADVERSE EVENTS

All AEs 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. AEs and SAEs will be reported if they occur within 1 hour after completion of the EEG-measurement.

9.4 SAFETY COMMITTEE

Installation of a safety committee is not deemed necessary, considering that an EEG-measurement is a safe, non-invasive and painless procedure that is used regularly in standard medical practice and only CE marked products are being used.

10. ALGORITHM DEVELOPMENT AND STATISTICAL ANALYSIS

ALGORITHM DEVELOPMENT

The EEG data obtained in the prehospital setting and in the ER will be divided in a training (80%) and validation (20%) set. Only the training set will be used to train novel AI-algorithms for LVO-detection. First, we will create a logistic regression model based on standard EEG-features, e.g. time domain characteristics, power spectral density in different frequency bands, coherence measures, and entropy measures. This model will be the reference to assess the improvement of the other novel AI-based models. We plan to base the final AI-STORKE algorithm on artificial neural networks, but other EEG classification algorithms (e.g. based on support vector machines and random forests) may be explored as well.[34] First, we will create convolution neural networks (CNN's) using the extracted EEG-features. Subsequently, we will evaluate whether the EEG-signals contain more information than these features by creating models that analyze the time series directly. To deal with the different timescales of features in EEG-signals and their dynamic behavior, we aim to study recurrent neural networks (RNN's). Examples of such RNN's include Long Short-Term Memory (LSTM)[35, 36], Gated Recurrent Unit (GRU) CNN's, and Deep Belief networks (DBN's)[37]. The first models will be built using a limited set of EEG data since data collection is part of this study. We will deal with the data sparsity using two approaches: (I) Transfer learning, we will train models for other EEG classification tasks (such as classification of stroke vs. healthy subjects or male vs. female), so that features from the time signals are trained. For this, existing fully anonymized EEG data will be used. The trained models will subsequently be used to fine-tune the classification of suspected AIS patients. (II) Reinforcement learning[38], and uncertainty-based learning in particular. We will update the models by feeding the data that are collected during the study. During the EEG data collection, the algorithm will be evolving, and the correct classification ratio will be improving as more data are added. The final algorithm will be considered successful if an AUC of >0.80 is reached in the validation set.

STATISTICAL ANALYSIS

EEG data quality will be monitored continuously to avoid an excessive drop-out rate due to malfunctioning EEG hardware. Two interim analyses for the AI algorithms will be performed: the first when 50 and the second when 100 LVO stroke patients are included in the study. Results of these analyses will be obtained by performing k-fold cross-validation on the training data, including data from the ER and the ambulance. The diagnoses (i.e. LVO stroke or no LVO stroke) as predicted by the developed algorithms will be compared to the diagnoses given by the adjudication committee. A receiver operating characteristic (ROC) curve will be plotted for each algorithm and the optimal cut-off value (i.e. highest sensitivity at a specificity ≥80%) for each algorithm will be determined. For these cut off values, the sensitivity, specificity, negative predictive value and positive predictive value will be reported, including 95% confidence intervals. The steering committee may decide to prematurely stop the recruitment in the study if the results of the interim analysis show that an accurate and stable algorithm can be developed with the data collected up till that point.

Eventually, we will evaluate the performance of the developed classification algorithm(s) and several existing algorithms on the validation data set. A receiver operating characteristic (ROC) curve will be plotted for each algorithm and the optimal cut-off value (i.e. highest sensitivity at a specificity ≥80%) for each algorithm will be determined. For these cut off values, the sensitivity, specificity, NPV and PPV value will be calculated.

11. ETHICAL CONSIDERATIONS

11.1 REGULATION STATEMENT

This study will be conducted according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (in Dutch: WMO).

11.2 RECRUITMENT AND CONSENT

The patient recruitment and informed consent procedure are the same as for the ELECTRA-STROKE study (NL65939.018.18).

PART A AND B

Patients will be screened for eligibility in the prehospital setting by the ambulance paramedic (part A) or in the ER by the investigators (part B). If patients fulfill the in- and exclusion criteria, an ambulant EEG will

be performed before obtaining informed consent. Furthermore, the ambulance centers will share personal patient data needed for patient identification and subsequent informed consent with the coordinating center. Along with these data, logistical data regarding prehospital transport and the EEG recording, and prehospital vital signs will be shared. As soon as feasible and preferably within 72 hours after arrival at the hospital or at discharge (whichever comes first), the patient or legal representative (see chapter 11.3) is informed and asked for informed consent by the investigator. If informed consent is granted, we will use the EEG data that have already been obtained and continue the retrospective study procedures. If informed consent is denied, the obtained EEG data will be destroyed. Figure 2 shows the procedure of obtaining deferred consent. If the patient is deceased before informed consent has been be asked from the patient or the legal representative, we will use the EEG data that have already been obtained and continue the retrospective study procedures (i.e. collection of data that have already been obtained as part of standard medical practice, see chapter 8.3), without having obtained informed consent.

ETHICAL CONSIDERATIONS REGARDING DEFERRED CONSENT

Informed consent is fundamental for patient participation in any type of research. However, in acute stroke research, the 'time is brain' principle conflicts with this. For study procedures that need to be performed in the acute setting, asking informed consent in a way that the patient or legal representative has the time to calmly consider the information and ask questions means losing valuable time: an hour delay in initiation of reperfusion therapy (intravenous thrombolysis (IVT) or EVT) in AIS causes a 5-8% decrease in chance of functional independence 3 months after the stroke.[5, 18, 39] Also, asking for informed consent in the acute setting is unlikely to result in a decision that is well thought through, because the patient or legal representative may be overwhelmed and under psychological stress.[40] Finally, many patients with an AIS are unable to comprehend information regarding study participation due to lowered consciousness, aphasia or anosognosia (not realizing the severity of one's own disease, often due to a lesion of the non-dominant cerebral hemisphere). Only including patients that are capable of giving informed consent would mean selecting a subgroup of patients with relatively mild neurological symptoms that is not representative of the population of patients with an LVO. A legal representative is often not present in the acute phase.[41] For the above-mentioned reasons, several acute stroke trials have been conducted where informed consent was not required prior to randomization.[42] According to the Medical Research Human Subjects Act (in Dutch: WMO), for research that can only be conducted in an emergency setting it is allowed to perform study procedures without prior informed consent, if inclusion

in the study may benefit the person in urgent need of medical treatment, for as long as the circumstances preventing the giving of consent exist.

Performing an EEG in patients with a suspected AIS in the short time window prior to initiation of treatment is necessary in this study, because the objective is to study the diagnostic accuracy of the ambulant EEG for LVO stroke. As soon as the occlusion is being treated (by IVT and/or IAT), this is no longer possible. Although participation in this study does not benefit the patient, it is very important that a reliable stroke triage method is found for stroke patients in the long term, as described in chapter 1. Considering that EEG is a safe, non-invasive and painless procedure that is used regularly in standard medical practice and does not involve electromagnetic radiation, alongside the above mentioned reasons, we deem it ethical to perform the EEG, while withholding the other study procedures until informed consent is obtained. We will ask informed consent as soon as feasible, preferably within 72 hours after arrival at the hospital or at discharge (whichever comes first). If informed consent is denied, the obtained EEG data will be destroyed. Figure 2 shows the procedure of obtaining deferred consent.

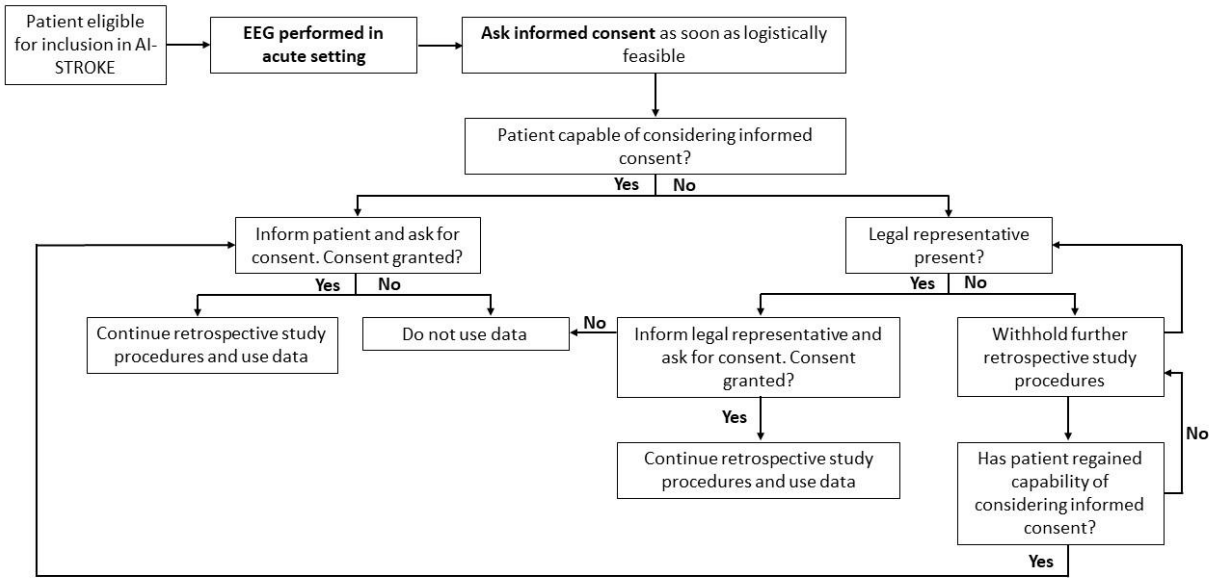

Figure 2: Flow chart showing process of obtaining deferred consent. Acute setting is in the ambulance for part A and in the emergency room for part B.

11.3 INCAPACITATED SUBJECTS

Due to lowered consciousness, aphasia or anosognosia (not realizing the severity of one's own disease, often due to a lesion of the non-dominant cerebral hemisphere), patients with an AIS frequently are unable to comprehend information regarding study participation. Therefore, they are often not able to give or to deny informed consent. It is essential that these patients are included in the study, as excluding them would mean selecting a subgroup of patients with relatively few neurological symptoms that is not representative of the population of patients with an LVO. If a patient is incapacitated, their legal representative (according to the Medical Research Human Subjects Act [in Dutch: WMO]) will be asked for informed consent. If an incapacitated patient becomes capable of considering informed consent during admission, informed consent will be asked. If denied, the patient will be excluded. Incapacitated patients that object to participation, will not be included in the study. Incapacitated patients that object during participation, will immediately be excluded at that moment. The patient or the legal representative, can refuse informed consent without any consequences for further treatment and can withdraw informed consent at any time during the study, which is stated in the information letter.

11.4 BENEFITS AND RISK ASSESSMENT, GROUP RELATEDNESS

EEG is a safe, non-invasive and painless procedure that is used regularly in standard medical practice and does not involve electromagnetic radiation. The Waveguard™ dry electrode cap and the eego™ amplifier are both CE marked and have been safely used in several clinical studies (see chapter 6.3). We expect no health risks and no to minimal discomfort associated with participation. For patients, there is no benefit of participation in the study.

11.5 COMPENSATION FOR INJURY

Since no risks related to participation in this study are expected, the METC has granted exemption from the obligation to take out insurance for subjects. A liability insurance has been taken out by the coordinating center.

11.6 INCENTIVES

For the patient, there is no benefit of participation in the study.

12. ADMINISTRATIVE ASPECTS AND MONITORING

12.1 HANDLING AND STORAGE OF DATA AND DOCUMENTS

After an ambulant EEG is performed, the EEG data will be sent to a secure external server, containing only EEG data, date and time of the EEG recording and an assigned study code. These data will be sent from the secure external server to the coordinating investigators and subsequently removed from the external server. The ambulance paramedic who has performed the EEG will fill out a predesigned form with the patient identification code, patient characteristics, and logistical and technical information regarding the patient's transport and EEG measurement. Data will be send to the local coordinating investigator per secured email. A log with all identification codes and identifying information will be kept digitally by the local coordinating investigator, separate from the study database. This log will be password encrypted and saved on the secured drive system of the participating center, only being accessible to the local research staff. The logistical and technical information regarding the patient's transport and EEG measurement will be stored in a separate mailbox, only accessible by the coordinating investigators. After informed consent is obtained, other study data, as described in chapter 8.3, will be retrieved from the electronic patient file. All study data - apart from identifying information, imaging data and EEG data - will be stored in a digital database (Castor), also password encrypted and only accessible to the research staff of the participating center and the coordinating hospital. EEG and imaging data will finally be stored on a network drive within the AMC, accessible only to authorized research staff of the coordinating hospital. For the algorithm development, we work together with external commercial parties. Therefore, all coded data will be shared with these parties. The log with all identification codes will never be shared, so external parties will not be able to trace the data back to the individual patient. All data will be stored for 15 years. Handling of data will comply with the General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming) and Good Clinical Practice (GCP).

12.2 MONITORING AND QUALITY ASSURANCE

Monitoring visits are conducted by the Clinical Monitoring Center of the AMC. Five on-site monitoring visits are scheduled. The timing of the monitoring visits is linked to the inclusion rate.

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.

12.4 ANNUAL PROGRESS REPORT

The investigator will submit a summary of the progress of the study 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 study, serious adverse events, amendments and other problems.

12.5 TEMPORARY HALT AND (PREMATURE) END OF STUDY REPORT

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The investigator 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 investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

13. RISK ANALYSIS

EEG is a safe, non-invasive and painless procedure that is used regularly in standard medical practice. It does not involve electromagnetic radiation. We will use CE marked products only. We expect no health risks and no to minimal discomfort associated with participation.

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